MODELS OF CARE
IN THE MANAGEMENT OF
CHRONIC LIVER DISEASE

By

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ABSTRACT

Cirrhosis or advanced stage of chronic liver disease (CLD) is an increasingly prevalent cause of morbidity and premature mortality in the Australian population. Furthermore, it is associated with increased health expenditure due to recurrent hospital admissions. These often occur due to inadequate monitoring, education and self-management support for cirrhotic patients after discharge from hospitals under the current models of care (MOCs). New MOCs with chronic disease management (CDM) principles are required to manage the increasing burden of CLD on the healthcare system. This thesis evaluated innovative MOCs in cirrhosis by studying the following:

- Impact of a coordinated care model on hospital readmissions and survival.
- Validation of a newly developed knowledge questionnaire.
- Assessment of a self-management tool, the Partners in Health (PIH) scale.
- Qualitative and cost-effectiveness analysis of a novel MOC, nurse-led cirrhosis clinics (NLCCs).
- Innovative MOC in delivering hepatitis C virus (HCV) screening and treatment in psychiatric inpatients as a micro-elimination project.
- Cost-effectiveness of decentralised MOCs in HCV treatment.

In the first study, liver-related emergency readmission (LREA) rates and survival in patients with decompensated cirrhosis managed within a coordinated MOC were compared to those managed with standard care. The study demonstrated lower incidence of LREAs and improved survival, supporting coordinated MOC in cirrhosis.

The second study aimed to develop and validate a knowledge questionnaire for cirrhotic patients. A 14-item questionnaire was evaluated for face, construct and known-group validity in 116 patients. A three-factor construct with seven items on ascites, variceal bleeding and hepatic encephalopathy was validated. Patients managed within a CDM model had higher knowledge scores.

The PIH scale is a validated tool for assessment of self-management knowledge and behaviours in patients with chronic diseases. The aim of the third study was to validate its use in cirrhotic patients. Prospective evaluation in 133 patients confirmed its four-factor structure: partnership

in treatment, knowledge, recognition and management of symptoms, and coping. Patients managed within a CDM model had higher self-management scores.

The fourth study aimed at a qualitative and cost-minimisation analysis of NLCCs, a unique MOC for patients with compensated cirrhosis. Patients expressed satisfaction and a good understanding of the model. Upskilling and provision of professional care in a holistic manner were important to the nurses. Hepatologists expressed confidence and satisfaction with the model, which was also cost effective.

The fifth study investigated HCV seroprevalence, risk factors and treatment model in an Australian cohort of psychiatric inpatients, who are under-served with HCV screening and treatment. The study established a high HCV seroprevalence and confirmed the efficacy of a multidisciplinary treatment model.

The sixth study evaluated the cost-effectiveness of four MOCs in HCV treatment, in a real-life cohort of non-cirrhotic HCV patients treated statewide. Using a Markov model-based analysis of liver disease progression the cost-effectiveness of general practitioner-led model and mixed consultant nurse model were demonstrated.

In conclusion, this thesis explored the unmet need for innovative, multidisciplinary CDM models in CLD management. It demonstrated positive clinical, economic and qualitative outcomes of alternative MOCs and evaluated tools to assess educational and self-management needs in cirrhotic patients.

DECLARATION

'I certify that this thesis:

1. does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university;

and,

2. to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.'

Jeyamani Ramachandran

Signature

Date: 17 November 2020

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PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS RELATED TO THE THESIS

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2. **Ramachandran J**, Woodman R, Muller K, Wundke R, McCormick R, Kaambwa B, Wigg A. Validation of knowledge questionnaire for patients with liver cirrhosis. *Clin. Gastroenterol. Hepatol*., **18(8)**:1867–1873, 2020.
3. **Ramachandran J**, Kaambwa B, Muller K, Haridy J, Tse E, Tilley E, Altus R, Waddell V, Gordon D, Shaw D, Huynh D, Stewart J, Nelson R, Warner M, Boyd MA, Chinnaratha MA, Harding D, Ralton L, Colman A, Woodman R, Wigg AJ. Cost-effectiveness of treatment models of care for hepatitis C: the South Australian state-wide experience. *Eur. J. Gastroenterol. Hepatol.*, 31 December 2019. doi: 10.1097/MEG.0000000000001659. [Epub ahead of print].
4. **Ramachandran J**, Budd S, Slattery H, Muller K, Mohan T, Cowain T, Tilley E, Baas A, Wigg L, Alexander J, Woodman R, Kaambwa B, Wigg A. Hepatitis C virus infection in Australian psychiatric inpatients: a multicentre study of seroprevalence, risk factors and treatment experience. *J. Viral Hepatitis*, **26(5)**:609–612, 2019.
5. **Ramachandran J,** Hossain M, Hrycek C, Tse E, Muller KR, Woodman RJ, Kaambwa B, Wigg AJ. Coordinated care for patients with cirrhosis: fewer liver-related emergency admissions and improved survival. *Med. J. Aust.*, **209(7)**:301–305, 2018.

PUBLICATIONS UNRELATED TO THE THESIS (DURING THE CANDIDATURE)

1. Coller JK, **Ramachandran J**, John L, Tuke J, Wigg A, Doogue M. The impact of liver transplant recipient and donor genetic variability on tacrolimus exposure and transplant outcome. *Br. J. Clin. Pharmacol.*, **85(9)**:2170–2175, 2019.
2. Wigg AJ, Narayana SK, Anwar S, **Ramachandran J**, Muller K, Chen JW, John L, Hissaria P, Kaambwa B, Woodman RJ. High rates of indeterminate interferon-gamma release assays for the diagnosis of latent tuberculosis infection in liver transplantation candidates. *Transpl. Infect Dis.*, doi: 10.1111/tid.13087. Epub 16 April 2019.
3. Wigg AJ, Wundke R, McCormick R, Muller KR, **Ramachandran J**, Narayana S, Woodman RJ, Efficacy of high-dose, rapid, hepatitis A and B vaccination schedules in patients with cirrhosis. *Clin. Gastroenterol. Hepatol.*, **17(6)**:1210–1212, 2019.
4. Haridy J, Wigg A, Muller K, **Ramachandran J**, Tilley E, Waddell V, Gordon D, Shaw D, Huynh D, Stewart J, Nelson R, Warner M, Boyd M, Chinnaratha MA, Harding D, Ralton L, Colman A, Liew D, Iyngkaran G, Tse E, Adelaide Liver Group, Real-world outcomes of unrestricted direct-acting antiviral treatment for hepatitis C in Australia: the South Australian statewide experience. *J. Viral Hepatol.*, **25(11)**:1287–1297, 2018.
5. Bera C, Thangaraj K, Pati PK, **Ramachandran J**, Balasubramanian KA, Ramachandran A, Zachariah U, Sajith KG, Goel A, Eapen CE, Raised plasma levels of H_2S and nitrate predict intrapulmonary vascular dilations: a preliminary report in patients with cryptogenic cirrhosis. *Indian J. Gastroenterol.*, **37(3)**:209–214, 2018.
6. Gupta P, Choksi M, Goel A, Zachariah U, Sajith KG, **Ramachandran J**, Chandy G, Kurian G, Rebekah G, Eapen CE, Maintenance zinc therapy after initial penicillamine chelation to treat symptomatic hepatic Wilson's disease in resource constrained setting. *Indian J. Gastroenterol.*, **37(1)**:31–38, 2018.
7. David D, Raghavendran A, Goel A, Bharath Kumar C, Kodiatte TA, Burad D, Abraham P, Ramakrishna B, Joseph P, **Ramachandran J**, Eapen CE, Risk factors for non-alcoholic fatty liver disease are common in patients with non-B non-C hepatocellular carcinoma in India. *Indian J. Gastroenterol.*, **36(5)**:373–379, 2017.

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ABBREVIATIONS

A

ABS	Australian Bureau of Statistics
ACLD	advanced chronic liver disease
ACLF	acute on chronic liver failure
AIHW	Australian Institute of Health and Welfare
ALD	alcoholic liver disease
ALT	alanine transaminase
APRI	aspartate aminotransferase to platelet ratio index
ART	anti-retroviral therapy
AUD	Australian dollar

B

BCFA	Bayesian confirmatory factor analysis

C

cACLD	compensated advanced chronic liver disease
CC	compensated cirrhosis
CDC	Centre for Disease Control
CDM	chronic disease management
CDSMS	chronic disease self-management support
CE	cost-effectiveness
CEA	cost-effectiveness analysis
CEACs	cost-effectiveness acceptability curves
CEPs	cost-effectiveness planes
CFR	case fatality rate
CHAMP	Cardiac Hospitalization Atherosclerosis Management Programme
CHC	chronic hepatitis C
CI	confidence interval
CKQ	cirrhosis knowledge questionnaire
CLD	chronic liver disease
CLDQ	Chronic Liver Disease Questionnaire
CLF	chronic liver failure

CLFP	Chronic Liver Failure Program
COPD	chronic obstructive pulmonary disease
CrI	credible interval
CSPH	clinically significant portal hypertension
D	
DAAs	Direct-acting antivirals
DALY	disability-adjusted life years
DBS	dried blood spots
DC	decompensated cirrhosis
df	degrees of freedom
DIC	deviance information criterion
E	
ECHO Project	Extension for Community Healthcare Outcomes Project
EFA	exploratory factor analysis
EIA	enzyme immunoassay
EUR	euro
F	
FDA	Food and Drug Administration
G	
GBP	Great Britain pound (British pound sterling)
GP	general practitioner
H	
HADS	Hospital Anxiety and Depression Scale
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HE	hepatic encephalopathy
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRRs	hospital readmission rates
HVPG	hepatic venous pressure gradient

I

ICD-10	International Classification of Diseases, Tenth Revision
ICER	incremental cost-effectiveness ratio
IDU	injection drug use
IIT	intention to treat
INR	International Normalized Ratio
IQR	interquartile range
IRR	incidence rate ratio
IU	international units
IVDU	intravenous drug use

K

KMO test	Kaiser–Meyer–Olkin test

L

LOCATE	LOcal Care And Treatment of chronic liver disease Evaluation
LREAs	liver-related emergency admissions
LSM	liver stiffness measurement
LT	liver transplantation

M

MAFLD	metabolic-associated fatty liver disease
MELD	Model of End-stage Liver Disease
MOCs	models of care
MRPs	medication-related problems

N

NACSELD	North American Consortium for Study of End-stage Liver Disease
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NLC	nurse-led clinic
NLCC	nurse-led cirrhosis clinic
NMB	net monetary benefit
NSAID	nonsteroidal anti-inflammatory drug
NSP	Needle and Syringe Program

O

OECD	Organization for Economic Cooperation and Development
OR	odds ratio
OST	opioid substitution therapy

P

PIH	Partners in Health
PNs	practice nurses
PP	per protocol
PROs	patient-reported outcomes
PSR	potential scale reduction
PWIDs	persons who inject drugs

Q

QALY	quality-adjusted life years
QIs	quality indicators
QoL	quality of life

R

RCT	randomised controlled trial
RDT	rapid diagnostic test
RMSEA	root mean square error of approximation
RMSR	root mean square residual

S

SBP	spontaneous bacterial peritonitis
SEMCD	Self-Efficacy for Monitoring Chronic Disease
SD	standard deviation
SMR	standardised mortality ratio
SNs	specialist nurses
SNAC	Supportive Needs Assessment tool for Cirrhosis
STD	sexually transmitted diseases
SUPPH questionnaire	Strategies Used by People to Promote Health questionnaire
SVR	sustained virological response

T	
TE	transient elastography
U	
USD	United States dollar
W	
WHO	World Health Organization
WWIDs	women who inject drugs

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1. INTRODUCTION

Chronic liver disease (CLD) is an important cause of premature mortality in the Australian population.[1] Common causes of CLD in Australia include hepatitis C virus (HCV) infection, alcohol misuse and nonalcoholic fatty liver disease. With ongoing chronic injury from these factors, cirrhosis of the liver, which is an advanced stage of CLD, ensues. Progression of cirrhosis from a clinically silent compensated stage to a symptomatic decompensated stage is associated with multiple complications, such as gastrointestinal bleeding, ascites, renal failure, hepatic encephalopathy and hepatocellular carcinoma.[2] These complications of cirrhosis often result in recurrent and prolonged hospital admissions that are very characteristic of the disease.[3] Worldwide, cirrhosis is a significant contributory factor to an increased burden on the existing healthcare system due to its morbidity and mortality.[4,5] Despite evidence-based guidelines that have established improvement in hospital survival of this chronic complex disease,[2,6] mortality in the early post-discharge period remains significantly high.[7] The morbidity of recurrent hospital admissions and post-discharge mortality continue to be major challenges facing the medical community caring for patients with cirrhosis of the liver. These problems often occur as a result of inadequate monitoring, education and self-management support for these patients after discharge in the current models of care (MOCs).

An important, current unmet need in the management of CLD is an efficient MOC that provides continuous, longitudinal care of patients between the relatively infrequent outpatient appointments with physicians. It is important that the care given to these chronic patients is sustained (even after a hospital discharge) and is multifaceted, providing education and self-management support in addition to clinical management. In the current management of other similar chronic diseases, such as heart failure and asthma, there is an increasing recognition of the need for a coordinated system of care known as chronic disease management (CDM), which has been successfully studied and implemented in these diseases.[8,9,10] Multidisciplinary care, home visits, telephone support, case management, planned follow-ups and self-management support are some of the successful CDM interventions employed in these diseases. Although cirrhosis, with its multiple complications leading to frequent hospitalisations, morbidity, mortality and poor quality of life, is the perfect prototype for research on CDM interventions, there are very few studies exploring its efficacy. In the only randomised trial of CDM in cirrhosis Wigg et al. demonstrated that patients with decompensated cirrhosis, when managed

within a Chronic Liver Failure Program (CLFP), were more satisfied with their care and more likely to attend clinic and surveillance (endoscopic and radiological) appointments.[11] Four key CDM elements (delivery system redesign, patient education and information support, and self-management support) were employed in this CLFP. The Gastroenterology Society of Australia has identified research into CDM models in cirrhosis as a key priority, due to the escalation in its prevalence and the costs involved in management.[4]

In the following six studies, this thesis attempts to further evaluate multiple aspects of novel MOCs with various inbuilt CDM interventions in CLD. It studies the entire spectrum of CLD ranging from chronic hepatitis through compensated cirrhosis to decompensated cirrhosis. The first three studies focus on clinical, educational and supportive needs in decompensated cirrhosis; the fourth study focusses on compensated cirrhosis and the final two studies focus on the management of chronic HCV.

1.1 FEWER LIVER-RELATED EMERGENCY READMISSIONS AND IMPROVED SURVIVAL IN CIRRHOTIC PATIENTS MANAGED WITHIN A COORDINATED CARE MODEL

Hospital readmission rates (HRRs) of specific chronic conditions, such as cardiac failure, ischemic heart disease and asthma, are accepted as quality of care indicators.[8] The role of various CDM interventions in reducing HRRs is well established in these diseases. Alternatively, the beneficial effect of CDM interventions on HRRs has not been consistent in all chronic diseases.[8] There are instances where a comprehensive disease management for emphysema, with education and action plans for disease exacerbations, was associated with higher HRRs and lack of survival benefit in comparison with standard management.[12] Cirrhosis of the liver is a chronic disease associated with high rates (50%) of readmission in the early discharge period.[13] It is suggested that this could reflect suboptimal post-discharge care as a significant proportion of these readmissions were assessed to be preventable.[3] However, some of the hospital readmissions may be essential in finetuning the management of this chronic complicated disease, known as high-value admissions. Their reduction may hamper the overall patient survival. Hence, this study was planned to bridge a knowledge gap in literature, on the impact of CDM interventions in cirrhosis readmissions and survival. The premise of the study was that when decompensated cirrhosis is managed within a coordinated MOC using a CLFP, with CDM interventions, there would be fewer readmissions in comparison to standard care.

The aim of the study was to analyse HRRs and long-term survival of patients with decompensated cirrhosis and compare these quality indicators among patients managed via a coordinated MOC at one tertiary-care public hospital and another major tertiary-care public hospital in another health region where there was no coordinated care model for patients with cirrhosis.[14]

Short of a prospective randomised controlled trial (RCT) this retrospective study was expected to test the novel model in meeting crucial clinical endpoints and provide a valuable sample size estimate for a prospective RCT.

1.2 VALIDATION OF A KNOWLEDGE QUESTIONNAIRE FOR PATIENTS WITH CIRRHOSIS

There is increasing evidence that careful monitoring of patients with decompensated cirrhosis may be beneficial in preventing recurrent hospital admissions.[3,13,15] In addition, there are some interventions that have the potential to mitigate hospital admissions but require patients' active involvement, such as salt restriction, monitoring of serum electrolytes to prevent diuretic-related complications and lactulose dose titration to prevent the occurrence of hepatic encephalopathy. Furthermore, lifesaving endoscopic and radiological surveillance examinations require patients' active participation. These changes can be enhanced by appropriate patient education. Well-informed and actively participating patients have better health outcomes and health-related behaviours.[16] Lack of educational support is increasingly recognised as an area of unmet need in the management of patients with cirrhosis.[17] Randomised controlled studies have established the beneficial effects of patient education on quality indicators (such as readmissions) and mortality in other chronic diseases (such as ischemic heart disease, heart failure and asthma).[18-20] Validated knowledge questionnaires can be used not only to assess disease knowledge in patients but also to periodically examine the performance of CDM interventions that provide educational support. However, there is no validated instrument available for assessing disease knowledge among patients with cirrhosis. To fill this critical gap, the second study developed a cirrhosis knowledge questionnaire (CKQ) and measured its face, construct and known-group validity.[21] The use of the validated CKQ may improve the assessment of patient knowledge and self-management of cirrhosis. Further confirmation of its dimensionality, sensitivity to clinical education and the clinical predictive value of disease knowledge requires assessment in RCTs.

1.3 PSYCHOMETRIC VALIDATION OF THE PARTNERS IN HEALTH SCALE AS A SELF-MANAGEMENT TOOL IN PATIENTS WITH CIRRHOSIS

Self-management support, enabling patients to acquire knowledge and confidence required to manage chronic diseases, is an essential CDM principle.[10] Highly activated and engaged patients manage their chronic disease better and experience positive health outcomes.[22] Measurement of self-management reflects the level of patient activation. The Partners in Health (PIH) scale (with its four subscales of knowledge, partnership with treatment, recognition and management of symptoms, and coping) is a generic tool that is well validated for measuring self-management knowledge and behaviours in patients with a wide range of chronic illnesses.[23,24] The PIH scale as a measure of self-management, and in turn patient activation, in cirrhosis was explored in the third study. The PIH scale was applied to patients with cirrhosis for the first time and psychometric validation of the tool in measuring self-management knowledge and behaviours was prospectively evaluated. Given the importance of self-management skills in cirrhosis, the structural validity (including dimensionality) and reliability of the PIH scale were assessed in these patients. The scale has the potential to measure self-management ability in patients with cirrhosis and to assess improvement with self-management support provided as a part of CDM programmes. Higher self-management scores may be associated with better clinical outcomes.

1.4 EVALUATION OF NURSE-LED CIRRHOSIS CLINICS: QUALITATIVE AND COST-EFFECTIVENESS ANALYSIS

The increasing health demands of an ageing population with multiple chronic comorbidities is challenging traditional health MOC in Australia.[25] Nurse-led clinics (NLCs) are an important part of the modern medical delivery chain. Examples of speciality NLCs that provide medical care for patients with chronic diseases includes those for diabetes, mental health, chronic constipation, eczema, rheumatoid arthritis, cancer chemotherapy and sexually transmitted diseases.[26] Overall, NLCs are well accepted by patients in view of improved access, satisfaction, affordability and convenience.[26] In hepatology, the role and efficacy of NLCs are well established in the management of hepatitis C virus (HCV).[27,28,29] However, there is no evidence for the use of NLCs in the management of cirrhosis of the liver. The increasing

prevalence of cirrhosis in Australia has placed significant workload on traditional specialist-led liver clinics. A nurse-led cirrhosis clinic (NLCC) model for management of stable, compensated cirrhotic patients is a potential solution for this capacity problem. The NLCC model integrates two principles of CDM, namely delivery system redesign with community access and multidisciplinary care in the management of CLD.

The fourth study in this thesis explored the perspectives of patients and healthcare providers, and the cost-effectiveness of the model. Understanding patients' priorities in accessing care for CLD and designing care processes accordingly were the key objectives of this study. Assessment of economic benefits of the model is essential prior to recommendations for wider implementation.

1.5 HCV INFECTION IN AUSTRALIAN PSYCHIATRIC INPATIENTS: A MICRO-ELIMINATION MODEL OF SCREENING AND TREATMENT

The field of hepatology has experienced a major therapeutic breakthrough with the availability of direct-acting antivirals (DAAs). Thus, HCV infection, previously a very common cause of liver-related morbidity and mortality, is now an easily treatable and thus a preventable cause of CLD. Sustained virological response is associated with clinical, survival and socioeconomic benefits in patients with chronic HCV infection.[30-33] One of the current challenges is to increase HCV treatment uptake in vulnerable but neglected patient cohorts. Mental health patients are one such population that has been previously neglected due to the adverse effects of the interferon-based therapy, despite worldwide reports of increased HCV prevalence in this patient group.

With the focus on the prevention of development of CLD in patients infected with HCV and to address the need for a robust Australian epidemiological study, the fifth study was planned. It measured the HCV seroprevalence in a cohort of psychiatric inpatients in a prospective fashion at multiple sites across South Australia. In addition, in this difficult-to-treat, harder-to-engage population, screening was linked to successful treatment delivery using a decentralised MOC with involvement of specialist nurses (SNs) and community mental health teams.[34] The study served as an example of a successful micro-elimination model.

1.6 COST-EFFECTIVENESS OF MOCs IN HCV TREATMENT: THE SOUTH AUSTRALIAN STATEWIDE EXPERIENCE

Traditionally, there has been a significant reliance on specialists for the management of HCV. In addition to long waiting times to access specialist services, specialist care also adds to the expenditure incurred by the health system. In Australia, HCV drug prescription by general practitioners (GPs) and innovative MOCs are being pursued to achieve the World Health Organization's goal of eradicating HCV by 2030. Although Australia is leading the world in HCV eradication, assisted by the use of decentralised treatment models, these models have not been evaluated from a health economic perspective. There is a scarcity of cost-effectiveness studies based on real-world data.[35] Hence, the sixth study, a multicentre statewide study, evaluated the cost-effectiveness of different MOCs adopted in South Australia, in a real-life cohort.[36] A cohort Markov model-based probabilistic cost-effectiveness analysis (CEA) was undertaken extrapolating up to 30 years from cost and outcome data collected from a primary study involving a real-life Australian cohort.[37] The MOCs were classified depending on the person providing patient workup, treatment and monitoring into MOC1 (specialist), MOC2 (mixed specialist and hepatitis nurse), MOC3 (hepatitis nurse) and MOC4 (GP). Considering the number of patients waiting to be treated, the lack of widespread access to specialist care and easy access to GP care, it is important that these nontraditional and cost-effective MOCs are considered worldwide to facilitate HCV elimination goals.

In conclusion, this thesis addressed the unmet need for innovative, multidisciplinary CDM models in the management of CLD. New MOCs designed with CDM principles are required to manage the increasing burden of the CLD on the healthcare system in lieu of traditional models. The thesis explored both clinical and economic outcomes of alternative MOCs and evaluated tools to assess the educational and supportive care needs in patients with cirrhosis. Thus, this thesis aimed to inform the future implementation and use of alternative MOCs in liver disease.

2. LITERATURE REVIEW

2.1 CIRRHOSIS

This section reviews the literature relevant to the first study in the thesis on liver-related emergency readmissions and survival in patients with decompensated cirrhosis. It includes relevant studies that contributed to important knowledge on the natural history, aetiology, staging, prognosis and burden of cirrhosis and readmissions due to the disease. It discusses the flaws with the existing model of care (MOC) and explains the rationale for novel MOCs with chronic disease management (CDM) principles.

2.1.1 *Introduction*

Cirrhosis of the liver is an advanced chronic liver disease (ACLD) that is characterised pathologically by the presence of advanced fibrosis and distortion of the liver architecture, as a result of chronic persistent and active inflammation. Although the term 'cirrhosis' reflects a pathological diagnosis, it is more commonly used in the clinical context to describe any ACLD. This is largely due to the similar clinical appearance of the disease in its advanced stages with the sequelae of varying combinations of portal hypertension and synthetic failure, despite different causes and patterns of histologically evident fibrosis.

A working group of the World Health Organization (WHO) defined cirrhosis as a 'diffuse process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules'.[38] The METAVIR scale, a tool that is used to evaluate the severity of fibrosis seen on liver biopsy samples in chronic hepatitis C, measures the progressive nature of fibrosis in four stages (F1–F4), as follows[39]:

Stage F0: absence of fibrosis;
Stage F1: portal fibrosis;
Stage F2: periportal fibrosis;
Stage F3: bridging fibrosis;
Stage F4: cirrhosis.

In a strictly pathological context, cirrhosis is viewed as an end stage of chronic liver disease (CLD). Common causes include alcohol misuse, infection with hepatitis B and C viruses (HBV and HCV, respectively) and nonalcoholic fatty liver disease (NAFLD). Frequently, multiple

aetiological factors, such as alcohol misuse, obesity and chronic viral hepatitis, co-exist. Patients with cirrhosis, due to a combination of these factors, are often encountered in clinical practice. However, progression from CLD, characterised by varying degrees of inflammation and fibrosis, to cirrhosis does not occur if the offending agent is removed as seen with alcohol abstinence and antiviral therapy for HBV and HCV. Progression of fibrosis follows a different trajectory in different aetiologies. Paired biopsy studies in patients with NAFLD have shown that the presence of inflammation is a key factor in the progression of fibrosis,[40] and in HCV infection the progression depends on age, gender and cofactors, such as alcohol and obesity.[41,42]

With the recent introduction of direct-acting antivirals (DAAs) against HCV infection, the landscape of cirrhosis has changed considerably in all aspects including aetiology, course and prognosis. Cirrhosis due to NAFLD is rapidly replacing HCV as a common cause of decompensated cirrhosis and hepatocellular carcinoma (HCC) requiring liver transplantation.[43,44]

2.1.2 *Aetiology*

Common causes of cirrhosis in Australia, such as NAFLD, alcohol misuse and HCV infection, are discussed in the following sections. Other rarer causes include HBV, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, alpha-1-antitrypsin deficiency and hemochromatosis.

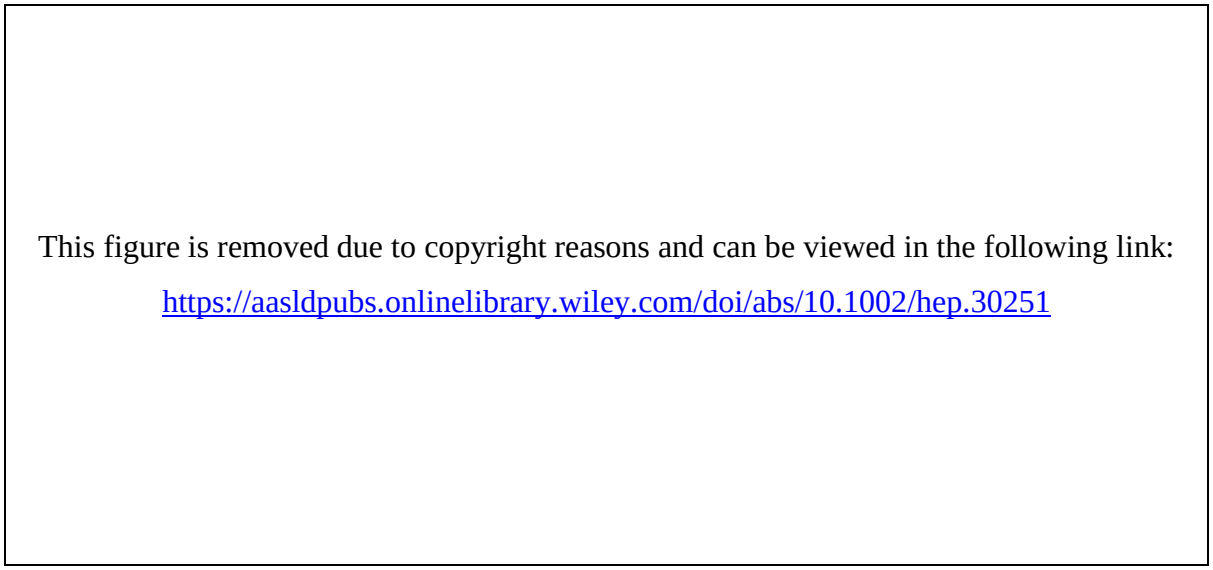
2.1.2.1 *Nonalcoholic Fatty Liver Disease*

NAFLD is defined as the presence of steatosis in excess of 5% in the hepatic parenchyma without significant alcohol consumption (<20 g/day for women and <30 g/day for men) or secondary causes, such as HCV and certain drugs.[45] The term NAFLD covers a spectrum ranging from simple steatosis, nonalcoholic steatohepatitis (NASH) to more advanced fibrosis and cirrhosis.

Common associations with NAFLD include hypertension, hyperlipidaemia, metabolic syndrome, obesity and type 2 diabetes mellitus. In addition to causing cirrhosis, NAFLD is also an important risk factor for hepatocellular carcinoma (HCC). The global prevalence of NAFLD is shown in **Figure 1**.[46] NAFLD is the commonest cause of CLD in Australia, in accordance with the global trend affecting up to 5.5 million people. This includes 40% of adults above 50

years of age and 15% of children.[46] NAFLD is a consequence of the increasing incidence of obesity, metabolic syndrome and type 2 diabetes mellitus in the general population.[47] Among patients with NAFLD, those with NASH and with metabolic syndrome and type 2 diabetes mellitus have a higher risk of liver-related mortality.[48] In addition, a linear relationship has been demonstrated between stages of fibrosis and mortality, with increasing mortality at more advanced fibrosis stages.[49] Although cardiovascular diseases have been reported as a more common cause of mortality, this association is only seen in non-cirrhotic patients.[50]

Figure 1. Worldwide prevalence of NAFLD (reproduced from Reference 46).



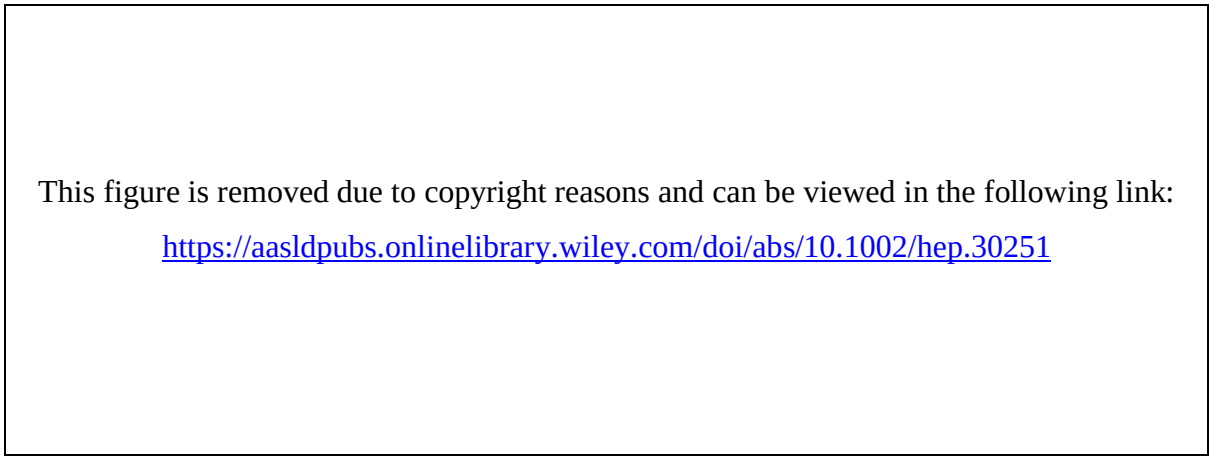
A longitudinal international cohort study revealed that liver-related causes were responsible for mortality in 50% of patients with severe (stage F3) fibrosis, 75% with early cirrhosis and 100% of patients with advanced cirrhosis.[46] Thus, as the severity of fibrosis increases, the probability of liver-related death increases proportionately in patients with NAFLD. Moreover, the occurrence of HCC is more common in NAFLD-related cirrhosis than other aetiologies, such as HCV infection, alcohol misuse and HBV infection. In an analysis of 158 347 liver transplant (LT) listed patients from the Scientific Registry of Transplant Recipients in the United States, between the period 2002 and 2016, NAFLD was found to be the most frequent cause of HCC.[44] The prevalence of HCC in NAFLD increased 11.5-fold, whereas the number of HCCs due to HCV increased only 6.2-fold.[44] The trend in the proportion of patients with HCC over the years increased 7.7-fold in NAFLD cirrhosis compared to the stable trends seen in alcohol-related and HCV-related cirrhosis.

The field of hepatology is facing a major challenge related to the increasing prevalence of NAFLD cirrhosis with its associated comorbidities as shown in **Figure 2**.[46] These coexisting illnesses and their complications add to the difficulties in clinical management of cirrhosis in these patients, in addition to increasing the economic burden of the disease.[51] There is no approved treatment for NAFLD to stop its progression to advanced fibrosis, other than weight loss.[50]

A concerning outlook has been predicted for Australia in terms of NAFLD-related complications over the next decade. Using a Markov model of disease progression and based on the proportion of obesity in the population (BMI cutoff value > 30 for Caucasians and > 25 for Asians) in 2019, Adams et al. estimated the number of patients with ACLD and deaths due to NAFLD by 2030.[52] They predicted that NAFLD cases would rise by 25%, resulting in approximately 7 million cases and a 40% rise in NASH resulting in approximately 2 million cases. A significant (85%) increase was estimated in the number of new cases of decompensated cirrhosis due to NAFLD from 2100 (range 1100–3800) cases to 3900 (range 2300–6900) cases during the time period 2019 to 2030, with a cumulative incidence of 35 800 (20 800–63 200) cases. Similarly, the number of new cases of HCC would escalate by 75% from 420 (range 280–660) cases in 2019 to 730 (with a range of 480–1100) cases in 2030; during the period 2019 to 2030, cumulative incident cases of NAFLD-related HCC would probably be 6800 (range 4500–10 700). The impact on mortality was estimated to be profound; 90% surge in the yearly liver-related mortality from 1700 (range 1000–3000) deaths to 3200 (range 1900–5700) deaths during the period 2019 to 2030 with cumulative liver deaths during the time period around 29 300 (range 17 300–51 500). This anticipated large increase in disease burden due to NAFLD cirrhosis on the health system justifies the development of improved MOC for cirrhotic patients.

A new concept known as metabolic-associated fatty liver disease (MAFLD) has been recently proposed that better describes the clinical relevance of NAFLD.[53] Rather than excluding other causes of CLD, such as alcohol and viral diseases, the new definition of MAFLD proposes diagnostic criteria that includes the presence of steatosis of the liver with one of the following: overweight/obesity, presence of type 2 diabetes mellitus or evidence of metabolic dysregulation. A recent study has also confirmed that the definition of MAFLD is more likely to be clinically useful, as it identified patients with a higher likelihood of progressive liver disease, such as those with older age, higher BMI or presence of metabolic comorbidities.[54]

Figure 2. Extrahepatic complications associated with NAFLD (reproduced from Reference 46).



2.1.2.2 *Alcoholic Cirrhosis*

Alcoholic liver disease (ALD) is a severe complication of alcohol misuse and is a preventable cause of premature mortality in these patients.[55] Worldwide, alcohol misuse is the most prevalent cause of CLD.[56] In 2010, as estimated by the global burden of disease methodology, alcohol was responsible for 48% of deaths due to cirrhosis of the liver, and 47% of cirrhosis disability-adjusted life years (DALYs).[56]

In addition, liver cancer due to alcohol led to 80 600 deaths and 2 142 000 DALYs globally.[56]

Alcohol misuse was the cause of cirrhosis in 50% of patients admitted to Queensland hospitals for cirrhosis-related decompensation during the period 2008 to 2016, as reported by Powell et al.[57] Alcohol misuse (>14–21 standard drinks per week in men and >7–13 drinks/week in women; 1 standard drink equals 14 g of alcohol) increases the risk of ALD.[58] The spectrum of ALD includes benign fatty liver, steatohepatitis, cirrhosis and HCC.[59]

Female gender predisposes to a higher risk of ALD, even with lower alcohol consumption. This relates to different gastric metabolism of alcohol, oestrogen-associated gut-mediated inflammation and body fat distribution-associated fibrosis formation. In addition to this, obesity and co-infection with hepatotropic viruses play a synergistic role in increasing the risk of advanced fibrosis in people who consume excessive alcohol.[60]

A Scottish study revealed a much higher adjusted relative risk of liver-related deaths [18.9 (95% confidence interval (CI), 6.84–52.4)] in obese men with excessive alcohol consumption in comparison to non-obese men [3.16 (95% CI, 1.28–7.8)], with equivalent alcohol use.[61] This study implied that the Australian population with a high prevalence of obesity is at a higher risk of developing advanced ALD.

HCV infection is up to 30 times more prevalent in people with alcohol misuse as compared to the general popualtion.[62] The increased risk of advanced fibrosis, cirrhosis and HCC seen in patients with alcohol misuse and HCV infection is attributed to an increase in oxidative stress among other factors.

HCV-related cirrhosis is discussed in Section 2.5.

2.1.3 *Natural History*

From a clinical perspective, there are two distinct stages of cirrhosis:

1. a clinically silent compensated stage,
2. a symptomatic decompensated stage.[2]

Compensated cirrhosis may or may not be associated with portal hypertension but is characterised by a long period of survival and a good quality of life.[63] Progression of liver damage caused by the persistence of the underlying insult (as in untreated HCV or HBV infections, continued alcohol consumption and uncontrolled risk factors for NAFLD), results in decompensated cirrhosis.[63] The decompensated stage is characterised by one or more of the following complications: ascites, variceal bleeding, jaundice and encephalopathy.[64] Other complications that are frequently encountered in more advanced stages of decompensated cirrhosis include refractory ascites, hyponatremia, hepatorenal syndrome, sepsis (such as spontaneous bacterial peritonitis, SBP), cardiopulmonary complications (such as portopulmonary hypertension and hepatopulmonary syndrome) and relative adrenal insufficiency.[65] Hence, decompensated cirrhosis is associated with significantly impaired quality of life and poor long-term survival in comparison to compensated cirrhosis.[63,66] At any stage, cirrhosis may be complicated by hepatocellular carcinoma (HCC), with a rate of 3% per year.[63] HCC often precipitates hepatic decompensation and confers a poorer prognosis. Given

gthe complexity of cirrhosis and its multitude of complications, the need for a holistic MOC is an important clinical need. Such a model should provide patient education and self-management support, in addition to longitudinal clinical management and surveillance for complications.

2.1.4 *Changing Definition and Stages*

Portal hypertension is the first and foremost consequence of cirrhosis. It is the result of increased intrahepatic resistance (due to the distortion caused by cirrhotic nodules and the effect of vasoconstrictor cytokines on sinusoidal endothelium) and increased portal venous flow. The latter is a consequence of a systemic and splanchnic vasodilatation due to elevated levels of nitric oxide, and thus vasodilatation is the pathophysiological basis of the complications of cirrhosis, such as development of varices and ascites. As the severity of splanchnic vasodilatation increases, the severity of the haemodynamic changes also increases, resulting in refractory ascites, hepatorenal syndrome and hyponatremia. The development of these haemodynamic changes underpins the development of clinical decompensation. Thus, the diagnosis of portal hypertension is of prognostic importance in the course of cirrhosis of the liver.[67]

Portal pressure, as measured by hepatic venous pressure gradient (HVPG), is an important determinant of development of complications in cirrhosis of the liver. Preclinical portal hypertension is defined by an HVPG between 6 mmHg and 9 mmHg. An HVPG value > 10 mmHg predicts the development of varices and/or clinically evident decompensation, the need for liver transplantation, and the likelihood of death.[68,69] Hence, it is appropriately defined as clinically significant portal hypertension (CSPH).

Therefore, better understanding of the prognostic significance of portal hypertension in cirrhosis has resulted in the reclassification of compensated cirrhosis into three stages[70]:

- *Stage 0*: In this stage the portal pressure is normal with HVPG < 6 mmHg.
- *Stage 1*: In this stage the portal pressure is below the threshold for development of varices or ascites, that is, < 10 mmHg. This stage is named compensated advanced CLD without clinically significant portal hypertension (cACLD without CSPH).

- *Stage 2*: In its advanced stage with portal pressure >10 mmHg, compensated cirrhosis is often associated with the presence of varices and is described as compensated advanced CLD with clinically significant portal hypertension (cACLD with CSPH).

These terms are proposed as meaningful alternatives to the simple term compensated cirrhosis in current guidelines.[71]

A combination of histological and haemodynamic correlations has established that cirrhosis is not a static event.[70] Its clinical evolution is variable dependent on a wide range of complex structural and haemodynamic changes that influence the occurrence of complications. A linear relationship was shown between the stages of fibrosis and the HVPG irrespective of the aetiology of cirrhosis.[72,73] Reversal of liver fibrosis can occur, as demonstrated with successful antiviral treatments in HCV and HBV cirrhosis, and with alcohol abstinence.[74]However, resolution of consequences of fibrosis and its clinical manifestations are long-term processes, and they do not follow a linear pattern. The impact of reversal of fibrosis on clinical outcomes is thus uncertain with the currently available evidence.[75] Paired HVPG measurements in patients before and after successful HCV clearance demonstrated a reduction with treatment in all but those with high baseline pressures and advanced liver disease.[76] Interferon-induced HCV clearance was shown to prevent the progression of portal hypertension only in those without established varices prior to treatment.[77]

Reclassification of the decompensated phase of cirrhosis into various stages is not as well established but can be achieved using the occurrence of variceal haemorrhage, refractory ascites and hepatorenal syndrome due to severe portal hypertension. Three stages have been described with worsening mortality:

- *Stage 1*: Occurrence of variceal haemorrhage without any other decompensating event.
- *Stage 2*: Non-bleed-related decompensation, ascites or less commonly hepatic encephalopathy.
- *Stage 3*: Any two of the decompensating events.[78]

A further stage of late decompensation or advanced decompensation has been added to include patients with a much shorter (≤1-year) survival (50–90%), such as those with hepatorenal

syndrome, refractory ascites, recurrent encephalopathy, deep jaundice, recurrent variceal haemorrhage, sepsis and acute on chronic liver failure (ACLF).[79] The three stages of compensated cirrhosis, three stages of decompensated cirrhosis and the additional late decompensation stage, therefore define a multistate model of cirrhosis with clearly delineated clinical prognosis.[78]

Several studies have investigated the role of portal pressure in predicting the prognosis of cirrhosis. In a cohort study of patients with compensated cirrhosis, followed over a median period of 51 months, a third developed clinically evident decompensation in the form of ascites, variceal haemorrhage and/or hepatic encephalopathy. HVPG, MELD score and serum albumin emerged as independent predictors of the development of decompensation. A baseline HVPG < 10mmHg was associated with 90% chance of remaining free of clinical complications of portal hypertension over a 4-year follow-up period.[69] The predictive value of HVPG for long-term mortality in patients with decompensated cirrhosis was analysed by Kim et al. in a retrospective study involving 97 cirrhotic patients over a median follow-up of 24 months. An HVPG < 17 mmHg was identified as the ideal threshold for predicting long-term mortality in these patients. Patients with HVPG < 17 mmHg had 1.9% 1-year mortality compared to 16.2% in patients with HVPG > 17 mmHg. In patients with ascites, HVPG and MELD score were strongly predictive of long-term mortality.[80] When HVPG was reduced to < 12 mmHg or by ≥ 20%, the occurrence of both first and recurrent variceal bleeding were reduced. A significant survival benefit was demonstrated when HVPG was reduced by ≥20%.[81] A HVPG cutoff of 16 mmHg could discriminate accurately between decompensated cirrhosis at high risk of mortality from those without high risk in a large cohort study.[82]

Ascites and variceal bleeding are clinically evident complications of portal hypertension, whereas the presence of varices is often asymptomatic. Identification of varices and prophylactic management prior to variceal bleeding are important clinical goals. Although HVPG is the best technique available for measuring portal pressures, noninvasive measurement of HVPG with liver stiffness measurement (LSM) using transient elastography has emerged as a reliable marker for detection of both fibrosis and portal pressures. In combination with the platelet count, LSM is the best test available to diagnose the presence of CSPH in a noninvasive manner, as recommended by the Baveno VI Consensus Guidelines on portal hypertension.[71] According to Baveno VI Consensus Guidelines, patients with LSM < 20 kPa and platelet count

>150 × 10^9 cells/L are at low risk of large varices and bleeding, and hence a diagnostic endoscopy could be avoided. This was validated by a study that reviewed LSM records and endoscopy findings of patients across a period of 9 years at two hospitals in the United Kingdom.[83] To avoid more unnecessary endoscopies, investigators proposed expansion of the Baveno Criteria to include an LSM cutoff value as 25 kPa and platelets >110 × 10^9 cells/L. This finding was subsequently validated in several other cohorts.[84] In all these patients with cACLD of varying aetiologies including HCV, alcohol and NAFLD, the expanded criteria would avoid 40% of endoscopies with a 0.6% risk of missing high-risk varices.

As the presence of significant portal hypertension and varices identify patients with advanced disease, it is important that it is assessed in all cirrhotic patients. This can often be missed in the traditional MOC delivered in busy hospital clinics. Management of cirrhosis with involvement of nurses in a multidisciplinary care model, as in nurse-led cirrhosis clinics (NLCCs), or with a CDM pathway providing variceal surveillance will be useful in ensuring adherence to endoscopy screening guidelines.[85] Expanded Baveno Consensus can be easily applied in these novel MOCs, thus enabling detection of clinically significant portal hypertension.

2.1.5 *Prognosis*

Three variables (Child–Pugh status, Mayo MELD score and HVPG) were the most commonly studied in the prognostic studies of cirrhosis as shown in a large systematic review of 118 studies by D'Amico et al.[63] Child–Pugh status (measured using serum albumin, bilirubin, International Normalized Ratio (INR), presence of ascites and hepatic encephalopathy) is the most often studied prognostic variable and consistently correlates with survival in patients with cirrhosis of the liver.[63]

In patients with compensated cirrhosis, HVPG is a good predictor of clinical outcomes.[69,82] MELD score (measured using bilirubin, INR and creatinine) takes into account the importance of renal dysfunction in cirrhosis and is used in allocation of donor livers in transplant programmes.

The MELD score is not useful in predicting prognosis in patients with compensated cirrhosis.

Stratification into compensated and decompensated cirrhosis is straightforward and can be easily used in clinical situations to predict the prognosis of the disease. Decompensation is defined as the presence of jaundice, ascites, variceal bleeding and/or hepatic encephalopathy. Ascites is the most common and frequently the first sign of decompensation. The prognosis of cirrhosis of the liver following the onset of decompensation is poor.

Patients with early decompensation (Child–Pugh class B) have a 2-year survival of 60%, but it falls to 35% in the advanced stage (Child–Pugh class C).[86] In a longitudinal study, Gines et al. evaluated the probabilities of developing decompensation and survival in a cohort of 293 patients with cirrhosis over a median period of 63 months. At 10 years from diagnosis, the chances of progression into decompensated stage and death were 58% and 47%, respectively.[87]

D'Amico et al. studied 6-year survival of 1155 consecutive patients with cirrhosis. Survival was 54% in those with compensated cirrhosis and 27% in decompensated cirrhosis. The aetiology of liver disease had no impact on the survival.[66]

Prospective studies have suggested that deterioration from a well-compensated to a decompensated state occurs at an annual rate of 5–7% (**Figure 3**).[63]

The median survival of patients in compensated and decompensated stages of cirrhosis were 12 and 2 years, respectively, as per natural history studies conducted by D'Amico et al. (**Figure 4**).[63,66] As shown in **Figure 4B**, when patients continued to be in compensated stage, their survival was better at any given time point.

A United Kingdom population-based analysis of the mortality due to cirrhosis was compared with controls derived from a general practice database matched for age, gender and practice. In a cohort of 4507 patients with cirrhosis and 44 000 controls, mortality rate due to compensated cirrhosis was approximately fivefold more than that of the controls [hazard ratio (HR) = 4.7; 95% CI, 4.4–5.0]. Patients with decompensated cirrhosis were almost tenfold more likely to die than the general population (HR = 9.7; 95% CI, 8.9–10.6).[88]

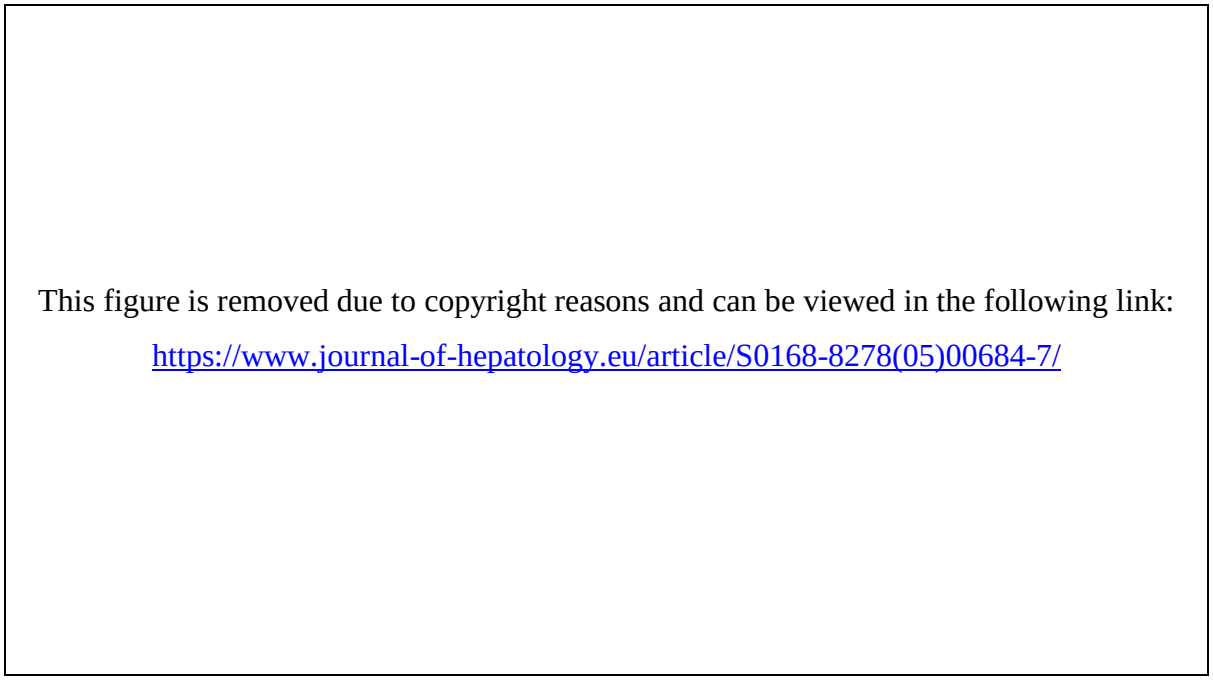
From the database of a prospective inception cohort, 494 cirrhotic patients were followed to assess the utility of this newly proposed multistate model of cirrhosis.[78] The stages with worsening prognosis were defined as follows:

Stage 1: Compensated cirrhosis without varices.
Stage 2: Compensated cirrhosis with varices.
Stage 3: Decompensated cirrhosis with variceal haemorrhage.
Stage 4: First non-bleeding decompensating event.
Stage 5: Second decompensating event.

Using competing risk analysis, patient movement across the five stages, over a mean follow-up period of 12 years was analysed, and the 5-stage model of cirrhosis was shown to be clinically applicable and appropriate.

Figure 3. Based on prospective natural history studies, the proportion of patients progressing from compensated stage to decompensated stage (reproduced from reference 63).

Figure 4. The median survival of patients (A) based on the stage of cirrhosis at diagnosis and (B) when they continue to be in the stage of the disease (reproduced from reference 63).



2.1.6 *Burden on the Health System*

The health and economic burden attributable to CLD has been steadily increasing over the last decade worldwide. In Australia it is estimated that 6.17 million people were affected by liver diseases in 2012. This is likely to exceed 8 million by 2030.[4] The direct health expenses associated with CLD were assessed to be 386.2 million Australian dollars (AUD) in 2012. The estimated total monetary cost of liver disease in 2012 including direct health costs, productivity impacts, informal carer costs, loss of taxation revenues and disability-adjusted life years (DALYs) was AUD 50.7 billion.[4] These costs were 40% higher than that associated with managing two other common chronic conditions: type 2 diabetes mellitus and chronic kidney disease. In addition, these costs are likely to increase substantially, reflecting a steady rise in the prevalence of decompensated cirrhosis due to NAFLD in Australia.[52] Evidence for this increase comes from a variety of sources. In Australia, death rates due to cirrhosis and chronic liver failure (CLF) increased by 31% between 2006 and 2015.[89] In addition to complications of hepatic decompensation, liver cancer has also contributed to an increasing number of cancer-related deaths in Australia.[90]

An analysis of ICD-10 (International Classification of Diseases, Tenth Revision) codes for CLF diagnoses shows a national increase of 25% in hospital admissions for decompensated cirrhosis between 2004–2005 and 2007–2008.[91] Data from the Adelaide Metropolitan Health region have shown a steep increase in CLF-related admissions between the years 2001 (422 admissions) and 2015 (1441 admissions).

Based on a study of hospital admissions for cirrhosis of the liver from Queensland, Powell et al. reported an escalation in the rate of hospitalisations due to cirrhosis from 8.5 to 11.6 per 10 000 person-years during the period 2008 to 2016.[57] This increase was most pronounced in Indigenous Australians (32 per 10 000 person-years) and in men aged 50–59 years (34 per 10 000 person-years). The number of hospital admissions due to cirrhosis escalated from 2700 in the year 2008 to 4307 in the year 2016. This study also highlighted the statistically significant predisposition of socioeconomically underprivileged patients to more frequent hospitalisation, up to 9.4% increase per year, compared to patients of higher socioeconomic status (3.2% increase per year). Residence outside a major city predisposed to a higher in-hospital mortality. In addition, older age, presence of comorbidities, advanced complications of cirrhosis (hepatorenal syndrome, HCC, jaundice, hepatic encephalopathy) were also associated with higher in-hospital mortality. Ascites, variceal bleeding and HCC were the most common causes of admission in this order of frequency.

An increasing prevalence of CLD is one of the reasons for the rise in hospitalisations. Drivers for this are likely to include an increase in alcohol misuse and obesity within Australian communities. A recent Australian Institute of Health and Welfare (AIHW) report has highlighted a higher prevalence of obesity (28%) in Australia, relative to other OECD (Organization for Economic Cooperation and Development) countries (19%).[92] In addition, the average adult Australian alcohol intake (9.7 L per person per year) is higher than the world standard (9 L per person per year). Misuse of alcohol was the cause of cirrhosis in 50% of hospital admissions in the recent statewide study from Queensland.[57]

The increasing prevalence of NAFLD as a cause of CLD has been shown to have significant implications for future health expenditure by recent modelling studies. Using a steady-state prevalence model, Younossi et al. studied the economic and clinical burden of NAFLD in the United States and four European countries (Germany, France, Italy and the United Kingdom).[51] Plotting data obtained from the literature against the real-world prevalence data in an

interlinked Markov model, the authors estimated that 64 million Americans had NAFLD with annual direct medical costs of USD 103 billion. Similarly, in the four participating European countries, 52 million were estimated to have the disease with predicted annual medical costs of EUR 35 million. The economic demands of the disease would be much higher if societal costs were also considered. These economic projections are likely to apply equally to Australia and many Western countries in view of their similar epidemiological pattern of NAFLD.[46]

2.1.7 *Hospital Readmissions*

Hospital readmissions account for a large fraction of the cost burden in cirrhosis. Fagan et al. evaluated the use of hospital resources over a year by 41 patients with cirrhosis and ascites treated with paracentesis in a single Australian centre.[93] The study was conducted retrospectively using clinical records. During the study period there were 127 hospital admissions, 1164 occupied bed-days and 733 episodes of medical imaging use for these 41 patients. The rate of 30-day unplanned readmissions after hospital discharge following paracentesis was 40%. Among the 40% of patients who had unplanned readmissions, there was a significantly higher occurrence of mortality and SBP. In addition to advanced liver disease, active alcohol misuse was also associated with frequent unplanned readmissions. The study established ascites requiring paracentesis to be a major cause of recurrent hospital admissions.

Volk et al. studied the frequency, aetiology, timing, nature and expense associated with emergency readmissions after a hospital admission for complications of cirrhosis in 402 patients over a median follow-up of 273 days;[3] 14% of the study cohort had readmissions within 7 days and 33% patients had readmissions within 30 days. Overall, the readmission rate was 3 per person-years. The mean cost associated with early readmission (within 7 days) was approximately USD 28 000, and for readmission within 4 weeks the cost was approximately USD 21 000. In addition to the cost, recurrent hospital admissions were also associated with higher mortality, similar to the findings by Fagan et al., but independent of the disease severity as measured by MELD score.

An interesting point that emerged in this retrospective analysis was that 22% of the readmissions were considered to be preventable by close monitoring of the discharged patients.[3] Within 30 days, there were 165 admissions, with 22% of these adjudicated as preventable.

The main reasons cited for preventable admissions included

- unmonitored diuretic use resulting in hypovolaemia precipitating hepatic encephalopathy,
- inadequate dosing of lactulose resulting in preventable hepatic encephalopathy,
- unplanned ascitic paracentesis resulting in emergency presentations.

The solutions presented were appropriate patient education, telephone consultations and intervention using disease management pathways, resulting in delivery of care in response to day-to-day developments. The post-discharge course of patients with cirrhosis is dynamic and hence infrequent outpatient appointments offered in most current MOCs cannot provide the longitudinal care required to prevent readmissions.

The North American Consortium for the Study of End-stage Liver Disease (NACSELD) was a prospective study engaging tertiary-care hepatology centres that recruited patients with cirrhosis of the liver during a nonelective hospital admission with follow-up that included hospital stay and up to 3 months after discharge.[94] Using the NACSELD database, Bajaj et al. studied hospital readmissions in cirrhotic patients who were discharged from hospital for a nonelective cause. The study was a major multicentre prospective study across 14 centres in the United States. Information on the severity of liver disease as measured by the MELD score, indications for hospitalisation, drugs used, complications of cirrhosis, presence of organ failure and second infections were collected and studied. Enrolled patients were followed for 3 months after hospital discharge with periodic telephone calls, medical records review and interviews. The frequency of 3-month readmissions and their predictive factors at initial admission and discharge were the study outcomes. Of the 1013 patients with 3 months' outcome, 53% had an emergency readmission; 62% of the admissions were liver related. Ascites, renal and metabolic causes were the predominant cause of liver-related readmissions followed by infections, hepatic encephalopathy and variceal bleeding.[13] Among these, hepatic encephalopathy and renal or metabolic causes were responsible for recurrent readmissions. At admission, high MELD score, lower albumin, presence of type 2 diabetes mellitus, lactulose use and SBP prophylaxis were identified as risk factors for readmission. MELD score, lactulose use, proton-pump inhibitor therapy and a shorter length of hospitalisation at index hospital discharge were

found to be significant predictive factors of 3-month readmissions. The authors calculated the predictive scores for readmission based on admission (MELD and presence of type 2 diabetes mellitus) and discharge variables (MELD, use of beta blockers, proton-pump inhibitors and shorter hospital stay). When the predictive score was tested on a random half of the study cohort, only 33% of the admissions were deemed to be unanticipated. Liver-related readmissions occurred more often in patients with nosocomial infections during their index hospitalisation [odds ratio (OR) = 1.9–3.0]. This study suggested that it was feasible to identify a subgroup of cirrhotic patients as highly vulnerable for readmission and by closely monitoring them for potential complications, subsequent hospital admissions could be avoided. These findings strongly support a role for a CDM-style MOC in cirrhosis to prevent readmissions.

With the aim of avoiding early readmissions, an automated predictive model for 30-day readmission was proposed by Singhal et al.[95] The authors collected clinical and socioeconomic variables from electronic medical records of 836 patients admitted during the period (2008 to 2009), with 1291 cirrhosis-related readmissions. Readmissions within 30 days were seen in 27% of the study cohort. A multivariate logistic regression model that was moderately predictive for 30-day readmissions in both the derivation and the validation cohorts was devised. Frequent address changes in the last year, the number of admissions in the previous year, high MELD score, low alanine transaminase (ALT), anaemia, thrombocytopaenia and hyponatremia were found to be the predictive factors. These parameters could be used to identify patients at high risk for reinfection.

Compelling evidence for cirrhosis of the liver as a principal cause of hospital readmissions was obtained from a large population-based retrospective study of patients admitted to all government hospitals during the year 2007 in Hong Kong.[96] Thirty-day readmissions in ten common medical conditions, namely cirrhosis, heart diseases, malignant neoplasms, cerebrovascular accidents, nephritis, aortic aneurysm, septicaemia, pneumonia, type 2 diabetes mellitus, and injury and poisoning were studied. Not surprisingly, cirrhosis of the liver and CLD had the highest number of readmissions (OR = 1.62; 95% CI, 1.39–1.87). This study provides further supporting evidence for the need for close monitoring and ongoing care in the post-discharge period for cirrhotic patients given their susceptibility for readmissions.

In a more recent population-based cohort study conducted across multiple states in the United States, Tapper et al. studied the frequency and causes for hospital readmissions in cirrhotic

patients.[97] Patients discharged with cirrhosis-related diagnoses in the year 2011 were found to have 30-day and 90-day readmission rates, 13% and 21%, respectively. This proportion increased to 24% and 36%, respectively, in patients with three major complications of cirrhosis. These figures were similar across the four states. Patients with ascites had more 30-day readmissions than 90-day readmissions. Hepatic encephalopathy was the liver-related complication, most frequently associated with both 30-day and 90-day readmissions (OR = 3.23; 95% CI, 2.97–3.52 and OR = 3.07; 95% CI, 2.86–3.30, respectively). As reported by Bajaj et al., the presence of hepatic encephalopathy was again a strong predictor of recurrent hospital admissions.[13] In patients with alcoholic cirrhosis, ongoing alcohol misuse was responsible for 25% of the hospital readmissions.[97] This finding highlights the importance of alcohol counselling as a part of the ongoing clinical care of these patients, which may be difficult to implement in the absence of a CDM pathway. The authors highlighted the need for post-discharge nursing outreach programmes in this patient population as they are at high risk for multiple medical complications, such as diuretic-related hyponatremia, hyperkalaemia, hypokalaemia and hepatic encephalopathy precipitated by sedatives after discharge. A coordinated care model designed with CDM principles meets these requirements better than the traditional MOC.

Hospital readmissions not only contribute to disease morbidity but are also a common cause of mortality seen in these patients. Volk et al. reported an increased risk of mortality in patients with recurrent readmissions (up to 1.08 per unit increase in readmission rate, $p < 0.001$) independent of MELD score, age, presence of comorbidities, number of prescribed drugs and serum sodium.[3] Ratib et al. compared the 1-year and 5-year survival rates of ambulatory cirrhotic patients among those who have had an emergency hospital admission either at diagnosis or during the course of their disease. In this population-based study they examined a large cohort of primary-care patients and secondary-care patients by linking primary-care and secondary-care databases with the national death registry.[98] Among the 5118 patients with cirrhosis studied from January 1998 to December 2009, the 1-year and 5-year survival were 84% and 55%, respectively, for ambulatory patients. In previously hospitalised patients the 1-year and 5-year survival were lower at 66% and 31%, respectively. The occurrence of an emergency hospital admission was identified as a sentinel event for the onset of poor prognosis in patients with cirrhosis (HR = 2.78; 95% CI, 2.53–3.06), at any stage of the disease.

A study on hospitalised patients from the United Kingdom also revealed a trend of higher mortality in cirrhotic patients discharged from hospitals compared to the general population. The mortality rate data of 8192 cirrhotic patients discharged from hospitals in the south of England during the period from 1968 to 1999 was analysed by linking hospital discharges to the death registry. Standardised mortality ratio (SMR) and case fatality rate (CFR) were calculated; 30 days after a hospital admission, SMR was 93 (compared to 1 in the general population) and CFR was 16%. At the end of a year after hospital admission the SMR was 16.3 and the CFR was 34%. These mortality statistics had not changed during the 30 years. When stratified according to aetiology, alcoholic cirrhosis was associated with the highest SMR of 27.4 at 1 year, compared with 11.4 seen in biliary cirrhosis.[99] Most of the deaths in alcoholic cirrhosis were due to accidents, suicides and mental disorders. This suggests the need for a new MOC with a holistic approach on global risk factor modification in addition to the management of cirrhosis-related medical problems.

Infections are frequently encountered in decompensated cirrhosis, and they significantly contribute to mortality both in the short term and long term.[100] Indeed, the occurrence of infection can be defined as a critical stage in the assessment of prognosis of the disease. In a systematic review that examined 225 cohorts and 11 987 patients with cirrhosis, mortality rate was increased by fourfold in the presence of an infection.[100] The mortality progressively increased with time, and 1-month, 3-month and 12-month mortality rates were 28%, 44% and 66%, respectively. This trend was probably due to the persistent haemodynamic changes that occur in the kidneys, heart and systemic and hepatic vascular bed, even following resolution of the infection. A majority of the infections that occurred in patients with cirrhosis were found to be hospital acquired, either healthcare associated or nosocomial, with only one third being community acquired.[101] Hospital readmissions in patients with decompensated cirrhosis increase the risk of nosocomial infections, which in turn exacerbate patient morbidity, expenditure, hospital stay and mortality.[13,102] In a large single-centre retrospective cohort study, 514 patients with decompensated cirrhosis, all with a history of hospital admission for ascites, were analysed for the development of nosocomial infections until death or liver transplantation.[102] Less than half of the cohort (42%) avoided nosocomial infection, 35% of patients developed at least one infection, 14% developed a second infection and 9% developed multiple episodes of infection. In 23% of patients, multiple infections were encountered in one admission episode. The infections encountered were, in the order of frequency, SBP, urinary tract infections and pneumonia. In patients with multiple episodes of infection, fungal

organisms were encountered more often in the third episode than in the first episode of infection. Every infection had an adverse effect on the transplant-free survival, independent of the MELD score.

These findings are in accordance with those reported by Bajaj et al.[94] They studied the effects of infection in cirrhotic patients in a multicentre prospective study of 207 patients at eight North American tertiary hospitals. The majority (71%) of the infections were healthcare related, 14% were nosocomial and 15% were community acquired. A second infection was defined as a separate episode during the same hospitalisation, a nosocomial infection. This was encountered in 24% of the study patients and were caused by respiratory and urinary tract infections, as well as *Clostridium difficile* infections. Second infections were more frequent in those with a prior nosocomial infection (as the first infection) and those in intensive care units on mechanical ventilation, with shock, dialysis or hepatic encephalopathy. Fungal infections and vancomycin-resistant enterococci infections were frequently seen. However, while in hospital, second infections were not associated with large-volume paracentesis or acute variceal bleeding. Within 30 days of hospitalisation, 24% of those patients died. Second infection, high MELD and low serum albumin were independent predictors of 30-day mortality. In view of the associated high mortality rate due to nosocomial infections, avoiding a hospital admission with frequent monitoring of patients with decompensated cirrhosis and ensuring adherence to well-defined guidelines to prevent nosocomial infections in hospitalised patients should be a focus in new MOCs.

2.1.8 *Flaws with the Existing MOCs*

As emergency hospital admissions portend a poor prognosis, preventing further episodes of hospitalisation in patients discharged from hospitals should be an important objective in the management of decompensated cirrhosis. Despite advances in therapeutic medicine that have improved hospital mortality in these patients, mortality within 30 days of hospital discharge has not improved, as shown in a mortality trend analysis over a decade based on a large sample size in the United States.[7] The authors analysed the 30-day and 1-year post-discharge mortality trends over the period from 2004 to 2013, in patients hospitalised for cirrhosis at 126 Veteran Administration hospitals in the United States. The study showed that mortality during hospital stay decreased over the decade from 11% to 7%, but the 1-year mortality only showed a slight decrease from 34.5% to 33% over this time period. In addition, the 30-day mortality surged

from 9.3% to 10.1%. Adjustments were made for comorbidities, disease severity and patient demographics, and the risk of death during the hospital stay was 30% lower in the year 2013 versus the year 2004 (adjusted OR = 0.70; 95% CI, 0.64–0.78), and risk of death within a year was reduced by 13% (adjusted OR = 0.87; 95% CI, 0.82–0.90). Nonetheless, the odds ratio of death within 30 days of discharge rose by 10% in comparison to the year 2004 (adjusted OR = 1.10; 95% CI, 0.99–1.21). Although the increase was not statistically significant, the early post-hospital phase did not see any improvement in survival. Indeed, this study highlighted that cirrhotic patients are the most susceptible to death after discharge from the hospital. This switch in mortality rate from the in-hospital phase to 30 days after discharge is an important reminder that care plans for decompensated cirrhotic patients should be designed to focus on them during this early post-discharge phase.

The field of hepatology has witnessed significant advances in the past few decades with many new effective, evidence-based treatments that have been shown to improve survival and the quality of life in patients with cirrhosis.[103] International liver societies regularly release updated guidelines to optimally manage cirrhotic patients, based on high-quality research.[6,65] These include disease-specific therapies, such as alcohol abstinence for alcoholic liver disease, antiviral therapy for HBV and HCV infections and immunosuppressive therapy for autoimmune hepatitis. In addition, several evidence-based therapies, such as

- antibiotic prophylaxis in patients with history of SBP,
- primary prophylaxis using nonselective beta blockers in patients with acute variceal bleeding,
- endoscopic variceal ligation for patients with high-risk varices,
- surveillance for patients with HCC,
- aggressive nutrition for severely malnourished cirrhotic patients,

have been shown to improve survival of patients with cirrhosis of the liver. For patients who fail to improve despite medical therapies, liver transplantation can restore normal liver function. Liver transplantation is associated with a 94% 1-year survival (20-year median survival) for patients in Australia and New Zealand.[104]

Nevertheless, studies have frequently reported inconsistencies in adherence to evidence-based recommendations. Examples include poor adherence to antibiotic prophylaxis following acute variceal bleeding (less than 50% adherence) and following an episode of SBP (65% adherence).[103,105] Using a modified Delphi approach, a set of quality indicators (QIs) covering important domains of care in cirrhosis were developed by Kanwal et al.[106] Based on an extensive literature review, 161 QIs were proposed, and the expert panel recommended 41 QIs. Of these 41 QIs, 18 were related to variceal bleeding care, 13 to ascites care, 4 to hepatic encephalopathy care, 3 to preventative aspects of cirrhosis care, 2 to assessment for liver transplantation and 1 to HCC surveillance. From these QIs, based on the level of agreeability of the panel, a set of eight most important QIs (**Table 1**), with agreeability ranging from 65% to 100%, were derived. Consistent adherence to these eight QIs should be the minimum requirement of any care process in the cirrhosis of the liver.

As this set of QIs were developed based on the best possible combination of evidence-based research and expert opinion, they provide a standard of care for cirrhosis for optimisation of outcomes. They also could serve as a measure of performance of interventions, such as CDM programmes in the management of cirrhosis.

The following were selected as the eight QIs related to ascites:

1. paracentesis after documentation of new onset of ascites,
2. paracentesis during hospitalisation with ascites or hepatic encephalopathy,
3. ascitic fluid cell count testing after paracentesis,
4. treatment of SBP,
5. secondary prophylaxis after documented SBP,
6. primary prophylaxis of SBP in hospitalised patients with gastrointestinal bleeding,
7. primary prophylaxis of SBP if low-protein ascites (<1g/dL),
8. use of diuretics.

Using these ascites-related QIs, the standard of ascites care was assessed in 774 cirrhotic patients with ascites managed in three veteran hospitals in the Unites States.[107] Adherence to the QIs was highly variable. Only 30% received antibiotic prophylaxis following an episode of SBP, whereas the initiation of antibiotic treatment for an episode of SBP was much higher at

72%. Routine diagnostic paracentesis during a hospitalisation for cirrhosis occurred only in 57% of the patients.

Table 1. QIs in the management of cirrhotic patients.

Domain	QIs
Ascites	If hospitalised patients with ascites have an ascitic fluid polymorphonuclear count ≥ 250 cells/mm^3, then they should receive empirical antibiotics, within 6 hours of the test result for hospitalised patients and within 24 hours for ambulatory patients.
	If patients have clinically apparent (that is, moderate to severe) ascites and normal renal function, then they should be managed with both salt restriction and diuretics (including a combination of spironolactone and loop diuretics).
	If patients with ascites are admitted to the hospital for evaluation and management of symptoms related to ascites or hepatic encephalopathy, then they should receive a diagnostic paracentesis during the index hospitalisation.
Variceal bleeding	If patients with cirrhosis survive an episode of acute variceal haemorrhage, then they should receive one of the following therapies to prevent recurrence of variceal haemorrhage: EVL every 1–2 weeks until obliteration, beta blockers or a combination of EVL and beta blockers.
	If patients with cirrhosis are found to have bleeding oesophageal varices, then they should receive EVL or sclerotherapy at the time of index endoscopy.
	If patients with cirrhosis present with UGIB, then they should receive upper endoscopy within 24 hours of presentation.
	If patients have cirrhosis, no documented history of previous GI bleeding and have medium or large varices on endoscopy, then they should receive either nonselective beta blockers or EVL within 1 month of varices diagnosis.
Hepatocellular cancer	If patients have cirrhosis, then they should receive surveillance for HCC by using imaging with or without AFP every 6–12 months.

AFP: alpha fetoprotein; EVL: endoscopic variceal ligation; GI: gastrointestinal; HCC: hepatocellular carcinoma; QI: Quality Indicator; UGIB: upper gastrointestinal bleeding.

In general, only 30% of patients received all the recommended aspects of ascites care. When the reasons for lack of adherence with the QIs were investigated, the majority of non-adherence was attributed to the medical practitioner failing to take the appropriate action. Kanwal et al.[107] analysed the implications of non-adherence to QIs on two important outcomes, such as 12-month survival and a readmission within 12 months. It was associated with 37% greater risk of death (OR = 1.37; 95% CI, 0.74−2.54) and 35% higher risk of readmission (OR = 1.35; 95% CI, 0.82−2.2). The authors suggested that the lack of statistical significance in these data was likely due to the limitations of study power. Analysis of variables that were predictive of better quality of care revealed positive associations with consultation with a specialist, treatment in a centre with academic affiliation, higher serum sodium and albumin levels and lack of comorbidities.

Further evidence in favour of a gastroenterology consultation contributing towards maintaining QIs comes from a population cohort study that compared a mandatory gastroenterology consultation compared with historic controls involving standard of care management of cirrhosis of the liver in a tertiary academic centre.[108] The former achieved better adherence in QIs compared to the standard care in the following areas:

- performing ascitic fluid paracentesis during an episode of hospital admission,
- ascitic fluid examination for total and differential white blood cell count,
- initiation of diuretic therapy and salt restriction for ascites,
- performance of endoscopy within 24 hours of a variceal bleeding,
- assessment for liver transplantation,
- investigating for the causes during a presentation with hepatic encephalopathy.

An Australian study examined the relationship between compliance with eight of the ascites QIs in patients with new onset ascites and hospital readmissions and 90-day survival.[109] Alcohol-related cirrhosis was the commonest cause of cirrhosis in this patient cohort (59%). Undergoing paracentesis during a hospital admission or within 30 days of diagnosis of ascites was associated with 50% reduction in the occurrence of 30-day readmission. Diuretic therapy at discharge was associated with reduced risk of dying at 90 days, whereas higher MELD score, older age and 30-day readmission were associated with higher risks of 90-day mortality.

The frequency of compliance with the recommendations for radiological surveillance is also variable. Review of surveillance records for 1873 HCC patients with previously diagnosed cirrhosis, using data linkage in a population-based cohort study from the United States, showed that fewer than 20% had regular HCC surveillance.[110] However, consultation with a gastroenterologist, hepatologist or academically affiliated physician for cirrhosis was associated with a higher (3–5 times) chance of undergoing surveillance for HCC. A multicentre prospective cohort study from Melbourne revealed HCC detection via surveillance in only 40% of cases who were diagnosed to have HCC over a period of 1 year.[111] Nevertheless, patients identified via surveillance were more likely to receive curative therapies and have better survival. Therefore, HCC surveillance that can be regularly provided via CDM pathways without reliance on specialists, offers the possibility of improved survival for cirrhotic patients.

By contrast, review of HCC surveillance over a 1-year period from 2008 to 2009 at the Michigan University Clinic revealed that 75% of cirrhotic patients underwent ultrasound screening as recommended by the guidelines. Male gender and patient involvement (OR = 3.4; 95% CI, 1.5–7.9) increased the surveillance adherence.[112] This surprisingly high rate of adherence to guidelines was potentially influenced by the tertiary location of care received. Patient level variables that were associated with higher HCC surveillance include better patient engagement, more frequent clinic visits (3.4 times higher probability of undergoing surveillance), higher socioeconomic status and presence of comorbidities.[113] These findings suggest that patient education and improved self-management behaviours could improve adherence to radiological surveillance.

An audit of compliance with endoscopic surveillance for primary and secondary prophylaxes for variceal bleeding, before and after management by a dedicated nurse coordinator in a tertiary medical centre, revealed a significant increase in the compliance from 13% to 79%.[85] In a prospective randomised study Singal et al. evaluated the impact of a radiological surveillance invitations sent out to patients by post, with or without patient navigation (assessment of barriers and education for patients who refused to undergo screening), in comparison to usual care.[114] Both the intervention groups had a significantly higher rate of HCC surveillance (47% and 44%, respectively) compared to 24% seen with standard care. Between the two interventions, the difference was not significant. These studies are examples of how adherence to medical interventions can be enhanced with specific changes to MOCs.

In a similar fashion, reminders to primary-care physicians were shown to have a beneficial effect on the radiological surveillance in cirrhosis (adjusted OR = 1.29; 95% CI, 1.03–1.61; $p = 0.02$).[115]

Patients with decompensated cirrhosis and ascites on treatment with diuretics are hemodynamically fragile due to persistent peripheral vasodilatation.[116] This renders them susceptible to the development of renal failure, electrolyte disturbances and, in many situations, hepatic encephalopathy. Weekly albumin infusion coupled with diuretic therapy was shown to reduce mortality in a pragmatic RCT from Italy.[117] Frequent monitoring of serum electrolytes and titration of diuretic doses are required to prevent these complications. Due to capacity constraints, medical review appointments may not occur more frequently than every 3 months, which is not the ideal interval for diuretic monitoring. Acute kidney injury should be detected, and intervention should be initiated early to prevent the progression to hepatorenal syndrome and renal failure, as these states are associated with poor prognosis. If diuretic therapy, either after hospital discharge or after a clinic visit, is monitored within a CDM programme, a significant proportion of hospital admissions due to renal failure, electrolyte disturbances and subsequent hepatic encephalopathy could be prevented. Similarly, action plans for patients with hepatic encephalopathy may avert the development of florid episodes requiring hospital admission for initially mild cases. The existing MOC with dependence on specialist clinic appointments and lack of monitoring between appointments leaves many crucial issues unattended, which contributes to recurrent, preventable hospitalisations for patients with decompensated cirrhosis.

In the advanced stages of decompensated cirrhosis, diuretic therapy is no longer effective, and patients often require regular large-volume paracentesis for symptomatic relief. In the absence of a dedicated, elective pathway for the abdominal paracentesis, patients are likely to present at a late symptomatic stage. In a retrospective study across England, healthcare costs of cirrhotic patients with ascites undergoing large-volume paracentesis in the last 12 months of life were analysed.[118] The investigators found significant cost savings (GBP 4240; 95% CI, 4829–3651; $p < 0{\cdot}0001$) for patients who had day-care paracentesis compared to those with unplanned paracentesis. In addition, the number of days spent in hospital as in-patients (OR = 16.98; 95% CI, 18.45–15.51; $p < 0.0001$), unplanned 30-day readmissions (OR = 0.35; 95% CI, 0.31–0.40; $p < 0.0001$) and in-hospital mortality (OR = 0.31; 95% CI, 0.27–0.34; $p < 0.0001$) were all lower when patients received day-care paracentesis. This study provided

evidence for organising planned cirrhosis care, as unplanned care was associated with increased healthcare resource utilisation. A notable finding from this study was the high mean cost of management of cirrhosis in the last year of life at GBP 21 113 (SD 16 881).

As cirrhosis is a chronic disease with multiple complications in its advanced stage, it is important that patients are monitored frequently within a CDM programme with a rapid access pathway for clinical deterioration. Infrequent clinical appointments provided in traditional models are unlikely to fulfil the large clinical and supportive needs of these patients.

2.1.9 *CDM Models*

In the management of decompensated cirrhosis, coordinated, longitudinal care that focusses on the vulnerable post-discharge period is important. Similar patient-centric management models have demonstrated the efficacy in decreasing hospital admissions and improving survival in patients with cardiac failure. Studies in cardiac failure have demonstrated 30–42% fewer heart failure-related admissions, 12–27% fewer all-cause admissions and 18–25% lower mortality with CDM-style interventions, relative to usual care.[119-121] These clinical improvements were also associated with significant cost savings in 15 of the 18 trials in which financial outcomes were evaluated.[119] As a result of these studies, CDM-style approaches are now considered the standard of care in heart failure and have been given a Class I recommendation in practice guidelines.[122]

Evidence in favour of CDM interventions in cirrhosis are preliminary at this stage. Currently, there are no randomised studies that have demonstrated an intervention that can reduce hospital readmissions in patients with cirrhosis. Nevertheless, the only randomised controlled trial (RCT) published to date is the pilot trial performed by Wigg et al.,[123] subsequently discussed in editorials.[124,125] In this single-centre trial, 60 patients with decompensated cirrhosis were randomised to intervention (n = 40) consisting of a multifaceted CDM model, known as Chronic Liver Failure Program (CLFP), or a standard treatment (n = 20), during a 12-month period. The study included patients with decompensated cirrhosis who had been recently discharged from hospital due to a liver-related event, namely ascites, variceal bleeding, renal dysfunction, sepsis or hepatic encephalopathy.

The main components of this intervention were listed as follows:

1. *Delivery system redesign*: This was a coordinated case management intervention within a multidisciplinary team consisting of hepatologists, specialist nurses, dietitians, alcohol counsellors and GPs. The nurses played a central role in performing weekly reviews using telephone conversations, home visits within a week of hospital discharge and organising reminders for clinic appointments. Patients in the study arm had a rapid access to care pathway during deterioration via phone call to the nurses.
2. *Decision support*: Clear protocols for each complication of decompensated cirrhosis guided the team in their management.
3. *Self-management support*: Patients and carers were provided education about nutrition, medications, adjustments required in cirrhosis, and the need for radiological (HCC surveillance) and endoscopic (variceal bleeding) surveillance. Patient action plans for ascites and hepatic encephalopathy were also provided, with patient self-monitoring and management requirements outlined.
4. *Clinical information systems*: Nurses maintained records with all the necessary patient information and made them accessible to doctors during clinical visits and discussions. A complete CLF registry of participants was maintained.

The nurses were contacted by patients in the study arm if they experienced an emergency. The nurses triaged the call with the assistance of the on-call hepatologist and offered continued outpatient management support whenever possible. The nurses continued to engage with patients both during and after a hospital admission and offered continuous education and support.

The primary objective of the study was to observe the differences in the rate of liver-related occupied bed-days per person per year due to the intervention. Furthermore, the study also explored total liver-related hospitalisation rate, unplanned and planned hospitalisation rates, and the duration of hospitalisation. The investigators also studied attendance rate at planned outpatient clinics, improvements in MELD score and Child–Pugh score, and quality of life measured by the Chronic Liver Disease Questionnaire (CLDQ). Quality of care was measured by adherence to endoscopic and radiological surveillance, screening for osteoporosis and referral for liver transplantation. The intervention arm had a significantly higher proportion of alcohol-related cirrhosis.

The major findings of this pilot trial were as follows:

- No reduction in the primary endpoint of liver-related occupied bed-day rates in the intervention versus usual care arms (17.8 vs. 11.0 bed-days per person per year, incidence rate ratio (IRR) = 1.6; 95% CI, 0.5–4.8; p = 0.39); however, there was a higher proportion of elective admissions in the intervention arm (47% vs. 21%)
- Significantly higher (30%) outpatient attendance rate in the intervention arm.
- Nonsignificant reduction in mortality in the intervention arm (HR = 0.6; 95% CI, 0.3–1.5; p = 0.32).
- Significantly improved quality of care as indicated by increased adherence to protocols for HCC screening, hepatitis A and B virus vaccination and bone density surveillance in the intervention group.
- Qualitative feedback from the nurses, patients and doctors was positive.

The negative findings of the study contrasted with the benefits seen with hospitalisation in heart failure. This may have been due to the inclusion of elective hospital admissions, which contributed to the higher liver occupied bed-days in the intervention arm. Another potential confounding factor may have been an imbalance in the aetiologies of cirrhosis between the two arms. The authors also considered whether the increased hospital admissions might be of value in this highly vulnerable group, and responsible for a lower mortality rate in the intervention arm. As this was a pilot study, the questions raised by this trial are currently being pursued by an appropriately powered, prospective RCT with stratified block randomisation.

The infrastructure and costs associated with the CLFP intervention in cirrhosis are an important consideration. Cost-effectiveness of the CLFP intervention delivered in the above-mentioned RCT was examined in a subsequent analysis by Wigg et al.[126] The cost-effectiveness analysis estimated the incremental cost for death avoided at 12 months and the incremental cost for each unit change in the quality of life (during the 12 months of the study). The number of deaths prevented at 24 months was also studied in a sensitivity analysis. The intervention with CLFP was more effective, as it resulted in five fewer deaths for every 100 patients and 0.67 unit higher CLDQ scores. The intervention cost was AUD 18 521 more per patient relative to the standard of care. CLFP emerged as a cost-effective option with incremental cost-effective ratio

(ICER) of AUD 370 425 per death avoided. Per unit improvement in the CLDQ total score cost AUD 27 547. Cost-effectiveness acceptability curves (CEACs) showed a 70% probability of CLFP being the more cost-effective option at willingness-to-pay values of approximately AUD 400 000 per additional death avoided and AUD 40 000 per unit improvement in the CLDQ score. When the results were analysed at 24 months, CLFP was the dominant option with fewer deaths and lower costs. The CEAC for deaths avoided at 24 months revealed that for a willingness-to-pay threshold of AUD 150 000 per additional death, the chances of CLFP being effective were 80%. An important finding of the study was that cost savings became more apparent following 24 months of intervention, at AUD 986 per patient.

In an Italian study, Morando et al. reported a reduction in costs associated with a care management programme for cirrhotic patients compared to the standard treatment.[127] The intervention patients had access to a care management check-up after hospital admission for cirrhosis, provided by a coordinated team of liver specialists, nurses and primary-care physicians. Both treatment groups could attend a day hospital for invasive procedures, such as ascitic paracentesis. The care management programme was associated with lower mortality and lower 30-day readmissions during the 12 months of the study. The costs (doctor visits, blood tests, hospital costs and global costs) were significantly lower than the standard arm, EUR 1479 versus EUR 2816 per patient per month. However, the intervention consisted of a day hospital with more expensive infrastructure. Moreover, this cost-effectiveness analysis did not report on ICERs or CEACs, and the study was not randomised.

Tapper et al. performed a prospective study utilising handheld checklists, followed by electronic ones, as interventions to ensure appropriate lactulose therapy, rifaximin and antibiotic secondary prophylaxis for SBP. They compared the effect of these quality improvement initiatives on 30-day readmission to those in the year preceding these interventions. Between the electronic phase, wherein the checklists were added to the provider entry system, and the control period, there were significant differences in the 30-day readmission rate (26% vs. 50%, $p = 0.003$). In addition, these interventions also resulted in fewer days of hospital stay in patients with hepatic encephalopathy (likely due to less severity) compared to the pre-intervention phase.[128] This study highlighted the feasibility of delivering quality care in accordance with guidelines without a structured programme but with electronic decision support, a CDM principle.

The role of a pharmacist-led intervention with a view to reducing medication-related problems (MRPs) and unplanned admissions in patients with decompensated cirrhosis was explored in a prospective RCT by Hayward et al.[129] The intervention (57 patients) consisted of review of medications by a pharmacist for MRPs in addition to usual care (59 patients). Unplanned admission rates over 12 months during the study period were not different between the two arms. However, after adjusting for other variables, such as previous variceal bleeding, number of medications and Child–Pugh score, the pharmacist intervention was associated with significantly less-frequent emergency admissions. Although MRPs were frequently associated with unplanned admissions in the intervention group, they did not have a significant impact on the emergency admissions overall. The study highlighted a large proportion of non-adherence to lactulose (at least on one occasion, 60%) that was intentional. Despite the dependence of study results on a single experienced pharmacist, the study reiterates the need for a holistic model of care with interdisciplinary involvement.

Although these studies are encouraging, more robust data are needed to support the routine implementation of a CDM intervention in decompensated cirrhosis. A large multicentre RCT examining the role of a CLFP in decompensated cirrhosis with clinically relevant endpoints, such as hospital readmissions and survival, is likely to provide more robust answers.

2.2 PATIENT EDUCATION AND ASSESSMENT OF DISEASE KNOWLEDGE IN CIRRHOSIS

This section reviews literature on the importance of patient education and examples of assessment of patient knowledge using questionnaires in cirrhosis. It also includes a general section on different types of validity and the analytical methods used for validation of knowledge questionnaires.

2.2.1 *Importance of Patient Education in Cirrhosis*

Patient education and the resultant improved knowledge on disease and its self-management underpin effective management of chronic diseases by promoting positive health-related behaviours.[130] A well-informed and engaged patient helps in closing the gap between the care actually delivered and the one that is recommended. The end result is the aim of chronic care

models, that is, better clinical outcomes.[16] A Cochrane Review of interventions that attempted to improve patient adherence to medications highlighted the added difficulty in achieving adherence with medications in chronic illnesses compared to acute conditions. Chronic illnesses were complicated and often required multiple interventions, such as education, self-management, supportive therapy, follow-up phone calls and psychotherapy, albeit with minimal benefits in clinical outcomes.[131] Studies have suggested that the more complex a treatment regimen, the less likely the patient would be compliant.[132] Therefore, patient education becomes more vital in a disease as complicated as decompensated cirrhosis, which results in a multitude of potential complications that need to be managed by interventions that require active involvement of patients. These include salt restriction, periodic monitoring of weight and electrolytes while on diuretics, adjusting lactulose dose according to the symptoms of hepatic encephalopathy, and regular endoscopies in case of variceal bleeding. In addition, regular 6-monthly HCC surveillance examinations require patients' voluntary participation.

A Commonwealth funded report on an international comparison of quality of health care in five developed countries (Australia, New Zealand, Canada, United States and United Kingdom) was provided by the Commonwealth Fund's International Working Group on Quality Indicators.[133] A particular focus of this report was the quality of patient–doctor communication. Patients with a major illness, history of hospitalisation or major surgery were asked to report on their satisfaction on the answers received for crucial questions relating to their illness, prior to leaving the doctors' office. Up to 33% of patients from the United States reported that they were unable to obtain a satisfactory reply, whereas in Australia the fraction of dissatisfied patients was only 20%. However, a more concerning finding was that half of the patients from Australia reported being left out of the decisions or opinions regarding their disease management. This sense of lack of partnership was the highest among patients from the United Kingdom at 67%. It is clear from this report that patients with chronic diseases expect to be provided with information about their disease and to have an active role in its management.

Research has confirmed that well-informed and actively participating patients have better clinical outcomes, and are known to practise good behaviours related to health.[16] Failure on the part of the physician to assess patients' understanding of illness and provide the necessary information was shown to have an adverse impact on patients' adherence to medications.[134] Lack of educational support is acknowledged as an unmet need in the management of patients

with cirrhosis.[17] Ischemic heart disease, heart failure and asthma are some of the chronic diseases in which many randomised controlled studies have established the beneficial effect of patient education as a part of CDM on quality indicators, such as readmissions and mortality. Efficacy of patient education as a part of discharge planning was analysed in a meta-analysis involving eight RCT and revealed a 6% reduction in hospital readmission rates in patients with chronic diseases, including heart failure and bronchial asthma.[18] However, it did not have any effect on the mortality. A meta-analysis that included 36 RCTs comparing asthma self-management education with usual care showed significant reduction in hospitalisations, unplanned doctor visits, absenteeism from school or work, emergency room visits, episodes of nocturnal asthma and improved quality of life.[20] Intervention including heart failure-specific education, as assessed in a meta-analysis including eight RCTs, showed significant reduction in hospital readmissions but not mortality.[19] Similarly, educating and counselling patients with heart disease about secondary prevention and medication adherence, as a part of a Cardiac Hospitalization Atherosclerosis Management Programme (CHAMP), resulted in better control of cholesterol levels in serum and reduced recurrence of myocardial infarction.[135]

In contrast, there is a lack of information on the effects of patient education in cirrhosis on mortality or readmissions to hospitals, the two crucial quality of care indicators. However, there is some preliminary evidence that patient education and engagement could promote radiological surveillance and hospital attendance in these patients.[11,112] In a single-centre RCT, Wigg et al. reported on a multifaceted CDM model that provided education and self-management support to cirrhotic patients in addition to reminders for radiological surveillance. There was significantly improved quality of care in the intervention group for outpatient attendance and adherence to protocols for HCC screening, vaccination and bone density surveillance.

In a prospective fashion, Singal et al. conducted a survey to assess knowledge, risk factors and information seeking behaviour in 160 patients with cirrhosis undergoing HCC surveillance in a tertiary-care liver centre.[112] In particular, the questions on knowledge-seeking behaviour examined how involved the patients were in decision concerning screening in addition to their self-reported confidence in their knowledge of HCC. A median of 85% of knowledge questions were correctly answered. Despite this, the majority of patients (77%) were keen to receive more information about HCC. Participation in the decision-making process was reported by 77% of patients. The most reassuring part of the study was the high level of participation in surveillance

(up to 75%) noted in the study population. This high rate of surveillance was consistent with rates reported in patients at a tertiary-level practice.[136] In addition to male gender (odds ratio, OR = 7.1; 95% confidence interval (95% CI), 1.2–43.2), patient participation in the decision-making process of screening (OR = 3.4; 95% CI, 1.5–7.9) was independently associated with having HCC surveillance. This study is a prime example of how patient engagement can modify their health-related behaviour: in this case, the surveillance for HCC. One of the reasons for the high degree of patient involvement could be the high level of knowledge the cohort had about HCC. However, surveillance for HCC is only a part of cirrhosis management. Cirrhotic patients also need to be educated about other complications and preventive aspects.

2.2.2 *Validation of Knowledge Assessment Questionnaires*

A knowledge questionnaire is an instrument of measurement of knowledge of an individual in a domain. Its verity has to be confirmed by validation studies before it can be recommended widely. The two cornerstones in the evaluation of an instrument of measurement are validity and internal consistency/reliability.[137] Validity, as defined by Bolarinwa, 'expresses the degree to which a tool measures what it purports to measure'.[138] Different types of validity include face validity, criterion validity, content validity and construct validity. When these attributes are studied within a study population it is known as 'internal validation'. Measurement using the tool in a different cohort representative of the study population is defined as 'external validation'. Bolarinwa defines internal consistency/reliability as 'the degree to which the results obtained by a measurement and procedure can be replicated'.[138] 'Internal consistency' is a measurement of the close relationship or correlation between the items used in the scale. In other words, it measures the consistency of the outcome of the scale; the higher the internal consistency, the less prone the scale is to the measurement error.[137]

Using a knowledge questionnaire prepared in-house, which was neither internally nor externally validated, Volk et al. assessed baseline knowledge on cirrhosis and its self-management in cirrhotic patients before and after an educational intervention using a booklet.[139] Prior to the intervention, correct responses were obtained for only 53% of the 15 questions by cirrhotic patients followed in clinic for a median period of 2 years.[139] The number of correct responses increased to 67% after intervening with the educational booklet. The survey used in this study was not a simple one because it included questions on sodium content in sea salt, safety of surgery, cholesterol-lowering medications and nonsteroidal anti-

inflammatory drugs (NSAIDs). It was highly technical for everyday use in patients with cirrhosis. Moreover, it did not include any questions on variceal bleeding, a common and serious complication associated with cirrhosis of the liver.

Another study on patient knowledge by Goldsworthy et al. demonstrated that in spite of being reviewed by specialists in clinic for over 3 years, the knowledge of cirrhosis was poor, in a cohort of 52 cirrhotic patients attending a liver clinic in a tertiary-care centre.[140] They used a 12-minute-long video explaining the physiology of liver, pathology of cirrhosis and its complications to educate patients about cirrhosis and its complications. The poor baseline knowledge score significantly improved from 21% to 60% after watching the presentation.[140] The questionnaire used to assess disease knowledge consisted of six single best response questions, one multiple response question and one descriptive question. Patients were asked if they had experienced a complication before being asked to respond to further questions about the complication. This strategy was helpful in avoiding nonresponses due to lack of awareness about complications that were not yet experienced. Despite providing useful evidence for the widespread lack of knowledge among cirrhotic patients, a drawback of the study was the use of an under-validated questionnaire, as the structure was not validated beyond face and content validity. In addition, the questionnaire had no mention of ascites, the commonest form of decompensation and recurrent hospital admission in patients with cirrhosis. The majority of the study cohort perceived the video presentation to be relevant and very useful. In contrast to a small proportion of patients (16%) who were anxious about receiving information about liver disease, the majority were very enthusiastic about learning more about their condition.

The need for patient-centred education in cirrhosis was confirmed by a pilot study by Hayward et al. involving 50 patients.[141] Patients were asked to answer 56 open-ended and closed-ended questions following which they received a pilot educational booklet. Subsequently, they answered 13 recall questions that were very similar to the survey by Volk et al.[139] This survey did not undergo any form of validation. In this study, only half of the study cohort had received information from their treating physicians. More than half of the cohort reported using other sources, usually the internet, to find more information about the disease outcome and its treatment. The search was not fruitful in most of the cases. This study showcased the gap between perceived needs of patients and the ground reality regarding patient education in cirrhosis.[141] This study also showed how satisfied patients were to receive reliable information about the disease and its self-management. No difference in knowledge scores between patients

with compensated and decompensated cirrhosis was reported by Volk et al.[139] and Hayward et al.[141] This may have been related to the lack of a CDM programme, customised to meet the educational needs of patients with decompensated cirrhosis, in both these studies.

It is imperative that the information given to cirrhotic patients is in simple language, without technical jargon. In addition, the information should be periodically reinforced using validated surveys. Hepatic encephalopathy and cognitive deficits due to alcohol may preclude conventional booklet-based methods of education. It is essential that different modalities are used to provide disease education. The use of multimedia in providing disease education, as adopted by Goldsworthy et al.[140], was innovative. However, the questionnaire that followed required detailed answers to be written for each question, whereas Hayward's survey had 56 questions. A knowledge questionnaire has to be long enough to account for the internal reliability. However, too long a questionnaire would compromise the most important aspects, namely the patient compliance and retesting.

A nonrandomised pilot study from Iran investigated the quality of life and knowledge of cirrhosis in 72 patients using Chronic Liver Disease Questionnaire (CLDQ) and a knowledge questionnaire (prepared by the investigators) before and after an extensive educational intervention. The educational intervention was delivered by personal interviews, text messages, phone calls and supplemented with booklet.[142] Not surprisingly, both knowledge scores and CLDQ scores improved significantly. In addition, the occurrence of ascites, oedema and hospitalisations decreased with the intervention. Nutritional information including meal planning was the major focus of this intervention. The drawbacks of the study included lack of a control group and the small number of participants. Moreover, the questionnaire used for knowledge assessment satisfied only the content validity. Another pre- and post-intervention study by Beg et al. consisted of answering a questionnaire before and after reading an educational leaflet.[143] As demonstrated in other studies, the baseline knowledge was poor, and it was improved by the educational intervention provided.[139,140]

Thus, inadequate knowledge of disease, its complications and self-management in patients with cirrhosis of the liver are demonstrated by these studies. It is also apparent that poor baseline knowledge can be enhanced using different types of educational interventions. However, none of the knowledge surveys available so far have undergone a structural validation process. This is a gap in the hepatology literature that needs to be bridged to enable optimal disease

management in cirrhosis. In addition to identifying patients who require support with disease education, a validated knowledge questionnaire can also assist in the assessment of efficacy of CDM programmes in cirrhosis that deliver disease education. This was explored in a prospective study as outlined in Chapter 4.

2.3 SELF-MANAGEMENT IN PATIENTS WITH CIRRHOSIS

This section discusses a key CDM principle, self-management support and its measurement in cirrhosis. It discusses measurement of self-management using the Partners in Health scale, in a variety of chronic diseases.

2.3.1 *Rationale for Self-Management Support in Cirrhosis*

One of the major health issues facing Australia is the increasing prevalence of chronic diseases. In fact, it is reported that every second Australian is likely to suffer from one of the eight chronic diseases, namely cardiovascular disease, diabetes mellitus, arthritis, back pain, mental health conditions, asthma, chronic obstructive pulmonary disease and cancer.[92] Chronic liver disease (CLD) is a frequent comorbidity encountered in patients with diabetes mellitus and ischemic heart disease due to nonalcoholic fatty liver disease.[46] These chronic conditions contribute to increased hospitalisations, health-related costs and societal costs due to disability and poor quality of life. Delivery of self-management support should be an integral part of the management of these chronic diseases. When patients were engaged in their care by playing an active role, a higher level of patient satisfaction and adherence were reported.[134] Activated patients (those with higher level of knowledge and skills required for management of their disease) have been shown to experience improved health outcomes.[22]

Despite medical advances, recurrent hospital admissions occur as a result of these complications and contribute significantly to the direct medical costs and to the poor quality of life.[7] As a quarter of recurrent admissions that account for most of the morbidity and mortality of the disease are preventable, patient education and self-management are a high priority in patients with cirrhosis.[3] Considering the complicated nature of cirrhosis, which frequently culminates in recurrent hospital admissions, self-management skills are highly desirable. Evaluation of self-management knowledge and behaviours is essential in cirrhosis to identify domains that can be improved to achieve optimal disease management. Since self-management

knowledge is a measure of how activated the patients are in their management, it is a key element of optimal chronic disease management.

Self-management support is the foundation of a successful CDM programme. It empowers patients with the knowledge and behaviour required to cope with a chronic disease successfully. Strategies include education about the disease, its complications, symptoms of deterioration, healthy lifestyle practices to cope with the disease and enjoy a better quality of life. An effective strategy acknowledges the pivotal role of patients in CDM to make decisions in partnership with healthcare providers. It encourages patients to take responsibility for their own health by managing their chronic disease appropriately, in line with medical recommendations.

In the field of hepatology, estimation of supportive care needs of cirrhotic patients is an area of need that is frequently overlooked.[17] A systematic review by Valery et al. on the supportive care needs of patients with CLD revealed a total of 26 eligible articles, but the majority of them focussed on chronic hepatitis due to HCV. Only three articles included patients with cirrhosis, the stage of CLD in which patients require more support from a physical, social, emotional and overall health point of view.[17] The three studies are as follows:

1. In a quasi-experimental study, Zandi et al. reported on the benefits of a self-care educational programme in a small cohort of cirrhotic patients (21 in the intervention group and 23 in the control group).[144] The educational programme was customised to one of four sessions, based on the needs of the patients assessed with a questionnaire. The four sessions covered were
    a. nature of the disease including symptoms and complications,
    b. coping with systemic symptoms,
    c. coping with anxiety and nutritional needs,
    d. medication management.

    Chronic Liver Disease Questionnaire (CLDQ) was used to measure the quality of life (QoL) as a marker of efficacy of the self-care programme. CLDQ is a disease-specific questionnaire developed by Younossi et al. to evaluate the HRQoL in patients with CLD.[145] This extensively validated tool includes 29 items in domains, such as abdominal symptoms, activity, emotional function, fatigue, systemic symptoms and worry. The responses range from ‘all the time’ to ‘none of the time’ in a seven Likert-

type scale. The study used a Farsi-translated version. The validity and reliability of the translated version were confirmed. The educational sessions were designed according to the needs of patients, and an interesting finding was that the majority of the patients required information on managing ascites and needed nutritional advice. CLDQ scores improved significantly in the group that received educational intervention, whereas the control group experienced a decline in the CLDQ score. Although it is not surprising that the educational intervention was associated with an improvement in CLDQ, it is difficult to explain the reduction in QoL in the control group within 3 months. In addition, the study reported only short-term results of the intervention. However, the authors acknowledged the low number of advanced cirrhosis in the original validation studies of CLDQ and expressed concern about the reliability of CLDQ in measuring the QoL in patients with decompensated cirrhosis.

2. Rakoski et al. reported on the impairment in the practical domain of performing daily activities and instrumental activities of daily living in 371 elderly patients with cirrhosis of the liver using structured interviews.[146]
3. The structured interviews used by Bajaj et al. reported on the financial and caregiver burden in patients with cirrhosis and hepatic encephalopathy.[147] The domains studied in this research included educational, emotional, financial and physical aspects of daily living.[147]

To address the lack of an instrument to measure the supportive needs of cirrhotic patients, Valery et al. developed and validated the Supportive Needs Assessment tool for Cirrhosis (SNAC).[148] This 39-item scale with subscales 'Psychosocial issues', 'Practical and physical needs', 'Information needs', and 'Lifestyle changes', was shown to have excellent internal consistency and correlation with CLDQ.

Wang et al. from China developed a self-management behaviour assessment tool specifically for patients with cirrhosis of the liver.[149] This was designed based on literature reviews, interviews, expert opinion and a preliminary study. This 30-item scale comprised four dimensions: daily-life management (11 items), dietary management (10 items), illness-monitoring management (5 items) and medication management (4 items). This was studied in 180 patients with cirrhosis of the liver. The scale was validated by factor analysis and a final version with 24 items and four dimensions was derived. This included daily-life management (7 items), dietary management (7 items), illness-monitoring management (5 items) and

medication management (5 items). The scale had a good Cronbach's scale demonstrating excellent internal consistency. Although test–retest correlation and content validity were demonstrated, confirmatory factor analysis was not performed, and its dimensionality was not validated externally. Furthermore, the study population had predominantly hepatitis B virus (HBV)-related cirrhosis, and those with Child–Pugh stage C cirrhosis were excluded. This questions the applicability of this scale to all patients with cirrhosis. Patients with advanced cirrhosis and decompensation are at-risk of recurrent hospitalisations, and hence should have been prioritised for self-management training and assessment.

Dong et al. from China performed a cohort observational study of self-management behaviours in patients with cirrhosis of the liver.[150] They evaluated the effect of disease knowledge, physical and mental well-being, and self-efficacy on self-management behaviours in 134 patients with cirrhosis of the liver. Self-management behaviour was studied using the scale developed by Wang et al.[149] The investigators studied disease self-management knowledge with a questionnaire designed by the study team that included 15 closed-ended questions on diet, medications used and self-monitoring strategies. The questionnaire was validated by content validity only. Using the Self-Efficacy for Monitoring Chronic Disease (SEMCD) 6-item scale, self-efficacy was evaluated.[151] Mental well-being was assessed with the Hospital Anxiety and Depression Scale (HADS). Physical well-being was assessed by liver disease severity using the Child–Pugh score. The study population had a mean self-management score of 2.51 (SD 0.77) with a maximum of 4.00. Lower depression score in HADS, lower Child–Pugh score and higher self-efficacy correlated with better self-management. The mean self-management knowledge score was 7.69 (SD 2.47). Although the majority were aware of the need to restrict salt and the urgent need to seek medical help with the occurrence of black stools, knowledge about lactulose dose titration to manage hepatic encephalopathy was poor. Hence, the study recommended that

- focussing on mental well-being,
- identifying and addressing depression,
- increasing confidence with resultant higher self-efficacy
- improving knowledge of self-management using multimodality learning methods

are essential in achieving improved self-management behaviours.

'Self-efficacy', defined as self-assurance in one's ability to perform actions necessary to attain one's goals, is a crucial concept in the management of chronic diseases.[152] Measurement of self-efficacy leads to customised provision of self-management education and training accordingly. A randomised controlled study from Iran measured the effect of training for self-management on self-efficacy in patients with cirrhosis.[153] An equal number of 37 patients participated in the control and intervention arms. The intervention was an intensive self-management training, consisting of six group sessions lasting for 90 minutes delivered twice a week. In addition to provision of information about the disease, problem-solving, decision-making and cognitive behaviour therapy sessions were also provided. Multimedia presentations and booklets were used for disease education. In addition to patients, carers were also invited for these sessions. Self-efficacy was measured using the 'Strategies Used by People to Promote Health (SUPPH)' questionnaire.[154] The scale was first translated into Persian and then translated into English to assess its validity. The overall score and the subscale scores increased significantly in the intervention arm immediately and after one month of the intervention. Consistent with other studies in chronic diseases, the study findings support delivery of educational and self-management support in promoting healthy behaviours. Nevertheless, the study suffered from the limitations of a small sample size and shorter follow-up period after the intervention. In addition, the SUPPH questionnaire used was not validated for cirrhosis.

Most of the self-management educational and assessment tools are in written form in English. In an increasingly multicultural Australian society, non-English speaking patients are thus disadvantaged. Development of audio visual aids will also be helpful to address patients with lower educational level.

2.3.2 *Partners in Health Scale and Self-Management*

A successful level of self-management is the overarching theme of optimal chronic disease care. The Partners in Health (PIH) scale is a generic tool that was developed to measure self-management knowledge and behaviours in people with chronic illnesses. It was developed during the SA HealthPlus trial, a controlled trial of a statewide (South Australia) application of a generic model of chronic illness care.[23,24] An important finding of the study was the importance of self-management behaviours for optimal management of chronic conditions, rather than disease severity. The time spent by coordinated care providers was dependent on

the patients' self-management capacity, not on the complexity of the disease process. Hence, the PIH scale was developed by Battersby et al. along the five major principles of self-management in chronic conditions. This included

1. knowledge about the disease;
2. adherence to a treatment plan made in accordance with the healthcare provider;
3. playing an active role in the decision-making process;
4. awareness of warning symptoms and their management;
5. coping with the effects of the chronic illness in relation to the physical, mental and social aspects of life.[23]

The initial 11-item scale was later changed to a 12-item scale that included adoption and practice of a healthy lifestyle. Thus, the five principles of self-management were broadened to six, and the 12-item scale became an integral part of Flinders Care Planning process. The structural validity and the internal consistency in the measurement of self-management in chronic diseases were established by Petkov et al. using the Sharing Health Care SA (SHCSA) chronic disease self-management demonstration database.[155] The 12-item scale is listed in **Box 1**.

Construct validity and internal consistency were first evaluated in an initial sample of 176 patients. It was subsequently verified with confirmatory analysis and a structural equation model in a further sample of 118 patients from another site. The study cohort had a variety of chronic diseases, including diabetes mellitus, osteoporosis, cardiac diseases, renal diseases, respiratory ailments, depression and arthritis. Factor analysis revealed a 4-factor structure, including knowledge, coping, recognition and management of symptoms and adherence to the treatment. Petkov et al.[155] concluded that the PIH scale was useful in measuring self-management in patients with a variety of comorbidities.

In a pragmatic RCT of the Flinders Program of chronic condition management in community healthcare services, the role of the PIH scale as an effective risk assessment tool at baseline was examined.[156] In addition, its utility in detecting improvement in self-management ability over time in response to CDM intervention was also highlighted.

Box 1. The 12-item PIH scale.

Knowledge

1. What I know about my illness is
2. What I know about the treatment of my illness is
4. How I share in decisions made about my illness is
8. My understanding of what to do when my symptoms get worse is

Adherence to treatment

3. I take my medication as asked by my doctor
5. I arrange appointments and attend appointments as asked by my doctor or health service provider

Recognition and management of symptoms

6. My understanding of why I need to check and write down my symptoms (such as blood sugar level, peak flow, weight, shortness of breath, pain and so on) is
7. I check and write down my symptoms
9. I do the right things when my symptoms get worse

Coping

10. How I deal with the effects of my illness on my physical activities (namely walking and household tasks) is
11. How I deal with the effect of my illness on the way I feel and how I mix with other people (that is, my emotional and social life) is
12. My progress towards living a healthy life (think about not smoking, not taking alcohol, taking healthy diet, doing exercise and so on) is

Scored as follows:

Items 1–4, 6, 8, 10–12 ranged from 0 = Very good to 8 = Very poor.

Items 5, 7, 9 ranged from 0 = Always to 8 = Never.

The aim of the study was to assess the efficacy of the Flinders CDM programme in a real-world scenario with liberal and flexible inclusion criteria. Patients with cerebrovascular disease, chronic heart failure, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus and musculoskeletal disorders were included, if they could understand the patient information sheet and consent forms in English.

As self-management support was an integral part of the Flinders Program, it was studied at baseline, at 6 months and at 12 months during the intervention, using the PIH scale. This was also correlated with other important health measures including health-related quality of life (HRQoL) with physical and mental health component summary measures of the 12-Item Short Form Survey (SF12 v2), fatigue with the Energy/Fatigue scale, self-management efficacy with the SEMCD and health distress using the Health Distress scale. Although 115 patients were supposed to receive the intervention, 52 patients were excluded as they did not receive the intervention. This loss of power was likely to have contributed to the lack of improvement in PIH score or other measures with the intervention.

Nevertheless, a significant relationship was found between the baseline PIH score with fatigue levels, mental component of HRQoL, self-efficacy score and health distress score. This implies that the PIH scale can be used as a surrogate measure of these above-mentioned scores. Mixed linear method models were used to investigate the change in the PIH scale over the duration of the intervention with changes in the other reported outcomes. The PIH scale was found to be reliable in detecting improvements in self-management behaviours. Therefore, the PIH scale simplifies the evaluation of self-management, and it can be used to assess the self-management behaviour at baseline, in response to an intervention and in lieu of other measures. Since it avoids the use of multiple tools, patient compliance with measurement of intervention can be easily achieved.

Supported by several discussions between Flinders-based investigators and Australia–New Zealand accredited trainers, the PIH scale was revised. Emotional and spiritual well-being were given importance; knowledge of treatment and medications was given importance in addition to the knowledge of disease; partnership in treatment and early identification of warning symptoms were also modified. The revised scale is provided in **Box 2**.

The revised scale was administered to a sample of households with chronic illness (904 of 2304) from the 2014 South Australian Health Omnibus Survey. Using the Bayesian confirmatory factor analysis (BCFA) the construct validity of the revised scale was established.

Box 2. The revised PIH scale.

Knowledge

1. Overall, what I know about my health condition(s) is
2. Overall, what I know about my treatment, including medications for my health condition(s) is

Partnership in treatment

3. I take medications or carry out the treatments asked by my doctor or health worker
4. I share in decisions made about my health condition(s) with my doctor or health worker
5. I am able to deal with health professionals to get the services I need that fit with my culture, values and beliefs
6. I attend appointments as asked by my doctor or health worker

Recognition and management of symptoms

7. I keep track of my symptoms and early warning signs (namely blood sugar levels, peak flow, weight, shortness of breath, pain, sleep problems, mood and so on)
8. I take action when my early warning signs and symptoms get worse

Coping

9. I manage the effect of my health condition(s) on my physical activity (that is, walking and household tasks)
10. I manage the effect of my health condition(s) on how I feel (that is, my emotions and spiritual well-being)
11. I manage the effect of my health condition(s) on my social life (that is, how I mix with other people)
12. Overall, I manage to live a healthy life (for example, no smoking, moderate alcohol, healthy food, regular physical activity, managing stress and so on)

Scoring for response categories

Items 1 and 2, 0 = Very little to 8 = A lot.

Items 3–8, 0 = Never to 8 = Always.

Items 9–12, 0 = Not very well to 8 = Very well.

Total score is a sum of all the scores.

The revised PIH scale is a 12-item scale with a four-factor structure: partnership in treatment, knowledge, the recognition and management of symptoms, and coping.[157]

The usefulness of the PIH scale in measuring self-management in chronic diseases is demonstrated by its widespread use. This structurally sound tool was successfully used to measure self-management skills in response to CDM interventions in patients with osteoarthritis and in dialysis patients.[158,159] An RCT by Reed et al. reported the benefits of a chronic disease self-management support (CDSMS) programme in 254 patients who were more than 60 years of age, with at least two chronic diseases in five general practices. The PIH scale was one of the tools used in the assessment and planning of the intervention arm of CDSMS. The intervention group reported significant improvement in self-rated health.[160]

While the PIH scale has already been validated in various Australian cohorts with several other chronic diseases, no research has been conducted on the application of this scale in patients with cirrhosis of the liver until the present. The crucial need for self-management in this complex disease warrants studying self-management behaviour with a validated, dimensionally strong scale with excellent internal consistency, both at baseline and regularly during the clinical course. The PIH scale may help identify patients who are likely to benefit from CDM interventions. Moreover, the efficacy of CDM interventions can be measured by monitoring with the PIH scale, as self-management is an essential element of CDM programmes. This hypothesis was explored in the study detailed in Chapter 5.

2.4 NURSE-LED CIRRHOSIS CLINIC MODEL

Provision of multidisciplinary care for CLD in the community is the focus of an innovative MOC evaluated in the thesis in Chapter 6 called nurse-led cirrhosis clinic (NLCC). This model is supported by an important chronic disease management (CDM) principle, namely delivery system redesign. This section describes examples of nurse-led clinics (NLCs) in the literature. It also includes a section on qualitative methodology as a preferred research methodology to study patients' perspectives of CDM models.

2.4.1 *Nurse-Led Clinics*

The increasing health demands of an ageing population with multiple chronic comorbidities is challenging the traditional MOC in Australia.[25] In accordance with patients' preferences the focus of healthcare delivery is showing a trend away from hospitals, towards providing care in the community. Nurse-led clinics (NLCs) are an important part of the modern medical delivery

chain. Hatchett defines NLCs as nurses managing their own patient load by providing health education, psychological support, assessment, treatment monitoring, referral to other healthcare professionals and hospital admission, as required by the clinical condition.[161]

The efficacy and acceptability of NLCs have been assessed both in primary care and in various specialities. The overarching finding was that the care was efficacious, inexpensive and easily available.[26,162] A systematic review examining 11 randomised controlled trials (RCTs) and 23 observational studies, assessed the equivalence of doctors' care and nurse-led care in primary practice. The care delivered by nurse practitioners working in primary care was associated with patient satisfaction, found to be equivalent to that provided by doctors and to be of better quality.[162] Within the literature, there are examples of speciality NLCs that provide medical care for patients covering specific chronic diseases, such as diabetes mellitus, mental health issues, chronic constipation, eczema, rheumatoid arthritis, cancer chemotherapy and sexually transmitted diseases.[26]

The effect of NLCs on patient outcomes, access, satisfaction and cost-effectiveness was explored in a systematic review by Randall et al.[26] Of the 701 titles listed in medical databases with terms suggestive of NLC, 15 articles that evaluated NLC in various settings were shortlisted. Eight of them relied on quantitative methods, four used qualitative methods and three used mixed methods in their evaluation of NLCs. Most of the studies observed high levels of patient satisfaction. Patients reported feeling secure, comfortable and respected. Edwall et al. reported that regular check-ups at nurse-run diabetic clinics provided a strong foundation for a good understanding of the disease and improved self-management, which in turn made patients confident and independent.[163]

The evidence for the many benefits of NLCs is growing. Community nurse-led ear clinics were successful in reducing waiting times and improving patients' convenience.[164] NLCs in a cohort of cardiac patients were shown to offer equivalent care as compared to non-nurse clinics in terms of risk factor assessment, patient education and continuity of care.[165] Bentley et al. reviewed ten studies that included 900 nurse practitioners and their patients in aged and primary-care settings.[166] The reported strengths of NLCs include longer consultation times that increase patients' engagement and resultant better patient satisfaction and compliance with treatment plans. Overall, NLCs are well accepted by patients due to improved access, satisfaction, affordability and convenience.[26]

Interestingly, NLCs have been shown to assist in risk factor modification as well.[26] The services offered by a nurse-run respiratory clinic at a primary health centre was compared to the standard hospital clinic care in patients with chronic obstructive pulmonary disease (COPD).[167] Patients randomised to the nurse clinic received a formal COPD education programme. The impact of the intervention on quality of life, knowledge and self-management efficacy of COPD and cessation of smoking was measured in both the groups immediately and after 3–5 months. Not surprisingly, there was a better quality of life and knowledge of the disease and self-management in the group that visited the nurse-run clinics. Most importantly, the much sought-after behavioural change in terms of reduction in number of patients continuing to smoke was observed in the intervention group. However, the researchers admitted to conflict of interest in that the main researcher's role was duplicated as the person providing the intervention. Nevertheless, the study provided evidence that the nurse-run clinics could potentially assist in risk factor control and result in behaviour modification.

Ingram et al. reported adoption of safe sex practices and less risk taking in the attendees of a nurse-run youth sex clinic.[168] In addition, these patients also favourably reported on the accessibility of these clinics and the quality of care provided by the staff.[168] Homeless adults managed in nurse-run clinics in a Midwestern city in the United States experienced improvement in HRQoL and substance abuse in a pre-pilot and post-pilot study reported by Savage et al.[169] Nurse-run primary-care obesity clinics were found to be non-inferior to specialist-run hospital clinics in achieving reduction in body mass index, compliance with treatment and quality of life.[170] Patients who attended nurse-led healthy lifestyle clinics that provided education and preventive care advice for patients with health inequalities, reported improved understanding of their health condition, medications and need for self-management.[171]

2.4.2 *Nurse-Led Community Liver Clinics*

Assessment of patients by dietitians in a gastroenterology clinic reduced the waiting time without compromising on patient satisfaction, as reported from Queensland, Australia.[172] The majority of patients were discharged back to GPs. Drawing from this study, community liver clinics run by trained liver nurses could have benefits for hospital clinic waiting times. This may enable stable patients with cirrhosis, with no clinical manifestations of decompensation, to be reviewed in nurse rather than specialist clinics. With appropriate training of nurse

practitioners and provision of evidence-based protocols for the management of cirrhosis and detection of early symptoms and signs of hepatic decompensation, safety of these clinics can be ensured. In addition to benefitting stable patients with reduced waiting times, it may create opportunities for sick patients who require specialists' input to be prioritised. This innovative MOC may improve the overall efficiency of healthcare delivery to patients with cirrhosis.

Nurse-run clinics are not new in the field of hepatology. There are many successful nurses-led MOCs working in isolation or as a pivotal unit of multidisciplinary care in the management of chronic HBV and HCV infections.[29,173] However. there are very few examples of community nurse-led cirrhosis clinics (NLCCs) in the literature.

The possibility of early detection and workup of advanced CLD was explored in the LOCATE study (LOcal Care And Treatment of chronic liver disease Evaluation).[174] In this cluster feasibility RCT, the number of new cases of significant liver fibrosis, defined by a FibroScan® reading >6 kPa, was explored using trained liver nurses in general practices. Ten practices, with a large number of referrals to the University Hospital Southampton, were chosen and randomised to control or intervention groups. Five practices received intervention and five continued regular practice. Intervention involved an NLC within the general practice, where trained liver nurses worked up high-risk cases for fibrosis. Cases were referred to the clinic by three pathways: by the GPs, by the nurses after reviewing case records of high-risk cases, such as diabetes mellitus, obesity and alcoholism, or by review of Alcohol Use Disorders Identification Test (AUDIT) questionnaire for alcoholism. Work up consisted of blood investigations for aetiological workup, fibrosis markers and FibroScan®. Patients detected to have borderline fibrosis (FibroScan >6 kPa) had their records reviewed in a virtual manner by GPs and by specialists. Thus, a treatment plan was formulated without patients physically being seen by specialists. New cases of significant liver fibrosis identified in both the arms were compared in the period before and after intervention. There was a significantly higher number of new cases of cirrhosis identified, following the introduction of liver nurses in general practice. The study was limited by the lack of longitudinal follow-up of the newly identified cases of CLD, to determine if the intervention-induced detection translated into better clinical outcomes. However, this would be a very long-term outcome as most patients had borderline significant fibrosis with scores of 6–8 kPa on transient elastography using FibroScan®. It is

expected that the screening induced awareness of liver disease may lead to subsequent lifestyle changes related to obesity management and reduction of harmful alcohol use.

The LOCATE trial has thus identified a novel and less expensive way of detecting new cases of CLD in the community. The virtual clinics, run under remote supervision of consultant hepatologists, could free up resources for sick patients and provide a management plan for newly detected patients in a timely fashion. Integration of liver nurse-led MOC in general practices would translate to early detection of CLD and its management at primary-care level. Although this has the potential to reduce CLD-related morbidity and mortality, with better control of risk factors at an early stage, it would require a large amount of resources to train and employ liver nurses at general practices. Instead, trained liver nurses who are already a part of healthcare delivery in secondary and tertiary care (viral hepatitis nurses) could be utilised in the management of CLD. Nurse-driven MOCs have been successfully used in Australia in the treatment of HCV.[29] Indeed, Australia is a world leader in the eradication of HCV with significant contribution from this model. This model could be explored for the management of cirrhosis as well.

The current MOC for cirrhotic patients, with reliance on specialists, is unlikely to meet the increasing demands caused by an escalation in the prevalence of CLD and by the obesity epidemic and harmful alcohol ingestion. The median survival of patients in compensated and decompensated stages of cirrhosis is 12 and 2 years, respectively.[63,66] During the prolonged compensated phase of cirrhosis patients often require only monitoring, disease education, surveillance procedures and nutritional advice, rather than active medical input. This can be provided safely by trained nurses or specialist nurses (SNs). This strategy will result in specialists' care being reserved for the management of complicated patients with decompensated cirrhosis. Australia has 11.5 nurse practitioners per 1000 people, compared to the average reported in the 34 member countries listed in the Organization for Economic Cooperation and Development (OECD) of 9 nurse practitioners per 1000 population.[92] With these numbers Australia is potentially resourced to provide NLC for stable patients with cirrhosis. Nurse-led practice gains more importance due to the estimated escalations in the prevalence of CLD in the years to come.[52]

Using a retrospective analysis of case records during the period 2009 to 2015, a study of efficacy of a nurse-led liver clinic in Western Australia reported on the rates of HCC

surveillance.[175] Patients who required HCC surveillance (HCV-infected patients with compensated cirrhosis, patients with advanced fibrosis and HBV patients) were referred to the nurse-run clinic. In addition to HCC surveillance, endoscopic surveillance and biochemical monitoring were also performed. Any abnormality detected was followed by referral to the doctors' clinic. A high rate of adherence to radiological (up to 70%) and endoscopic surveillance (83%) was noted in these clinics, catering predominantly to patients with advanced CLD due to HCV infection. However, the clinic attendance over a 6-year period was only 86 patients, with no increase in the trend of new patients over the years (range from 10 to 16 patients). Details about the training provided to nurses, prior to running these clinics, was not discussed in the methodology.

In an ongoing pragmatic RCT, initiated in the year 2016 and expected to recruit patients until 2020, Hjorth et al. from Sweden described their study design of an NLCC.[176] A total of 500 patients will be studied with 250 in each arm. The intervention consists of annual nurse clinic visits in patients with compensated cirrhosis, and twice a month for decompensated cirrhosis. At each visit, the nurses will check for disease progression, provide education and motivation towards self-management and assessment, advise on nutrition, and give psychosocial support as well as perform risk factor assessment and modification. The intervention plan is customised to suit the needs of an individual patient. Standard of care includes physician visits, ascites drainage as needed and phone counselling by nurses not involved in the study. This study provided details of training received by the nurses, which is likely to be useful in planning further nurse-led interventions. The nurses had a minimum experience of 2 years in both inpatient and outpatient management of cirrhosis. In addition, they attended a 6-hour seminar followed by 3 days of training.

The primary endpoint of the study will be the effect on HRQoL as measured by Rand-36 (Rand 36-Item Health Survey) Questionnaire.[177] The validity and reliability of the scale in various chronic diseases is well established. The secondary endpoints planned are as follows:

- *Measurement of quality of care* using the questionnaire Quality of care from the Patient's Perspective (QPP) that includes four dimensions: (1) identity-oriented approach, (2) medical–technical competence, (3) physical–technical conditions and (4) sociocultural atmosphere.[178]

- *Healthcare consumption* by measuring outpatient hospital attendance, emergency admissions to hospital, occupied bed-days and days spent in the intensive care unit.
- *Progression of disease using* Child's score, Model for End-stage Liver Disease (MELD) score and the Royal Free Hospital-Nutritional Prioritising Tool (RFH-NPT) score for assessing malnutrition (this score has been shown to predict disease severity in cirrhosis).
- *Episodes of hepatic decompensation* at baseline, and at 12 and 24 months of intervention.

Inclusion of patients with grade 1 hepatic encephalopathy, the prolonged study period of 4 years and multiple sites with varying nurses' experience may be some of the limitations of the study. However, the pragmatic design and the large numbers proposed will provide the much-needed results of both the quantitative and the qualitative aspects of nurse-led care in cirrhosis of the liver.

The cost-effectiveness of NLCs has been addressed in different settings. Management of chronic leg ulcers with evidence-based protocols by experienced nurses in either nurse clinic setting or home clinic was compared in an RCT with ulcer healing as a primary outcome, and resource utilisation as one of the secondary outcomes.[179] Both the rate of healing and the costs were not different between the two settings emphasising the fact that delivery of appropriate care mattered more than the mode of delivery. However, walk-in clinics run by nurses at existing free clinics in a low-income area were found to be cost effective in the United States.[180] It was suggested that they could be utilised for non-emergency indications, thus reducing the workload on emergency departments.

Even though Randall et al. observed that patients' perception of NLCs was favourable, they noticed that research in the assessment of community NLCs was limited without a standardised format.[26] NLCC management of stable cirrhotic patients is a relatively novel concept; there is limited medical literature on their use in cirrhosis, which is an increasingly prevalent complex chronic disease with significant economic impacts. Since 2013 community NLCs that cater to compensated patients with cirrhosis have been an integral part of hepatology services at Flinders Medical Centre.[181] There is a unique opportunity to explore experiences of these patients and the process of care delivery of this MOC, and to provide preliminary evidence for

the value of NLCCs. If well accepted, this MOC has the potential to enable management of cirrhosis of the liver in a cost-effective and timely manner.

2.4.3 *Qualitative versus Quantitative Analysis*

The open research process of qualitative analysis is ideal for studying patient experiences, preferences and the quality of care provided by NLCC, as it allows for more details and insights. Qualitative analysis captures the nuances of patient responses better than numeric data. Unlike quantitative research methodology that collects data in numbers and explores the association between variables, qualitative methodology collects data in words, and their meaning is explored in a given context.[182] Qualitative type of research is less restricted and more fluid as it allows the researcher to focus on individual patient's perceptions, which are vital for the intended purpose. Qualitative analysis with semi-structured interviews also has the potential to reveal unexpected themes, in contrast to the unequivocal responses obtained in quantitative methods.

This methodology also provides the option to enhance and enrich the collected data in a creative manner. As discussed by Braun and Clarke, 'it captures the complexity, mess and contradiction that characterise the real world, yet allows us to make sense of *patterns* of meaning'.[182] Hence, evaluation of NLCCs by a qualitative research process is preferred to quantitative methodology. However, it is important to note that due to the bias of the researcher responsible for data collection, qualitative methodology may not always be accurate and valid, and it may be necessary to have the findings replicated by another independent study. Since the qualitative methodology generates complex data from each patient, it becomes time consuming and participation may thus be limited. Moreover, data analysis itself is a time-consuming process in qualitative analysis. Unlike the simplified statistical programmes that generate results in quantitative analysis, data analysis in qualitative research is complex. It follows six principles as outlined by Clarke and Braun: browsing the data, applying initial codes, identification of themes, review of themes, finalising themes and producing the final report.[183]

Qualitative analyses of nurse-led practice are scarce in the medical literature. Mahomed et al. performed a qualitative analysis of patients' experience with practice nurses (PNs) on chronic disease management (CDM) in general practice.[184] This study from Australia included three practices and 38 patients. Interviews were conducted with patients managed by PNs within a

randomised trial that examined PN-led care of chronic diseases, such as diabetes mellitus, hypertension and ischemic heart disease. Grounded theory was used on the data collected. Navigating care was identified as the basic process, in which patients responded to the question of 'Is PN care the right one for me?' by analysing three interrelated steps:

1. patients' understanding about the need for monitoring,
2. forming relationships with PNs,
3. having confidence in PNs.

The first and crucial step was the patients' understanding that they needed monitoring of their chronic diseases rather than treatment, which is usually reserved for acute and severe medical conditions. This promoted self-monitoring of their chronic disease, better understanding of their needs and less dependence on the health professionals for the same. If PN-led care met patient requirements, then patients proceeded to 'forming relationship with PN' and 'having confidence in them'.

Due to the fact that PN consultations were less hurried and more relaxed, patients felt they could discuss their health issues and obtain practical solutions, such as weight loss strategy or dietary advice. The firm but friendly approach of the PNs and being made to feel responsible for their health were some of the factors that made patients form a relationship with PNs and develop confidence in their care. Continuity of care was found to play a key role in this process. This study suffered from the bias that all these patients had provided consent for the PN-led study. There was no comparison made with the patients managed only by GPs.

The LOCATE RCT was followed by qualitative research exploring the experiences of the practice managers, nurses and GPs of the nurse intervention in GP practice.[185] Open-ended questions were included in semi-structured interviews, and 29 healthcare workers participated. Three distinctive themes emerged:

1. The impact of the LOCATE intervention.
2. Facilitators and barriers to implementing the LOCATE intervention into primary care.
3. Facilitators and barriers to providing lifestyle advice.

The study concluded that the LOCATE intervention was well received by the medical and practice staff. The GPs felt confident with the new knowledge gained from the interpretation of liver tests, assessment and early detection of CLD. However, the study highlighted the uncertainty of utility and lack of consistency in lifestyle modification advice. Thus, the qualitative process identified areas where the healthcare workers required support.

Recording patients' experiences and performing qualitative analysis clearly outline the aspects and outcomes of care that are deemed important by the patients.[186] It thus facilitates a patient-centred approach in care delivery and designing care in accordance with patients' needs, which is likely to promote patient adherence to day-to-day demands of cirrhosis. This was explored in a prospective study as outlined in Chapter 6.

2.5 HCV INFECTION

This section reviews the literature relevant to the fifth study in this thesis (Chapter 7) on HCV prevalence in psychiatric patients and an innovative treatment MOC in these patients. It covers the risk factors for HCV, epidemiology (both in global and in vulnerable populations), screening tests, cost-effectiveness of screening, diagnosis, treatment and benefits of treatment in various models of care (MOCs) in different patient populations.

The World Health Organization (WHO) defines chronic viral hepatitis (B and C) to be a major public health challenge, as the attributed global mortality exceeds that of other communicable diseases, such as malaria and tuberculosis.[187] Australia shares this challenge with an estimated 230 000 HCV-infected people. Hepatitis C virus (HCV) infection is the most frequent cause of preventable CLD requiring liver transplantation (LT) in Australia.[188] Because the infection is usually asymptomatic, it can only be detected when specifically looked for. Less than 15% of chronically infected patients in Western countries are knowledgeable about their infective status.[189,190]

Moreover, this lack of awareness leads to further transmission to other people. In view of the asymptomatic nature of the illness, HCV infection is aptly described as a quiet epidemic by Gravitz.[191]

2.5.1 *Risk Factors*

HCV is the commonest infection transmitted by contact with infected blood across the world.[192] The mode of acquisition varies in different parts of the world. The general mode of transmission in developed countries is by sharing infected needles via injection drug users. The prevalence of HCV antibodies in persons who inject drugs (PWIDs) is estimated to be 67%.[193] In developing countries, it is often transmitted by poorly disinfected medical supplies, blood transfusion and organ transplantation. As seen in the example of Egypt, with 4.4% HCV RNA prevalence, poor infection control practices and a high prevalence can increase the risk of acquiring the infection.

Other high-risk populations include children born to mothers with HCV, people with a history of incarceration, people with HIV infection, people with sexual partners who are infected with HCV and people with tattoos and piercings. Sexual transmission is rare but reported in homosexual males and in those with HIV infection.

2.5.2 *Natural History*

HCV infection in the acute stage is rarely symptomatic. In 80% of cases, infection with HCV leads to chronic hepatitis that causes progressive liver damage when untreated. However, the disease does not progress in the same manner in all those infected. In a large natural history study of progression of fibrosis in HCV-infected patients, Poynard et al. reported that HCV infection progresses to cirrhosis of the liver with a median period of 30 (28–32) years.[39] When untreated, up to 33% of the infected patients could develop cirrhosis within 20 years.

The study also reported a wide variation in the natural history depending on the presence of certain cofactors that affect progression. Cofactors that can accelerate disease progression to fibrosis and cirrhosis include age at the onset of infection of more than 40 years, male gender, significant daily alcohol use over 50 g, co-infection with hepatitis B virus (HBV) and obesity. Alternatively, female gender and younger age at infection may be associated with lack of progressive liver disease up to a period of 30 years. The median duration of development of cirrhosis was as short as 13 years in men who acquired the infection after the age of 40 years, as compared to 42 years in women infected before 40 years of age.[39]

2.5.3 *Diagnosis*

Enzyme immunoassay (EIA) detects HCV infection in most instances except in the very early phase of acute infection or immunocompromised patients, such as in those with HIV infection, in those with organ transplant and in patients on haemodialysis. In these special groups of patients, HCV RNA should be tested when HCV infection is suspected. Once detected, HCV antibodies continue to be positive even in successfully treated patients and in those with spontaneous clearance. Hence, detection of HCV antibodies should be followed by a confirmatory test for HCV RNA using a sensitive method. It is recommended that the assay has a lower limit of detection up to <15 international units (IU)/ml.[194] Acute infection can be diagnosed with certainty only if HCV seroconversion can be demonstrated in the presence of active biochemical changes. In the uncommon occurrence of spontaneous viral clearance, HCV RNA disappears within 4–6 months of acute infection. In more than 80% of instances, chronic HCV infection persists, characterised by HCV antibodies and positive HCV RNA. HCV core antigen can also be indicative of a replicative status, in the absence of availability of HCV RNA testing.

2.5.4 *Screening*

Diagnosis of HCV infection by screening assumes importance because the majority of chronic infections due to HCV are asymptomatic. Identification of at-risk individuals and screening them for HCV are pivotal steps prior to engagement with treatment pathways. Screening methods in different countries are guided by the local epidemiology. WHO recommends that the following groups be screened for HCV[195]:

- Individuals from a population with high HCV prevalence or who report a history of HCV risk exposure/behaviour.
- Adults, adolescents and children when viral hepatitis is suspected.
- In settings with >5% HCV-antibody prevalence in the general population.
- Among populations with overall low prevalence, birth cohort testing or testing of older persons.

The Australian recommendations for HCV management advocates HCV screening in the following situations[196]:

- people who inject drugs;
- people in custodial settings;
- people with tattoos and body piercings;
- people who received a blood transfusion or organ transplant before 1990;
- people with coagulation disorders who received blood products or plasma-derived clotting factors before 1993;
- children born to HCV-positive mothers;
- sexual partners of HCV-infected persons;
- people infected with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV);
- people with evidence of liver disease;
- people who have had a needlestick injury;
- migrants from high-prevalence regions (namely, Pakistan, Egypt, Mediterranean countries, Africa, Asia and Eastern Europe).

Recent CDC guidelines for HCV screening among adults in the United States recommend that HCV screening be performed universally for all adults above 18 years and all pregnant women, in addition to other high-risk groups as mentioned.[197]

Screening can be done using EIA on serum obtained by venepuncture or by rapid diagnostic test (RDT) methods. In the case of a positive screening test, confirmation of the infection should be performed by HCV RNA testing. Reflex testing, which involves testing for RNA in the same sample after the detection of HCV antibody, can be a very cost-effective option.[198] In comparison, the two-step process, wherein patients return for a repeat phlebotomy after an initial HCV-positive serology, could be associated with a higher dropout and failure to obtain RNA testing results. Hence, reflex testing is recommended to decrease the loss to follow-up.[194] Nevertheless, screening done by serological testing requires venepuncture, separation of plasma and immediate access to laboratory or storage conditions, which in turn involves a significant cost. Moreover, these are not readily available in settings where HCV screening is

essential, such as opioid substitution therapy (OST) clinics for PWIDs, prisons, homeless shelters and in low-income countries.

These limitations can be addressed by many newer technological advances. One such advance is the use of dried blood spots (DBS) as an alternative to venepuncture. Blood obtained from finger prick or heel prick, when dried on a filter paper and transported in room temperature, can be used for both HCV antibody and HCV RNA testing. There are successful examples of DBS testing for RNA detection from the Republic of the Congo and among PWIDs in Australia.[199,200] DBS can be used for EIA detection with excellent reliability, and when positive can be followed by reflex testing for HCV RNA using another spot on the same card.[201] HCV RNA quantitation may be underestimated with DBS samples, but genotypes can be diagnosed with certainty. Thus, DBS samples can replace venepuncture in the diagnosis and also the monitoring of HCV treatment.

Several RDT methods are also used for antibody screening in DBS in addition to EIA. The diagnostic accuracy of five RDTs (Assure HCV Rapid Test, First Response HCV Card Test, HCV Rapid Antibody Test, Multisure HCV Antibody Assay and OraQuick), when assessed for the detection of HCV antibodies in DBS using whole blood have yielded encouraging results. The RDTs resulted in a specificity of 100% and a sensitivity varying from 98.6% to 100%, making these tests a viable option for screening large numbers of patients or when repeated screening is required as in PWIDs.[202]

In addition to capillary blood and dried blood, many point-of-care tests have been developed using serum and saliva for rapid diagnosis in low-cost settings As the name suggests, these point-of-care tests can be administered without the need for venepuncture, complex instruments, storage conditions, infrastructure and special training. This particularly applies to screening PWIDs, sex workers, homeless people and immigrants with limited access to screening facilities. These single use tests can be performed by nurse practitioners, pharmacists and even by trained non-medical staff. As the test is simple and can be read visually, the results are available with a short turnaround time of 30 minutes, hence the loss to follow-up is minimised. Thus, point-of-care tests have the potential to increase the number of people tested outside of standard medical facilities.

A systematic review and meta-analysis of the efficacy of 30 point-of-care RDTs revealed that OraQuick had the highest sensitivity and specificity for detection of HCV and performed better than EIAs.[203] OraQuick is the only test that is approved by the Food and Drug Administration (FDA) for HCV screening done either by capillary blood or by blood collected through venepunctures. OraQuick is also included as a first-line HCV RDT for screening in whole blood or plasma by the Centre for Disease Control (CDC). A more recent meta-analysis has also confirmed these findings.[204]

2.5.4.1 *Linkage of Screening to Treatment*

Increased uptake of testing and linkage of testing to care are identified as areas of need by the WHO to meet its target of HCV elimination by the year 2030. Clinician reminders to test for HCV, testing at community levels using trained lay workers, and integrating HCV testing and treatment at substance abuse centres and mental health clinics are some of the steps suggested by the WHO.[195]

2.5.5 *Global Prevalence*

Seroprevalence studies, in general, overestimate HCV burden because they include both treated and spontaneously resolved infections. However, due to the low cost and easy availability, seropositivity is a measure of HCV prevalence that is reported widely in most of the medical literature. To provide a comprehensive estimate of the disease burden prior to the availability of direct-acting antivirals (DAAs), Gower et al. conducted an extensive literature search looking at both anti-HCV prevalence and HCV RNA viraemic prevalence in addition to that of genotypes for all countries.[190] Among the 23 248 studies searched via PubMed and EMBASE database, 4901 were chosen for the analysis. This included seroprevalence data from 87 countries that made up 88% of the adult world population, and thus measured 84% of the HCV population worldwide. Information on HCV RNA positivity was available for 54 countries. Countries with higher than 5% HCV seroprevalence included

- Mongolia (10.8%; 95% CI, 8.7–15.6%), Turkmenistan (5.6%; 95% CI, 1.1–6.7%) and Uzbekistan (11.3%; 95% CI, 6.4–13.1%) in Central Asia;
- Pakistan (6.7%; 95% CI, 1.6–10%) in South Asia;
- Egypt (14.3%; 95% CI, 10.3–18%) in North Africa;

- Gabon (11.2%; 95% CI, 2.1–20.7%) in Sub-Saharan Central Africa;
- Nigeria (8.4%; 95% CI, 3.9–12.8%) and Cameroon (11.6%; 95% CI, 4.3–12.8%) in Sub-Saharan Western Africa.

The viraemic prevalence was also correspondingly higher in these countries. Overall worldwide prevalence, as measured by antibodies, was 1.6% amounting to 115 million individuals. When measured by RNA it was 1.1% equating to 80 million individuals. This analysis excluded populations at risk, such as patients with haemodialysis, cancer patients and PWIDs, as it was thought to be not representative of the general population.

2.5.6 *Disease Burden in Vulnerable Population*

As currently DAAs are widely available, it becomes more critical to know the exact prevalence of HCV infection in vulnerable population. As per the popular quotation by Lord Kelvin, a Scottish physicist, "If you cannot measure it, you cannot improve it".

2.5.6.1 *Among Prisoners*

Chak et al. reported the seroprevalence of HCV in those incarcerated in prisons in the United States to be in the range of 23% to 39%.[205] The Bureau of Justice Statistics from the United States reported a seroprevalence of 31% on screening 57 018 individuals from 1209 correctional facilities.[205]

Vital information on the HCV prevalence in Australian prisoners was obtained from the National Prison Entrants' Bloodborne Virus Survey (NPEBBVS) report.[206] This unique epidemiological service is conducted every 3 years in multiple jurisdictions in Australia to monitor the trajectory of prevalence of HCV, other bloodborne viruses and sexually transmitted infections in prisoners. In 2016, the survey was conducted for 2 weeks, in 17 correctional centres across Australia, excluding New South Wales and Western Australia. There were 431 study participants with a participation rate of 50%. Notably, there was over-representation of the indigenous people in the survey (27% as against the national standard of 2.8%). The HCV-antibody prevalence was 22%, reduced from 31% detected in the previous survey. As expected, there was a significantly higher prevalence in the PWIDs.

2.5.6.2 *Among PWIDs*

In the Western world, injection drug use (IDU) is the commonest mode of acquisition of HCV. A recent multistage review has reported on the overall prevalence of IDU in people aged between 15 and 64 years and that of bloodborne viruses in this population.[207] This study estimated that globally about 15.6 million people between the age of 15 and 64 years inject recreational drugs. Women comprise about 30% of this population in Western countries compared to 3% in Asia. Among PWIDs, 52.3% (95% uncertainty interval, 42.4–62.1%) were HCV-antibody positive, 9.0% (95% uncertainty interval, 5.1–13.2%) were HBV-surface-antigen positive and 17.8% (95% uncertainty interval, 10.8–24.8%) were HIV positive. The prevalence in PWIDs reported elsewhere in the literature varies from 27% to 93%.[205] This wide variation is due to the age difference in the populations studied, as younger patients had a lower incidence of HCV. The prevalence also varies according to the gender of PWIDs. Based on an Australian survey of 16 000 PWIDs visiting Needle and Syringe Program (NSP) sites between the period 1998 and 2006, it became apparent that women who inject drugs (WWIDs) are at a higher risk of developing HCV and HIV infections. This risk was the highest during the early years of injecting practice, due to the repetitive use of injecting apparatus.[208]

Harm-reduction measures aimed at PWIDs to reduce HIV and HCV spread include anti-retroviral therapy (ART), condom distribution, HIV testing, NSPs and opioid substitution therapy (OST). Larney et al. reviewed the availability and provided an assessment of the extent of these harm-reduction services globally.[209] They measured this against the standard set by the WHO, the UN Office on Drugs and Crime (UNODC) and the Joint United Nations Programme on HIV and AIDS (UNAIDS). Of the 179 countries with PWIDs, NSPs were available in 93 countries and OST in 86 countries. When the actual extent of these services was measured, it was far below the WHO indicator (<100 needles and syringes distributed per PWID per year; <20 OST recipients per PWID per year).

Four countries, namely, Australia, Austria, Norway and the Netherlands provided high coverage of both NSP and OST services. Unfortunately, only 1% of the world's PWIDs live in these four countries. The study highlighted the insufficient extent of provision of harm-reduction services globally. In part due to these services in Australia, the number of new HCV infections, 14 000 in the year 1999 have dropped to 8500–9000 in the year 2013 and have been stable since then.[210,211]

2.5.6.3 *Among Psychiatric Patients*

Due to the contraindications of anti-HCV therapy with interferon, psychiatric patients were a marginalised group with no incentive for proactive HCV screening until the availability of HCV treatment with DAAs. Research worldwide has revealed that patients with serious mental illness are more susceptible to infection with bloodborne viruses, such as hepatitis B and C viruses (HBV and HCV, respectively) and human immunodeficiency virus (HIV).[212-214] This is due to the frequent prevalence of risk factors, such as IDU, high-risk sexual behaviour, sexual exploitation, social isolation, lack of awareness and living in poor socioeconomic conditions.[212-214]

A systematic review of published prevalence studies of bloodborne viruses in patients with severe mental illness from 1980 to 2015 in various databases including Cochrane Library, Medline, Cumulative Index of Nursing and Allied Health Literature (CINAHL), PsychInfo, EMBASE and Database of Abstracts of Reviews of Effects (DARE) was conducted by Hughes et al.[214] The report included a meta-analysis with an estimated pooled prevalence in addition to data for each continent and a sensitivity analysis on the quality of prevalence studies. From the initial selection of 373 reports, the authors chose 91 publications for review after excluding duplicates and those deemed unsuitable. HCV prevalence was assessed in 28 studies covering 14 888 patients. Regions, such as Europe and North America, with low-prevalence rates of bloodborne viruses, paradoxically showed higher HCV prevalence in mentally ill patients. The 17 studies from North America revealed a pooled prevalence estimate of 17.4% (95% CI, 13.2–22.6%), which is strikingly higher than the 1.6% prevalence reported from the general population.[190] The prevalence rate from Asia was 4.4% (95% CI, 2.8–6.9%) as measured by seven studies. From Europe, six studies were included and revealed a prevalence of 4.9% (95% CI, 3.0–7.9%). There was only one study included from Australia in this analysis that revealed a prevalence of 3.1% (95% CI, 1.0–9.3%).[215] Apart from Australia, a paucity of studies from Europe and the United Kingdom was also noted. Most of the studies were conducted on inpatients and used a convenience method of sampling. Hence, the authors urged policy-makers and researchers in mental health services to prioritise the conduct of high-quality epidemiological research, avoiding the aforementioned limitations with the help of representative patient samples.

Gunewardene et al. set out to measure HCV prevalence in all patients who gave consent in two psychiatric acute inpatient units in an Australian major city hospital.[215] Unfortunately, due to limited funding, the study included only high-risk patients in one centre. Unit A, which screened 77 of all consenting patients with a participation rate of 80%, revealed a prevalence rate of 3.2%. Identifiable risk factors were present in all HCV-positive patients in this unit. In Unit B, those with IDU or a history of blood transfusion, were invited to participate. In 40 patients thus tested (which constituted 18% of admissions), the HCV prevalence was 41.7%. Thus, the authors concluded that in both instances of selective and not-so-selective screening of psychiatric inpatients, HCV prevalence was higher than that of the general population of 1%. The authors also suggested that pre-test and post-test counselling were crucial in this patient population and commented on the burden screening placed on a busy inpatient unit. Utilising drug and alcohol counsellors may help mitigate this and increase screening rates. The study did not report on HCV RNA status of the antibody-positive individuals. In addition, Unit B screened only patients with IDU or a transfusion history, omitting other significant risk factors, such as incarceration and migrant status. Selective screening may not be ideal, as patients may not be aware of the risk factors or admit to risk factors.

In contrast to these findings, the only other Australian study on HCV in psychiatric patients reported an HCV prevalence of 19.7%.[213] Lacey et al. initially measured the proportion of patients screened for HCV in a busy inpatient unit in a major Australian capital city.[213] They offered an education and counselling programme for a period of 6 months, delivered by a research assistant. This included delivering written information on HCV to psychiatric inpatients, pre-test counselling, risk factor assessment, serological testing followed by post-test counselling and a referral to an infectious diseases unit if serology was positive. A detailed risk factor assessment was also carried out in all consenting patients. The authors were primarily interested in finding whether the programme made a difference to the number of psychiatric inpatients screened for HCV, in addition to measuring the seroprevalence of HCV. As expected, the HCV screening doubled from 9% to 18% with the intervention. However, only 25% of the admitted patients consented to the study. Nearly 20% of the study cohort was HCV positive. Interestingly, two-thirds of the study participants reported sharing injecting equipment. Among those with HCV seropositivity, IDU was present in all of them, with 92% reporting sharing injecting equipment. In addition, high-risk sexual behaviours were also highly prevalent in this cohort with 40% reporting unprotected anal intercourse. A quarter of them were also receiving money in exchange for sex. In summary, this study confirmed the

high risk of HCV in patients with mental illness that could be responsive to educational and counselling interventions.

2.5.6.4 *Screening in Psychiatric Patients*

The acceptability and feasibility of routine screening of psychiatric patients for bloodborne viruses were confirmed in a practice improvement study by Sanger et al.[216] The authors approached 105 adult patients in a psychiatric hospital at London for bloodborne viruses screening over a year. Of this 105, although 87 had the capacity to consent, only 57 (66%) consented to the study. Interestingly, neither patients nor staff were distressed by the testing process. A total of ten patients were found to have current or past evidence of these infections including four patients with HCV. Three new HBV cases and one new HIV case were identified. The authors suggested that, given the high prevalence of bloodborne viruses and the acceptability of screening among these patients, routine screening of psychiatric patients for bloodborne viruses should be given priority.

Despite this high prevalence, only a small minority receive screening.[217] Lack of sufficient knowledge about the spread of HCV infection and treatment methods among mental health support workers could also be a contributory factor in poor screening.[218] In Australia, there is a significant disparity between the number of patients living with HCV infection and the number of patients treated, despite a sharp increase in the number of infected patients with advanced liver disease.[219] The fact that 25% of infected patients still remain undiagnosed implies that certain marginalised but high-risk patient groups need to be screened. Screening performed by practitioners focussing on high-risk populations has been shown to be beneficial in terms of both the number of patients tested for HCV and identifying those who are seropositive.[195]

Psychiatric patients with the frequent coexistence of multiple risk factors for HCV, such as IDU, incarceration and high-risk behaviours, represent a target population that can be easily accessed with health facility-based screening. Health provider-based screening during an admission to a psychiatry unit would be an ideal opportunity to look for this potentially curable infection. Screening for HCV infection in high-risk patient populations is the first step towards the goal of its eradication.

2.5.7 *Cost-Effectiveness of Screening*

Screening people born during the period 1945 to 1965 with HCV-antibody testing in primary health settings in the United States was found to be cost effective, provided screening was followed by treatment with either interferon or non-interferon therapy.[220] Screening followed by interferon and ribavirin therapy was associated with an incremental cost-effectiveness ratio (ICER) of USD 15 700 per quality-adjusted life year (QALY) gained, whereas the ICER increased to 35 700 for each QALY gained when DAAs were used.[220] Eckman et al. evaluated the cost-effectiveness of one-time screening of all adults over 18 years of age in the United States, using Markov modelling in comparison to birth cohort testing as mandated by guidelines.[221] When compared to no screening, universal screening of all adults in the setting of a population prevalence more than 0.07% and treatment for those who tested HCV positive, was associated with a cost less than USD 50 000 per QALY. The cost was USD 11 378 per QALY when one-time universal screening and treatment was compared to birth cohort screening. Hence, the authors concluded that universal one-time screening and treatment for HCV infection was cost effective.

The recent European Association for Study of Liver (EASL) guideline has recommended screening for HCV in areas of intermediate prevalence, that is 2–5%.[194] The cost-effectiveness of HCV screening is topical with the current unrestricted availability of DAAs in Australia. Screening a high-risk population, such as psychiatric patients for HCV, has the potential to diminish lifetime risk of developing advanced liver disease and hence may be cost effective. Although it has not been studied in this patient population, a Belgian study examined the cost-effectiveness of HCV screening and treatment in the general population and in certain high-risk groups, such as emergency department attendees, PWIDs and men who have sex with men (MSM).[222] The investigators applied the Belgian data to a theoretical model. They used a combination of a decision analytical model for HCV screening and diagnosis, and a Markov model for treatment simulation. They arrived at the conclusion that the outcome was cost effective (ICER less than EUR 10 000 per QALY) to screen the general population once and every 5 years, PWIDs once, and the emergency room patients once. The ‘screen and treat’ strategy is also supported by a recent Australian study confirming the cost-effectiveness and the QALY gain in treating PWID.[223]

2.5.8 *Treatment*

Treatment of HCV infection with easily administered oral DAAs has been a pivotal medical breakthrough. It has transformed HCV infection from a progressive disease leading to cirrhosis of the liver and requiring liver transplantation to a simple viral infection that can be easily cured. Australian guidelines for HCV management recommend that all people with HCV should be treated, with the only exclusion being poor survival over the next 12 months due to a non-HCV-related illness.[196] Historically, chronic HCV infection was treated with a combination of interferon injections and ribavirin over 6–12 months. This treatment was associated with many adverse effects and low efficacy. With the advent of DAAs, which act on multiple steps in the HCV replication cycle, anti-HCV therapy is of shorter duration ranging from 6 to 16 weeks (depending on the genotype and viral load). In addition, it is associated with high SVR and better tolerability. The first-generation DAAs, such as Harvoni (sofosbuvir+ ledipasvir), were specific for HCV genotypes. The current generation of DAAs, such as Epclusa (sofosbuvir + velpatasvir) and Maviret (glecaprevir + pibrentasvir), are pan-genotypic, obviating the need for genotypic assessment in limited resource settings. Treatment should be preceded by a thorough assessment of the disease severity and the extent of liver involvement. Although there are no treatment restrictions in Australia, people with advanced liver disease should be identified for ongoing surveillance and variability in treatment regimen. A FibroScan® cutoff value of 12.5 kPa identifies patients with cirrhosis. In the absence of its availability, aspartate aminotransferase to platelet ratio index (APRI) >1 can be used to identify such patients with advanced liver disease.

2.5.8.1 *Sustained Virological Response and Its Benefits*

Sustained virological response (SVR) is defined as lack of detectable virus (HCV RNA) at 12 weeks after antiviral treatment and is the goal of HCV treatment. In view of the excellent correlation between SVR at 12 and 24 weeks, SVR at 12 weeks is accepted widely as the endpoint of HCV infection.[224] Cure of HCV infection is synonymous with SVR, with minimal chance of the virus relapsing after it is achieved. The strongest evidence in favour of the superior efficacy and tolerability of DAAs comes from a systematic review of 42 English language studies with at least two Food and Drug Administration (FDA)-approved regimens with two DAAs.[225] The review concluded that SVR rates were in excess of 95% in genotype 1 (GT-1) HCV infections without cirrhosis even in HIV-infected patients.

The lower SVR (78–87%) was for genotype 3 (GT-3), especially in the setting of decompensated cirrhosis. It was reassuring to note that the safety profile of DAAs was favourable, with <10% discontinuation rate.

Achieving SVR is associated with many benefits including those associated with improvement in liver function tests, resolution of inflammation and regression of fibrosis in patients without established cirrhosis. Achievement of SVR in non-cirrhotic patients enables them to be discharged from hepatology services in the absence of reinfection or other causes of liver disease, such as obesity, alcohol or HBV infection. In patients with cirrhosis, the benefits include regression of fibrosis, regression of cirrhosis, reduction in portal pressures, reduced risk of hepatic decompensation, avoidance of liver transplantation, reduction in rate of new HCC formation or recurrence of HCC after locoregional therapy, and liver-related and all-cause mortality.[226] The risk of HCC is often diminished but never abolished completely.

SVR (regardless of therapy) was shown to reduce the incidence of cirrhosis-related complications and all-cause mortality in HCV-infected patients, even in the presence of significant comorbidities and cirrhosis.[32,227] There was more than 70% reduction in the risk of progression to hepatic decompensation and HCC. Moreover, with SVR, there was a 58% reduction in the incidence of cardiovascular events and a 56% risk reduction in the occurrence of bacterial infections. Thus, it is clear that the benefits of SVR extend far and beyond improvement in liver function.

The mortality benefits of DAAs were demonstrated in both patients with and without advanced liver disease due to HCV.[30,31] In the Veterans Affairs Hepatitis C Clinical Case Registry, 15 509 patients with Fibrosis-4 (FIB-4) score > 3.25, who received DAAs, were studied and a 84% reduction in the incidence of HCCs in those who had SVR was demonstrated.[31]

With the help of a hybrid decision making and Markov model, both the short-term and long-term economic advantages of ledipasvir and sofosbuvir combination therapy in patients with HCV GT-1 was demonstrated by Younossi et al.[228] Cost-utility analysis has confirmed the cost-effectiveness of DAA therapy from the perspective of society with a lower willingness-to-pay threshold in many developed countries.[33]

HCV infection is appropriately described as a systemic disease in view of its hepatic and extrahepatic adverse effects on the well-being of patients and patient-reported outcomes (PROs) in addition to the economic impacts.[33] Younossi et al. compared HRQoL scores (using Short Form 36 Health Survey, SF-36) between patients at baseline and while on treatment: 12 and 24 weeks of therapy with interferon + ribavirin, DAA + ribavirin and DAA without ribavirin.[229] DAAs were associated improved PROs even during therapy. Higher mental health scores were also reported with DAAs. The importance of obtaining SVR was further highlighted by a comparison in PROs between those who attained SVR and those without SVR.[230] SVR was associated with improved scores from baseline in addition to sustained increase over the follow-up time. As expected, lack of SVR was associated with sustained reduction in PRO during the same time.

Eradication of HCV has been shown to favourably influence the outcome of certain extrahepatic manifestations including occurrence of new onset diabetes, improved glycaemic control and decreased the risk of diabetic complications in patients with diabetes, occurrence of myocardial infarction and neurological events, stroke, cryoglobulinemic vasculitis, glomerulonephritis and non-Hodgkin's lymphoma.[226]

Therefore, the benefits of HCV treatment extend well beyond the medical frontier into social and economic aspects as well. Moreover, due to the lack of adverse effects with the DAAs, treatment of patient groups that had contraindications to interferon and ribavirin therapy, such as patients on haemodialysis, immunosuppression and psychiatric illness, is facilitated.

2.5.9 *MOCs for Treatment of HCV Infection in Australia*

Australia has become a world leader in HCV treatment uptake since DAAs have become available and is on track towards the WHO target of HCV elimination by 2030.[231] The number of HCV-infected people awaiting treatment was about 227 000 people in the pre-DAA era.[219] With the availability of easily administered and effective DAAs the uptake of antiviral therapy has improved. Between the period 2016 and 2018, a quarter of this population has been treated.[232] Providing unrestricted access to DAAs led to increased treatment uptake. The Pharmaceutical Benefits Scheme (PBS) permits DAAs to be prescribed "by a doctor well versed in the management of chronic HCV or after consultation with a gastroenterologist, hepatologist or an infectious disease physician with experience in treating chronic HCV".[196]

Thus, general practitioners (GPs) can prescribe DAAs after they have consulted specialists through phone, teleconferencing, email, telefax or mail.

In addition, DAAs are available for use in prisons through PBS under Section 100 of the National Health Act (NHA) 1953. With prescription by GPs, DAAs can also be dispensed by community pharmacies under Section 85 of the NHA. These strategies by the Pharmaceutical Benefits Advisory Committee facilitate unrestricted and easy access to DAAs for all types of prescriptions.

Extending the benefit of HCV eradication to rural and remote populations of Australia is a major undertaking; however, the ease of administration of DAAs facilitates the delivery of care in a nontraditional manner. Innovations in models of care (MOCs) and decentralisation of HCV care to avoid bottlenecks associated with specialist tertiary care in hospitals are the strategies employed to augment treatment capacity.

2.5.9.1 *Traditional Specialist-Led MOCs*

Gastroenterologists, hepatologists and/or infectious disease physicians have been the major care providers in the management of HCV infection through tertiary clinics in the public or private health systems in Australia. They are responsible for assessment of disease severity and planning of antiviral therapy in addition to prescribing and patient monitoring during and after therapy. Their involvement is essential in the management of complex patients, such as those with advanced chronic liver disease, comorbidities, decompensated cirrhosis, hepatocellular carcinoma, renal dysfunction and post-transplantation, and those with HIV co-infection. However, relying on them for management of uncomplicated chronic HCV patients without advanced fibrosis could slow down treatment uptake and prolong the disease burden in the population. Instead, these patients can be easily managed with well-developed protocols by GPs or nurse practitioners.

In recent times, the primary role of specialists has appropriately transitioned to a supportive one that remotely monitors and assists treatment delivery by these alternate providers as discussed in the following sections.

2.5.9.2 *GP-Led MOCs*

Even in the interferon era, there were successful examples of GP-led MOCs for HCV treatment with remote input from specialists. The Extension for Community Healthcare Outcomes (ECHO) is one such example.[233]

The ECHO model was designed by the University of New Mexico Health Sciences Centre to promote delivery of HCV-infection treatment to the under-privileged rural communities on par with that provided at academic teaching hospitals. This model capitalised on the trust placed by rural communities on local GPs and easy access to local clinics to deliver expert advice and guidance to them. The model took advantage of advances in telecommunication and conducted virtual HCV clinics to achieve communication between experts (in hepatology, infectious diseases, pharmacy and psychiatry) at the university health centre and healthcare providers in the community. The model catered to 16 community sites and five prison sites. The community providers presented their cases and the university experts provided treatment advice and clinical mentoring. HCV treatment consisted of pegylated interferon alpha-2a (peginterferon) and ribavirin. A prospective cohort study was conducted to evaluate the efficacy and safety of HCV treatment in the model, relative to the standard of care provided by the University of New Mexico Health Sciences Centre. Among the 261 patients treated in the ECHO model and 146 treated at the university centre, there was no significant difference in SVR-24 (58%). Interestingly, the incidence of adverse effects leading to cessation of therapy was significantly higher in the traditional model cohort. Thus, this study established that successful treatment for a complex condition, for example HCV, can be provided in the community by local providers with adequate support by specialists, without increased adverse effects. It also achieved its purpose of treating many underprivileged Hispanics who were otherwise unable to obtain tertiary care.

Baker et al. reported a successful example of a primary-care model in New South Wales, Australia, delivering interferon-based treatment with specialist supervision for 41 GT-1 patients in seven GP practices, with SVR as high as 70%.[234] With unrestricted access of interferon-free DAAs in Australia, HCV treatment by GPs is a far easier option than interferon-based treatment. Assessment of liver fibrosis is essential, and uncomplicated patients without significant fibrosis can be treated in the community with no need for referral. Simple tools for

GPs and nurses to assess fibrosis are provided by the Gastroenterological Society of Australia at http://www.gesa.org.au/resources/hepatits-c-treatment/.

Using liver stiffness measurements, the feasibility of identifying advanced fibrosis due to HCV in the community was established by Bloom et al.[235] In their study of 780 patients in the community, the authors concluded that the prevalence of advanced fibrosis in the community (17%) was similar to that seen in tertiary hospitals. Identification of advanced fibrosis facilitated prediction of liver-related events.

Australia has appropriately responded to the challenge of the HCV burden by increasing treatment uptake since the availability of DAAs on PBS.[231] From March to December 2016, DAA uptake in Australia was estimated based on an analysis of a sample of PBS database. It was encouraging that the number of prescriptions by GPs for DAAs increased from 8% in March 2016 to 31% in December 2016.[231] However, the bulk of prescriptions (62%) were still given by specialists in 2016. Nevertheless, according to a report issued by the Kirby Institute on new HCV treatment initiation, over the time period from March 2016 to December 2018, the number of GP prescriptions of DAAs rose to 40% in March 2017 and was maintained around 39% until the end of 2018.[236] The overall percentage of prescriptions by specialists stood at 49%, but the number of specialist prescriptions reduced to 33% in the year 2018.[232,236] Across the different states in Australia, prescriber frequency trends were different. Queensland had the highest percentage of GPs prescribing DAAs (37%), followed by Tasmania (35%) and Western Australia (34%). This healthy trend of GP prescriptions must be supported with education, training and feedback because it plays a pivotal role in meeting the WHO target of eradication of HCV by 2030.

2.5.9.3 *Nurse-Led MOCs*

Nurse-led MOCs have been in practice for the management of HCV since the interferon era, well before DAAs. In this model experienced and qualified specialist nurses or nurse practitioners deliver and/or support HCV treatment within protocols under remote supervision by specialists. There are several successful reports of HCV care delivery by advanced practice nurses or nurse practitioners in many states sponsored by state governments.[29,173] The Western Australian model described the successful use of telehealth, nurse practitioners, and enhanced

shared care pathways between specialists and GPs to improve case detection and treatment initiation for HCV-infected rural and remote patients.[29,237]

Hepatitis nurses serve as a bridge between specialist tertiary centres and rural GPs. Their role in the HCV management cascade is crucial as they provide education, support to patients, case detection, treatment initiation and training, and support to GPs.[29,238] The role of nurses in HCV care, complementing that provided by specialists, was reported by Biddle et al. from a nurse-led clinic (NLC) at Geelong, Victoria.[173] The nurses were primarily involved in the preliminary assessment of patients including their fitness for treatment. They ensured the completion of appropriate tests prior to appointment with the physicians. In addition, they assessed the patient's social situation, including alcohol misuse and coexisting psychiatric morbidities. They also provided education about secondary prevention for HBV and HCV infections. This resulted in more efficient use of the doctors' time. The authors designed the primary outcome to be a comparison of the waiting time between new referrals to a physician clinic with and without a prior nurse clinic appointment. There was no significant difference in the waiting time for a physician appointment, but patients who attended the nurse clinic first were less likely to miss a subsequent physician appointment. The authors attributed this to allaying anxiety faced by patients about a doctor visit. Although the study lacked a qualitative approach, it is highly likely that the NLC provided the necessary education and information, and mentally prepared patients for the HCV therapy offered by the physicians. Patients respected and positively evaluated the educational and psychological support provided by specialist nurses during HCV therapy.[239] This was evident from a questionnaire-based data collection of 106 patients receiving HCV therapy in Ireland. Hence, it is clear that the specialist nurses can enhance the HCV care provided by physicians by offering preliminary assessment and education, along with monitoring and ongoing psychological support during therapy.

In addition to the above-mentioned roles, hepatitis nurses also perform diagnostic tests, such as transient elastography, and plan antiviral treatment. Authorised nurse practitioners with certain experience are permitted to prescribe DAAs under the general schedule (Section 85). This has expanded their role from a supportive to a main role in HCV treatment.

Furthermore, it has enabled these nurse-led models to play a unique role in promoting HCV treatment uptake in difficult-to-treat populations, such as prisoners, people on OST and mental health patients where traditional doctor-based models have not been successful. Recent

evidence for the efficacy of nurse-led HCV treatment has come from the New South Wales prison system with 36 correctional centres.[27] The authors described HCV treatment uptake in 698 inmates within the first year of DAA availability from March 2016 to February 2017. After initial screening for HCV, HBV and HIV by the prison authorities, confirmatory RNA tests, genotype, viral load, liver function tests, platelet count and prothrombin time were ordered by population health nurses within each prison. Confirmed cases were then reviewed by visiting clinical nurse consultants who operated within well-defined protocols for obtaining a detailed history, physical examination, fibrosis assessment by transient elastography and further investigations for cirrhosis, if identified. They subsequently discussed the cases suitable for treatment with infectious disease physicians who then prescribed DAAs. Patients identified to have cirrhosis were reviewed by specialists in person or via telemedicine, and then DAAs were prescribed. For patients deemed unsuitable for self-medication, drug therapy was administered by the nurses. Only 10% of the patients had to be reviewed by specialists, reiterating the fact that nurse-led models can manage most HCV infections within a specific protocol in the era of DAAs. SVR per protocol was 92%, reflecting the safety and efficacy of this remote MOC.[27]

Prisons offer exclusive opportunities to screen and offer HCV treatment to otherwise-difficult-to-reach populations. The Victorian prison sites, managed by the Victorian State-wide Hepatitis Program, reported a successful decentralised care in the form of nurse-led HCV care assisted by telemedicine.[28] During the 13-month study period, 546 patients were identified as suitable for treatment of the 962 patients assessed. 416 were prescribed DAAs. Similar to the New South Wales' experience, 82% of the patients were low-risk patients and managed by nurses under remote supervision by specialists. Per protocol SVR was reported as 96%.

2.5.9.4 *Community-Based MOCs*

There are several reports in favour of community treatment models for HCV.[240,241] Hashim et al. reported a community healthcare model for HCV called Integrated community-based Test stage TREAT model (ITTREAT model), in a substance misuse service centre (drug and alcohol treatment centres), which they described as integrated, multidisciplinary and one stop.[240] The project was developed to fill the gap of a model with a focus on HCV treatment as well as addiction services to improve compliance with HCV treatment. The all-inclusive model was developed with a view to provide assessment of liver fibrosis, HBV vaccination, nurse-initiated HCV treatment under supervision of hepatologist, OST, screening of bloodborne viruses and

social and psychiatric input in one place. Personnel who delivered care included a community nurse who performed transient elastography under supervision of a hepatologist, and a psychiatrist in the clinic with the support of social workers and peer advocates. The model did not exclude but supported those with ongoing alcohol and drug addiction by providing home delivery of medications when needed.

The real-world outcomes of project ITTREAT (2013–2021) were recently reported.[242] There was a good uptake of HCV DBT in these clinics. Up until the year 2018, 573 people were recruited and more than 90% had past or current alcohol and drug exposure. In this study 74% received DAAs and the remaining 26% received interferon-based treatment. SVR in the intention-to-treat analysis was 87% (90% on DAAs). Patient response to HCV testing and treatment uptake was in excess of 95% with a low risk of HCV reinfection (2.63 per 100 person-years; 95% CI, 0.67–10.33). There was a significant improvement in HRQoL as measured by EQ-5D-5L (the 5-Dimension 5-Level Health Scale version by the EuroQol). In addition, the cost associated with the project was also reported. It cost GBP 171 per case detection, and the mean cost for SVR (excluding medication) was GBP 702 ± 188. A subsequent qualitative evaluation of the project examined the experiences and understanding of parties concerned, including the patients and project staff.[243] Personal interviews using semi-structured questionnaires captured the in-depth experiences of patients, whereas the staff participated in focus group discussions. The consensus was that the project enabled HCV treatment uptake without any stigma. Patients welcomed the lack of negative hospital experiences that they had experienced in the past; they were well engaged with the drug and alcohol services. However, those who had quit drug and alcohol addiction attached a stigma to obtaining HCV services through the same services. One of the important barriers was the unstable nature of the patient population. Despite these, the all-encompassing community project delivered by dedicated hepatitis nurses was well received.

Excellent treatment uptake (81%) and SVR (85%) were reported from a multidisciplinary community clinic servicing disadvantaged and uninsured patients in the United States.[241] The team comprised a nurse practitioner, nurse, psychologist, gastroenterologist, social worker, dietitian and a pharmacist. It is important to note that many of these patients were difficult to treat with psychiatric comorbidities, were unemployed or had a history of illicit drug use.

An interesting study by Tait et al. provided a snapshot of the healthcare response to HCV in the geographical region of Tayside, Scotland, during the period 1994 to 2014.[244] The MOC evolved from a predominantly hospital-based provision of HCV care with interferon-based treatment, towards a nurse-assisted HCV treatment service to a multidisciplinary-managed care network with full-time specialist nurses providing care. The latter included routine DBS testing of all patients presenting to addiction services, opening more outreach clinics and a pathway that could be accessed by all health professionals working in prison and addiction services. This observational cohort study found a striking reduction in all-cause mortality in the group that accessed HCV care by the multidisciplinary pathway, independent of HIV status or SVR. In particular, engaging in HCV treatment in interdisciplinary addiction centres positively impacted drug-using behaviour, resulting in reduced drug-related deaths. This study supports multidisciplinary care accessed in the community resulting in expansion of HCV diagnosis and treatment services, without reliance on tertiary medical care. Improved survival of a difficult-to-treat population was an important outcome of this treatment model.

2.5.9.5 *MOCs for Rural and Remote Communities*

Lack of access to specialist medical care is a major challenge for the rural and remote communities in Australia. Geospatial analysis of HCV treatment uptake and prescriptions in the first years of its availability revealed an unequal distribution.[245] Compared to regional areas, major cities had a higher proportion of treatment initiation rates per individual. In addition, these areas saw a high proportion of treatment prescriptions by specialists compared to regional areas. Models that are based in major city hospitals and support care in remote areas with visiting specialists in outreach clinics are needed to ensure equitable distribution of care. These models should also focus on educating local GPs and community nurses to enable self-sufficiency in the future.

One such successful MOC for regional Queensland was described in a prospective cohort study by Lee et al.[246] The model involved categorising HCV treatment referrals into uncomplicated and complicated patients. Patients with history of prior treatment, major comorbidities and with decompensated cirrhosis were reviewed in a tertiary-care hospital liver clinic. Uncomplicated patients were managed by addiction specialists, sexual health physicians and GPs. The model was coordinated by dedicated nurses who performed transient elastography and collected patient information. GPs were provided with clearly defined protocols to guide them in

treatment initiation and monitoring. Remote assistance was provided by phone calls when required. Regular information sessions for GPs were provided by gastroenterology specialists and sexual health physicians, with support from Australasian Hepatology Association (AHA), Australasian Sexual Health Alliance (ASHA) and Australasian Society for HIV Medicine (ASHM), as well as from pharmaceutical industry. Community awareness of HCV treatment was facilitated by advertisements (such as Cairns: Hep C Free by 2020), billboard signs, posters in local buses and newspapers, and by creating volunteer groups (such as CHAT, the Cairns Hepatitis Action Team). These campaigns were aimed at GP clinics, needle exchange centres, shelters for the homeless and addiction health support groups to create awareness among the most vulnerable populations. From February 2016 to December 2017, in North Queensland, 734 patients including Indigenous Australians (9%) received DAA therapy. The SVR rate in per protocol analysis was 94% with lower rates only in treatment-exposed patients. A quarter of the patients were detected to have cirrhosis, but they did not have lower SVR. The proportion of decompensated cirrhosis was low (<10% of cirrhotic patients). This study highlights the safety and efficacy of treatment initiation by nonspecialists. As expected, the treatment outcome, the SVR rate, was similar among specialists, GPs and sexual health physicians (92–94%). Hence, by presenting a decentralised model that utilised the services of clinical nurse consultants, GPs and sexual health physicians, Lee et al.[246] have demonstrated a model that can be successfully employed in rural and remote communities.

2.5.9.6 *MOCs for PWIDs*

Sharing unsterile injecting equipment is the commonest cause of chronic HCV infection in Australia. Ongoing drug use is no longer considered a contraindication to commencing HCV treatment as the rates of reinfection are quite low.[243,247] Moreover, treatment works as prevention in this vulnerable population. With network-based treatment of PWIDs, Hellard et al. have shown how HCV treatment with DAA can favourably influence HCV prevalence in these injecting communities.[248] The investigators collected information about injecting practices and networks for a cohort of PWIDs in Melbourne during the period 2005 to 2007. With the help of a discrete time, stochastic transmission model, HCV transmission was simulated in a network of 524 nodes in this cohort. Of the five treatments strategies tested, ‘treat your friends’ was the one associated with a significant decline in the prevalence rate from an assumed 50% to 33%.

This patient population would benefit from a holistic model that includes harm-reduction steps including opioid substitution, access to safe injecting equipment and addiction counselling, in addition to HCV disease assessment and treatment. This requires a team of professionals working in collaboration that is preferably delivered in the community. Project ITTREAT is one such successful example as outlined in the previous section.[240] There are many successful Australian studies showcasing HCV treatment in PWIDs in liaison with addiction clinics. Approximately 50 000 Australians receive OST. These clinics are ideally poised to initiate HCV treatment in these patients. Jeffrey et al. reported excellent SVR rates with interferon (up to 62%) in PWIDs attending a naltrexone implant clinic similar to non-injection drug use patients.[249] A prospective observational cohort called ETHOS (Enhancing Treatment for Hepatitis C in Opioid Substitution settings) was established in New South Wales to study HCV patients attending one Aboriginal community clinic, two community health centres and five OST clinics.[250] HCV care offered by specialists and nurses was integrated into OST services. Even in the interferon era, the study reported a good trend in HCV treatment uptake, particularly in those patients with good social support. This study also discussed patients' perspectives of HCV treatment. A total of 331 of 387 (86%) patients consented to treatment, but 213 of 387 (55%) did not proceed due to insufficient knowledge about HCV. These clinics also used peer support workers to promote discussion on HCV spread, education and need for treatment, which complimented the role of nurses who provided HCV assessment and treatment.[251] Despite ongoing IDU, HCV patients in the ETHOS cohort were shown to have good adherence rates and SVR with interferon-based therapy.[252]

Another successful multidisciplinary Australian model predominantly led by nurses, the Nepean Liver Clinic Model, was described by Fragomeli et al.[253] This model included several satellite clinics and served as a one-stop clinic for all HCV-related services in an IDU patient population. The aims were to promote knowledge of HCV and HBV infections, screening and diagnosis, to mitigate spread of the disease with education, to augment treatment uptake and ongoing management of the liver disease, and to promote adoption of healthy lifestyle practices related to liver health. By establishing collaborative practices with OST and alcohol addiction staff, the project minimised stigma associated with addiction and created a conducive, familiar atmosphere for patients to seek HCV therapy. Hepatitis nurses delivered HCV care, including performance of transient elastography and planned treatment in liaison with hepatologists. The nurses coordinated care with other satellite clinic staff, OST clinic staff, and drug and alcohol

clinic staff. OST clinic nurses also assisted by administering interferon and monitoring for adherence to therapy.

The model also offered educational resources to GPs about HCV management. In the 11th year since its inception, 300 patients had been reviewed and 40 were initiated on antiviral treatment. Patients were able to start treatment in satellite centres facilitated by this model. In addition, GP education resulted in more referrals to the clinic. However, poor patient attendance was a major barrier to successful treatment completion.

In addition to the obvious benefit of linkage to treatment, HCV screening and notification in newly infected PWIDs was found to have a sustained beneficial effect on drug-injecting behaviour, with up to a reduction of 10% over a mean follow-up period of 39 months.[254] Caven et al. performed a systematic review on the effect of engagement with HCV treatment on the drug-injecting behaviour of PWIDs. Analysis of five studies that investigated this revealed a positive influence of HCV treatment in terms of drug-injecting frequency and sharing of injecting apparatus.[255]

The ramifications of HCV detection and initiation of treatment on both all-cause mortality and deaths directly related to drugs in PWIDs were described in multiple retrospective case–control studies as a part of the 'hooked C' project.[256] Comparison of HCV polymerase chain reaction (PCR)-positive patients and spontaneously resolved PCR-negative patients did not show a difference in overall survival or drug-related deaths. However, patients who did not engage in treatment had a much higher risk of dying than those who showed engagement (adjusted OR = 12.15; 95% CI, 7.03–20.99; $p < 0.001$).

In a similar fashion, drug-related deaths were also significantly different between the two groups as engagement with screening and treatment reduced the risks. Since DAA treatment is protocol driven with less need for much interaction between patients and medical care providers, the authors investigated the differences in mortality between those who had treatment with interferon and those who were treated with DAAs. Surprisingly, survival in both the groups was the same. The act of seeking treatment, rather than the actual treatment per se, provided the observed benefits. It was thus concluded that engagement with HCV treatment was associated with lower all-cause mortality and drug-related mortality in PWIDs with HCV infection.[256]

2.5.9.7 *MOCs for Psychiatric Patients*

Interferon therapy has been the standard of care for treatment of chronic HCV infection until recently. Psychiatric comorbidities that are often encountered in HCV-positive patients were relative contraindications to HCV treatment in the era of interferon therapy. Treatment with interferon was frequently associated with the occurrence of moderate to severe depression, and it was more frequent in patients with history of depression.[257] With DAAs, the prospect of successful HCV treatment is high for this patient population. The safety of DAAs and ease with which the treatment can be integrated within psychiatric services have opened the possibility of novel models of care for psychiatric patients.

Compliance with daily ingestion of DAAs for 12 weeks may be a challenge for psychiatric patients. Psychiatrists can play an important role by sharing HCV care in addition to their ongoing psychiatric management in the era of DAAs.[258] Herold et al. reported a successful case of reverse integration, wherein psychiatrists coordinated the delivery of physical health needs, such as HCV treatment.[259] In a patient with schizophrenia, HCV treatment was organised by a community psychiatrist and delivered along with clozapine therapy, aided by remote supervision of a hepatologist.[259] Mental health nurses ensured intake of DAAs along with clozapine, and blood tests were monitored periodically resulting in successful viral clearance.

The treating psychiatrist is also the best person to identify the appropriate time to initiate treatment, as compliance with treatment is likely to be better when the psychiatric comorbidity is in remission.

More work needs to be done to define the disease burden in this population and plan strategies that will enable screening and linkage to care. Engaging with care, initiation of therapy and subsequent adherence to therapy are challenges that would require a team of professionals with designated roles. This should ideally include a psychiatrist, mental healthcare worker and hepatitis nurse who can liaise with a hepatologist and a pharmacist. There is limited evidence in the literature for such a multidisciplinary model to address HCV burden in this vulnerable patient group.

Chapter 7 describes a multicentre study of HCV prevalence in psychiatric inpatients, a MOC developed and subsequent treatment experience.

2.6 COST-EFFECTIVENESS OF MOCs IN THE TREATMENT OF HCV INFECTION

This section describes various studies on the cost-effectiveness of HCV treatment relevant to the last study in the thesis in Chapter 8, which examines the cost-effectiveness of various MOCs in the management of HCV infection.

Several studies have established the cost-effectiveness of DAAs over interferon and ribavirin therapy at any stage of liver disease.[41,260] Using a decision analytical Markov model of liver disease progression, on a base-case of a 50-year-old patient with chronic HCV, treatment using interferon and interferon-free DAAs were compared in two scenarios: one treating all patients and the other with staging-driven treatment.[41] Unrestricted DAA therapy was associated with the most improvement in life expectancy and the most reduction in the development of cirrhosis, decompensated cirrhosis, HCC and the need for liver transplantation. DAA therapy for all was associated with an ICER of AUD 15 709 per QALY and emerged as the most cost-effective option.

The cost benefits of increasing DAA uptake were estimated by disease progression models based on the numbers treated during the year 2013 across Australia.[261] It was predicted that an increase in the HCV treatment efficacy with DAAs and increased uptake without any restriction would be associated with a reduction in HCV mortality of 43%, a reduced development of compensated and decompensated cirrhosis of 52% and 48%, respectively, and a 24% reduction in cumulative costs of management of HCV by 2030, compared to the base-case situation (as in the year 2013) with no increase in uptake or efficacy of treatment.[261] If DAAs were given without any increase in uptake, the benefits would be very modest with just a 4% reduction in mortality and a 2% reduction in the development of cirrhosis of the liver, with no significant reduction in the economic impact.

Cost-effectiveness of DAAs was assessed in a cohort of newly infected PWIDs with a deterministic model of HCV treatment and progression of liver disease.[223] It was estimated that compared to 40% cumulative mortality seen in the scenario without antiviral treatment, mortality with late treatment (only for patients with advanced fibrosis) was 8% and that with early treatment (before advanced fibrosis) was 7%. In terms of the QALYs gained, the late treatment scenario was better than no treatment, resulting in 19.43 QALYs against 16.45,

respectively. This was achieved with an added cost of AUD 15 132 (11 246–18 922). The ICER for late treatment was AUD 5078 (2847–5295) per QALY gained in comparison to no treatment at all. On the other hand, the early treatment scenario was associated with much higher QALYs (21.70) at an extra cost of AUD 53 926 (95% CI, AUD 51 115–55 781) compared to no treatment, resulting in an ICER of AUD 10 272 (95% CI, AUD 5689–13 690) over the latter. When late and early treatment strategies were compared, it resulted in a QALY gain of 2.27, if patients were treated early with an increase in expenditure to AUD 38 794 (95% CI, AUD 34 789–41 367) for an ICER of AUD 17 090 (95% CI, AUD 2847–63 282). Although this was still cost effective in 90% of the simulations, at a willingness-to-pay threshold of AUD 50 000 per QALY gained, it did not achieve statistical significance. Sensitivity analysis at a treatment cost of AUD 100 000 revealed similar findings for cost-effectiveness with ICERs below the Australian threshold of AUD 50 000 per QALY gained in both the treatment strategies, compared to not treating with DAAs. However, when the DAA cost was reduced to AUD 10 000 per course, the cost-effectiveness of all treatments was improved, and early treatment resulted in an incremental improvement in ICER of AUD 1365 per QALY relative to late treatment. These costs did not include the benefits of early treatment on further transmission of HCV, resulting in reduced prevalence, and hence less need for treatment. Using a dynamic HCV transmission model with the existing Australian prevalence rates, it was calculated that if 40 of 1000 PWIDs were treated per year, it would result in 50% reduction in HCV prevalence in 15 years. This reduction in prevalence could increase to 75%, if 54 per 1000 PWIDs were treated every year.[262] However, the cost-effectiveness of such interventions was not studied.

Project ECHO is a hub-and-spoke model that enables the care of complex chronic patients to be centred at primary health clinics with community physicians, with the remote assistance of specialists at tertiary care medical centres via weekly video conferences.[233] The sustainability of any novel model of care (MOC) should be established with a thorough economic evaluation. Therefore, cost-effectiveness analysis was used to compare the benefits of management of HCV infection in the primary-care setup, with and without Project ECHO.[263] Applying the Markov model of disease progression, QALY in years, costs and life expectancy were compared between ECHO and non-ECHO patients with HCV. Compared to the non-ECHO model, more patients were evaluated for treatment in the ECHO model (17% vs. 58%). The QALYs gained in the ECHO model were 15.04 compared to 13.63 in the non-ECHO model. The total healthcare expenses were higher in the ECHO model by USD 158. The ICER for

ECHO model was USD 10 351 per QALY. The study confirmed the cost-effectiveness of the ECHO model and supported the need to reimburse the model.

Kondili et al. compared the cost-effectiveness of 'prioritised' treatment of HCV-infected patients with advanced (more than F3 stage) fibrosis versus universal treatment of all those infected with HCV (irrespective of the stage of fibrosis), in a real-life Italian cohort who underwent HCV management in all public centres in Italy from May 2014 to December 2015.[260] The analysis was performed using an adapted multicohort Markov model from the perspective of healthcare providers (from National Health Service) in a lifetime horizon. The simulations were performed in the above-mentioned two scenarios for 8125 treatment-naive patients in the Italian cohort. Using Italian costs, fixed DAA costs (EUR 15 000 per patient) and SVR rates derived from the literature based on genotypes, ICER and QALYs were calculated. It was determined whether the universal policy resulted in ICERs below the willingness-to-pay thresholds considered acceptable for Europe (EUR 20 000–40 000 per QALY). Treating all patients was associated with a cost of EUR 301 788 399 and resulted in 93 131 QALYs, whereas prioritised treatment cost EUR 269 841 561 and yielded 89 490 QALYs. Thus, universal treatment was cost effective with an incremental cost of EUR 31 946 839 and incremental QALYs of 3641. The ICER was EUR 8775 per QALY gained. When the analysis was repeated from a European perspective with the DAA costs being EUR 30 000 per person, it revealed an ICER of EUR 19 541.75 per QALY gained for the universal treatment pathway. The ICER was the most sensitive to DAA costs.

These findings were replicated in another smaller Italian study that analysed a cohort of 1000 HCV-infected patients undergoing two treatment plans with elbasvir and grazoprevir combination therapy. Patients were above the age of 35 years, and the analysis was over a 60-year time horizon using a Markov model.[264] The treatment plan that was unrestricted to the category of severe fibrosis was associated with more costs and higher QALYs, resulting in an ICER of EUR 15 555–74 804 per QALY.

Therefore, the cost-effectiveness of early treatment with DAAs, irrespective of the fibrosis stage, is well established. However, there is scarcity of data on cost-effectiveness of different MOCs employed to address various patient populations with HCV.

The cost-effectiveness of HCV testing and treatment (Hepatitis C Community Alliance to Test and Treat, HepCATT) intervention, with a dedicated nurse assisting in case findings and treatment linkage at addiction centres, in comparison to standard HCV treatment in England was analysed.[265] The reduction in HCV infections and deaths due to HCV resulting from the intervention were assessed from the year 2016 to over 50 years. Costs and QALYs as health benefits were assessed. For every 1000 PWIDs, over 50 years, the intervention was found to prevent nearly 50% of infections and prevent 75 deaths. The mean ICER achieved was GBP 7986 per QALY. As in other studies, the intervention was more cost effective with further reduction in DAA costs.

A systematic review of the methodological approaches of cost-effectiveness modelling studies by Chhatwal et al. revealed the lack of real-world patient data.[35] Cost-effectiveness analysis supporting alternate MOCs that are uniquely practised in Australia, using real-life data, are not available. Such studies would be useful to help validate current Australian MOC and to help formulate health policies across other regions. This in turn could potentially enhance HCV treatment uptake worldwide and assist with meeting the worldwide WHO target of HCV eradication by 2030. One of the studies in this thesis (discussed in Chapter 8) describes the cost-effectiveness of the four MOCs used to treat HCV by DAAs.

Thus, the review of literature highlighted the need for designing novel MOCs in the management of various stages of CLD and evaluation of their impact on clinical, health education, self-management and economic aspects of disease management.

3. THE IMPACT OF A COORDINATED CARE MODEL ON LIVER-RELATED EMERGENCY ADMISSIONS AND SURVIVAL IN PATIENTS WITH CIRRHOSIS OF THE LIVER

A major part of this chapter was published in the *Medical Journal of Australia*, and the publication details are as follows:

> Coordinated care for patients with cirrhosis: fewer liver-related emergency admissions and improved survival.
> **Ramachandran J**, Hossain M, Hrycek C, Tse E, Muller KR, Woodman RJ, Kaambwa B, Wigg AJ. *Med. J. Aust.*, **209(7)**:301–305, 2018.

Authors' contribution details are given below:

> **Jeyamani Ramachandran**: Study conception and design, data collection, analysis and interpretation of data, drafting of the manuscript, editing and approval of final manuscript.
> **Monowar Hossain, Chris Hrycek**: Data collection.
> **Richard Woodman**: Statistical analysis.
> **Alan Wigg, Kate Muller, Richard Woodman, Billingsley Kaambwa**: Critical revision of the manuscript for important intellectual content and overall supervision.

3.1 SYNOPSIS

Background and aims: Cirrhosis of the liver is a chronic disease associated with frequent hospitalisations and high mortality. A coordinated model of care (MOC), comprised of specialist care during hospitalisation and post-discharge care by a nurse-led Chronic Liver Failure Program (CLFP) is practised for patients with decompensated cirrhosis in Flinders Medical Centre since 2010. The study postulated that this coordinated MOC would lead to reduced frequency of liver-related emergency admissions (LREAs) and improved survival in comparison to standard care. The prime aim of this study was to compare the incidence of LREAs and survival in patients after hospitalisation for decompensated cirrhosis between two major hospitals, one with a coordinated care model (U1) and the other with standard care (U2). The second aim was to study the predictors of mortality.

Methods: In this retrospective observational cohort study, patients discharged after cirrhosis-related decompensations over a year from October 2013 were followed up until the end of October 2016, liver transplantation (LT) or death. All hospitalisations were analysed using electronic medical records. The incident rate ratio (IRR) for LREAs was calculated by negative binomial regression. Survival analysis was performed using the log-rank test and Cox-regression analysis.

Results: Sixty-nine patients from U1 and 54 patients from U2 were studied for a median (interquartile range, IQR) of 530 (690) days. The incidence rate of LREAs was higher in U2, with a mean 1.6 (95% CI, 1.29–1.86) admissions per person-year, compared to 1.1 (95% CI, 0.94–1.35) admissions per person-year in U1. The adjusted IRR showed a significantly lower rate in U1 (IRR = 0.52; 95% CI, 0.28–0.98; $p = 0.042$). The adjusted probability of LT-free survival in U1 and U2 at the end of 3 years was 67.7% and 37.2%, respectively. Independent predictors of LT-free survival were Charlson's comorbidity index (hazard ratio, HR = 1.27; 95% CI, 1.05–1.54; $p = 0.014$), LREAs within 90 days of discharge (HR = 3.60; 95% CI, 1.87–6.92; $p < 0.001$) and admission to U2 (HR = 2.54; 95% CI, 1.26–5.09; $p = 0.009$).

Conclusions: Management of decompensated cirrhosis using a coordinated MOC was associated with significantly improved survival and lower LREAs. The model should be evaluated in prospective trials before further recommendations can be made.

3.2 INTRODUCTION

Cirrhosis of the liver is a chronic disease that is associated with multiple complications, as it progresses from a compensated stage to a decompensated stage.[2] The decompensated stage is characterised by recurrent hospital admissions that can be as frequent as 50% within 90 days of hospital discharge.[13] Hospital admissions are often associated with significant deterioration in the health status of cirrhotic patients due to hospital-acquired infections that contribute to morbidity and mortality.[94] In short, hospital admissions in cirrhosis translate to a tremendous burden on the healthcare system from both the clinical and economic aspects.

In the management of chronic liver disease (CLD) there is increasing recognition of the need for a coordinated system of care known as the chronic disease management (CDM). This has been successfully studied and implemented in cardiac failure and chronic obstructive pulmonary disease.[266] In cirrhosis of the liver, the CDM is at a preliminary level, with no substantial evidence base to support it. In a randomised pilot trial, Wigg et al. demonstrated that patients with decompensated cirrhosis, when treated within a Chronic Liver Failure Program (CLFP) based on CDM principles, were more likely to attend clinic and surveillance (endoscopic and radiological) appointments.[11] Since 2010, the CLFP has been an essential part of care at Flinders Medical Centre for patients with decompensated cirrhosis. Hospital readmission rates (HRRs) and survival data are considered key quality indicators for evaluating cirrhosis management. Therefore, the aim of this study was to compare these measures between a unit with coordinated model of care (MOC) for the management of decompensated cirrhosis and another major hospital in the health region, where only standard care is practised without a coordinated MOC.[8]

3.3 METHODS

3.3.1 *Study Design*

The study was a retrospective observational cohort study involving two major hospitals with different models of care (MOCs) for the management of decompensated cirrhosis.

3.3.2 *Models of Care*

Unit 1 (U1) is a 593-bed hospital located in the periphery of the city. It contains all services including an intensive care unit, accident and emergency unit, and inpatient gastroenterology

and hepatology units. It is also the centre of the state liver transplantation (LT) service. In U1, a coordinated MOC is practised, patients with decompensated cirrhosis are managed in a liver unit, staffed by gastroenterologists with a special interest in hepatology, and the post-discharge care is coordinated through the CLFP. The CLFP is a CDM type of intervention as described in a previous study.[10] It is a multifaceted intervention covering four CDM domains including delivery system redesign, decision support, self-management support and clinical information systems.

Key aims of the intervention are improving adherence to evidence-based care and enhanced post-discharge monitoring of patients with the provision of protocol-based checklists and subsequent care plans for post-discharge care, post-discharge phone calls, home visits, self-management support with enhanced patient and carer education, patient action plans for complications (ascites and hepatic encephalopathy), access to day care therapeutic large-volume paracentesis and a rapid access to care pathway for deteriorating patients.

Two experienced hepatology nurses, both working 0.6 full-time equivalents, supported the CLFP in close consultation with the hepatologists. Patients are provided with emergency contact numbers of the nurses during office hours and are encouraged to call when they feel unwell with worsening abdominal distension, altered sensorium or gastrointestinal bleed.

Unit 2 (U2) is a 680-bed hospital located in the city centre. It also contains all services including an intensive care unit, accident and emergency unit, and inpatient gastroenterology and hepatology unit. Here, patients with decompensated cirrhosis are managed either on a general gastroenterology ward or on a general medical ward. There is no organised nurse follow-up. Patients attend the follow-up clinics as advised at the time of discharge. There is no nurse liaison between the specialists and the patients. There is no planned elective paracentesis. Patients present to the emergency department when they become unwell. Patients in both the units had equal access to liver transplantation (LT) via referral to the South Australian Liver Transplant unit at U1.

3.3.3 *Inclusion and Exclusion Criteria*

Using International Classification of Diseases, Tenth revision (ICD-10) codes for cirrhosis and its complications (C22.0, K65.2, K65.9, K70.0, K72.0, K72.1, K72.11, K72.90, K72.91,

K74.0, K76.6, K76.7 and R18.0) patients who were admitted to both U1 and U2 with a diagnosis of cirrhosis and related decompensating event during the recruitment period (October 2013 to October 2014) were considered for the study. The following patients were excluded:

- death during the initial admission or referral to palliative care;
- lost to follow-up after initial admission;
- admission for an elective procedure in the absence of hepatic decompensation.

From U1, 62 patients were excluded due to the following reasons. 44 were elective admissions with no decompensation of cirrhosis, 3 were lost to follow-up immediately after their index admission discharge, 15 died or were discharged to palliative care during their index admission; and 129 patients did not have any evidence of liver disease. 69 patients were included and formed the study cohort in U1.

From U2, 68 patients were excluded for the following reasons. 22 patients died during the index admission, 27 patients who were admitted for HCC procedures without any decompensation and 19 patients did not have cirrhosis. 54 patients were included and formed the study cohort in U2.

Included patients were followed up until the end of October 2016, LT, loss of follow-up or death. As this study involved voluntary access to the public health system, overlap between U1 and U2 admissions was unavoidable. Patients were assigned to U1 or U2 according to their predominant care unit. In this manner, we also excluded patients who had an equal number of admissions to both hospitals (n = 5) and patients who were admitted to other hospitals in the state health system after initial admission in either of these U1 or U2 (n = 4).

3.3.4 *Classification of Admission Types*

The electronic medical records of the study cohort were analysed for all hospital readmissions during the study period. These hospitalisations were classified into liver-related emergency admissions (LREAs), liver-related elective admissions, liver-unrelated emergency admissions and liver-unrelated elective admissions:

- *LREA* was defined as a hospitalisation that was unplanned and resulted in a patient hospitalisation via presentation to the hospital emergency department for any of the following conditions: variceal bleeding, ascites, hepatic encephalopathy (HE), sepsis, cellulitis, pneumonia, urosepsis, hepatorenal syndrome, hepatic hydrothorax, electrolyte disturbances and hepatopulmonary syndrome.
- *Liver-related elective admissions* included planned admissions that did not involve the emergency department. Common examples of these admissions included abdominal or thoracic paracentesis, radiological procedures for hepatocellular carcinoma (HCC), LT workup and same-day admission for deterioration detected in the outpatient clinic.
- *Non-liver-related emergency admissions* included chest pain, abdominal pain unrelated to liver disease, fractures, trauma, and alcohol intoxication or substance abuse wherein the patients did not have any liver-related issues.
- In a similar vein, when patients had planned admissions for non-liver-related issues, such as cataract surgery, wound grafting, plastic surgery, fracture internal fixation, hernia surgery or gall bladder surgery, they were classified *non-liver-related elective admissions*.

The presence of significant medical comorbidities was measured using Charlson's comorbidity index. As this study was a quality improvement initiative it was exempt from formal ethics committee review, but approval was obtained from both the institutional ethics committees.

3.3.5 *Statistical Analysis*

IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA) and Stata, version 14.1 (Stata Corp, USA) were used for statistical analysis. The total number of hospital readmissions (that is, the number of admissions between discharge from their initial admission and either death or the end of the follow-up period) for each patient was calculated. The number of admissions in each of the various categories (LREAs and others) in the same time period was also estimated, in addition to the total number of readmissions during the first 30 and 90 days after their initial discharge. The median time to first readmission after discharge was also estimated.

The mean incidence rates (with 95% confidence intervals [CIs]) of liver-related and non-liver-related emergency and elective admissions were calculated with Poisson exact methods.

Admission rates for the two units were compared and incident rate ratios (IRRs) calculated by negative binomial regression, adjusted for age, sex, aetiology, comorbid conditions (Charlson's index), and the unit treated (UI and U2), and Model for End-Stage Liver Disease (MELD) score.

Independent *t*-tests and chi-squared (χ^2) tests of independence were used to compare patient characteristics of the two hospitals for normally distributed continuous and categorical variables, respectively. Mann–Whitney *U*-test was used to compare non-normally distributed data. Parameters with a *p*-value < 0.20 from a univariate analysis of 30-day and 90-day LREA were considered for inclusion into a multivariate logistic regression model to identify independent predictors, in which variables with $p < 0.05$ were considered significant.

Differences in estimated transplant-free patient survival rates between U1 and U2 were analysed using Kaplan–Meier methods and log-rank test (univariate analysis) and Cox regression (multivariate analysis). Censoring was performed at the time of death, LT, the end of the study period or when patients were lost to follow-up.

Variables with a *p*-value ≤ 0.15 in univariate Cox regression were considered for inclusion into a multivariate model, in which variables with $p < 0.05$ were considered as significant predictors of LT-free survival.

3.4 RESULTS

A total of 123 patients (69 from U1 and 54 from U2) were studied and the median (IQR) of follow-up time was 530 (690) days. The baseline clinical characteristics and demographics of the patients are provided in **Table 2**.

U2 had more patients with alcoholic cirrhosis than U1. However, there were no statistically significant differences between the two groups of patients other than a higher Charlson's comorbidity score for U1 patients (5.99 vs. 5.22; $p = 0.043$). The median (IQR) time to first readmission was 67 (179) days and was not different between the two hospitals – U1: 74 (169) days versus U2: 51 (200) days, $p = 0.80$.

Table 2. Comparison of baseline clinical and demographic characteristics of patients from UI and U2.

Demographic characteristics	**U1 (*N* = 69)**	**U2 (*N* = 54)**	***p*-value***
Age (years) mean (SD)	59.2 (10.4)	56 (10.2)	0.08
Gender, male, *n* (%)	47 (68.1)	36 (66.7)	0.86
Nonalcoholic aetiology, *n* (%)	23 (33.3)	10 (18.5)	0.07
Charlson's comorbidity index, mean (SD)	6.0 (2.3)	2.2(1.9)	0.043
Diabetes, *n* (%)	29 (42)	14 (25.9)	0.06
MELD score, mean (SD)	17.4 (6.3)	16.8 (5.8)	0.61
Follow-up, days, median (IQR)	622.00 (702)	508.50 (700)	0.35

IQR: interquartile range; MELD: Model for End-stage Liver Disease; SD: standard deviation; U1: Unit 1; U2: Unit 2.

*Independent *t*-tests and chi-squared tests of independence were used to calculate *p*-values.

3.4.1 *Liver-Related Emergency Readmissions*

The complications of cirrhosis encountered at initial hospitalisation and first LREA for the entire study cohort and for the individual hospitals are given in **Tables 3** and **4**, respectively. At baseline ascites-related readmissions were the most frequent, whereas HE showed a nonsignificant increase in frequency at the subsequent hospitalisation.

Table 3. Indications for hospital admission at baseline and first LREA in the entire study cohort.

Indications	**Baseline admission (*N* = 123)***, ***n* (%)**	**First readmission (*N* = 80)***, ***n* (%)**
Ascites and related	70 (57%)	38 (48%)
HE	33 (27%)	32 (40%)
Variceal bleeding	33 (27%)	14 (18%)
Sepsis related*	21 (17%)	18 (23%)
Miscellaneous**	8 (10%)	12 (14%)

HE: hepatic encephalopathy; LREAs: liver-related emergency readmissions.

*Sepsis-related admissions included spontaneous bacterial peritonitis or cellulitis, pneumonia, urosepsis, bacteraemia and septic arthritis.

**Miscellaneous included portal hypertensive gastropathy-related bleed, portal vein thrombosis, peptic ulcer bleed causing decompensation, alcoholic hepatitis and bleeding due to thrombocytopaenia.

***The sum of the numbers does not equal the total number in the cohort, as patients often had more than one complication.

Table 4. Comparison of indications for hospital admission at baseline and first LREA between U1 and U2.

Indications for hospital admission	**U1**, ***n*** **(%)**	**U2, *n* (%)**
Ascites related		
Baseline admission	45/70 (64%)	25/70 (36%)
First readmission	22/38 (58%)	16/38 (42%)
Hepatic encephalopathy		
Baseline admission	17/33 (51.5%)	16/33 (48.5%)
First readmission	19/32 (59%)	13/32 (41%)
Variceal bleeding		
Baseline admission	11/33 (33%)	22/33 (67%)
First readmission	4/14 (29%)	10/14 (71%)
Sepsis related		
Baseline admission	10/21 (48%)	11/21 (52%)
First readmission	14/18 (78%)	4/18 (22%)

U1: Unit 1; U2: Unit 2.

When this was compared between the hospitals, at initial admission, the frequency of ascites-related admissions was higher in U1 than in U2 (65% vs. 36%) with a drop in subsequent ascites-related readmissions to 58% in U1 and increase in U2 (42%). Sepsis-related readmissions were more frequent in U1 than in U2, whereas variceal bleeding was the commonest decompensation seen in U2 both as an initial admission and as a readmission.

The observed rate of LREA across the whole study period for the entire cohort was a mean of 1.31 per person per year (95% CI, 1.15–1.48), consisting of 241 admissions over 184 person-years. The mean incidence rate of LREAs in U2 was 1.55 per person per year (95% CI, 1.28–1.85), comprising 119 admissions over 77 person-years. In U1, the mean incidence rate of LREA was lower at 1.14 per person per year (95% CI, 0.95–1.36), comprising 122 LREAs over 107 person-years. The unadjusted incidence rate ratio (IRR) for U1 versus U2 was 0.58 (0.32–1.05; $p = 0.07$).

This difference became significant after adjustment for age, gender, baseline MELD, alcoholic aetiology and the presence of medical comorbidities (IRR = 0.52; 95% CI, 0.28–0.98; $p = 0.042$).

Sixty-six per cent of the study cohort experienced at least one LREA; 62 (50%) had two or more LREAs and 41 (33%) had more than three (recurrent) LREAs. The number of recurrent LREAs was more frequent in U2 (41% vs. 26%, $p = 0.08$).

LREA within 30 days was observed in 13 (24%) and 9 (13%) patients in U2 and U1, respectively ($p = 0.10$). Significant predictors of 30-day admission were being managed in U2 (OR = 4.21; 95% CI, 1.27–13.91; $p = 0.02$), presence of ascites at baseline admission (OR = 4.57; 95% CI, 1.11–18.76; $p = 0.03$), encephalopathy on admission (OR = 3.81; 95% CI, 1.11–13.09; $p = 0.03$) and nonalcoholic aetiology (OR = 6.21; 95% CI, 1.81–21.3; $p = 0.004$).

LREA within 90 days was noted in 23 (47%) and 29 (41%) patients in U2 and U1, respectively ($p = 0.57$). The only significant predictive factor for 90-day readmission was the presence of HE on initial admission (OR = 5.05; 95% CI, 1.59–16.08; $p = 0.006$).

The incidence of elective (both liver and non-liver) and emergency (both liver and non-liver) admissions were compared between the two hospitals as listed in **Table 5**.

The incidence of liver-related elective admissions was higher for U1 compared to U2 (IRR = 4.60; 95% CI, 1.92–11.04; $p < 0.001$).

As CLFP organised and facilitated elective procedures, such as abdominal paracentesis and hepatocellular carcinoma-related radiological procedures, more often, liver-related elective admissions were significantly more frequent in U1.

3.4.2 *Liver Transplantation*

During the study period. two patients referred from U2 successfully underwent liver transplantation. Of the 12 patients from U1 listed for transplantation, nine had successful liver transplantations, one was delisted, and two died while on waiting list.

Table 5. Comparison of incidence rates of elective and emergency liver-related and non-liver-related readmissions between U1 (107 person-years) and U2 (79 person-years).

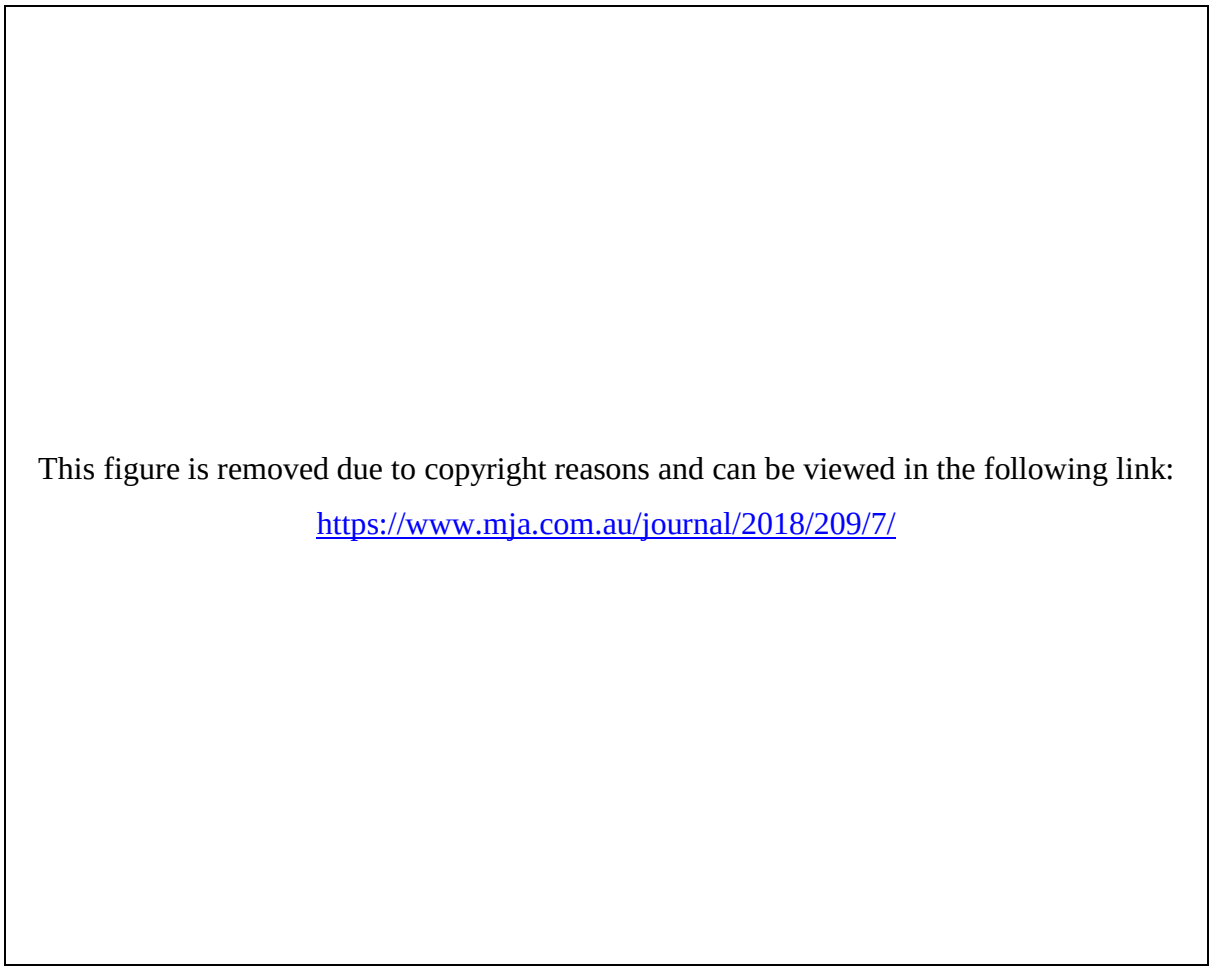
Admission category	**Rate of admissions Mean (95% CI/person-year)**		**IRR* (95% CI; *p*-value)**	
	U1	**U2**	**Univariate analysis**	**Multivariate analysis**
Emergency readmissions				
Liver related	1.14 (0.95–1.36)	1.55 (1.28–1.85)	0.58 (0.32–1.05; $p = 0.071$)	0.52 (0.28–0.98; $p = 0.042$)
Non-liver related	0.53 (0.40–0.69)	0.51 (0.37–0.70)	0.95 (0.51–1.81; $p = 0.89$)	0.72 (0.38–1.38; $p = 0.33$)
Elective readmissions				
Liver related	3.48 (3.14–3.85)	0.50 (0.36–0.69)	4.60 (1.92–11.04; $p < 0.001$)	4.42 (1.69–11.6; $p = 0.002$)
Non-liver related	0.22 (0.14–0.33)	0.08 (0.03–0.17)	2.62 (0.94–7.34; $p = 0.07$)	1.39 (0.47–4.10; $p = 0.55$)

*Incident rate ratio (IRR) was calculated by univariate and multivariate negative binomial regression.
U1: Unit 1; U2: Unit 2.

3.4.3 *Survival Analysis*

Estimated transplant-free survival functions were analysed using the Kaplan–Meier method. The unadjusted survival functions were different between the two units (at 2 years, it was 68% in U1 and 54% in U2), as shown in **Figure 5**, but did not reach statistical significance (p = 0.11, log-rank test).

Figure 5. Unadjusted survival functions compared between U1 and U2, analysed using Kaplan–Meier method and log-rank test.



On univariate survival analysis, the following factors were significantly ($p \leq 0.15$) associated with survival:

- unit treated (U2 vs. U1);
- MELD score;

- occurrence of any LREA;
- LREA within 30 and 90 days of discharge;
- nonalcoholic aetiology;
- presence of significant medical comorbidities.

Including these significant univariate predictors, age and gender were entered into multivariate analysis, carried out using Cox-regression method. The results are depicted in **Table 6**.

Table 6. Cox-regression survival analysis model of study patients with cirrhosis after adjusting for variables significant on univariate analysis.

Factors	**Model (*n* = 108)***
Age (years)	HR = 1.02; 95% CI, 0.99–1.07; *p* = 0.169
Female gender	HR = 0.76; 95% CI, 0.38–1.59; *p* = 0.477
Baseline MELD	HR = 1.04; 95% CI, 0.99–1.10; *p* = 0.074
Alcohol aetiology	HR = 0.83; 95% CI, 0.37–1.89; *p* = 0.673
Admission to U2	**HR = 2.54; 95% CI, 1.26–5.09; *p* = 0.009**
LREA within 90 days	**HR = 3.60; 95% CI, 1.87–6.92; *p* = <0.001**
Charlson's comorbidity index	**HR = 1.27; 95% CI, 1.05–1.54; *p* = 0.014**

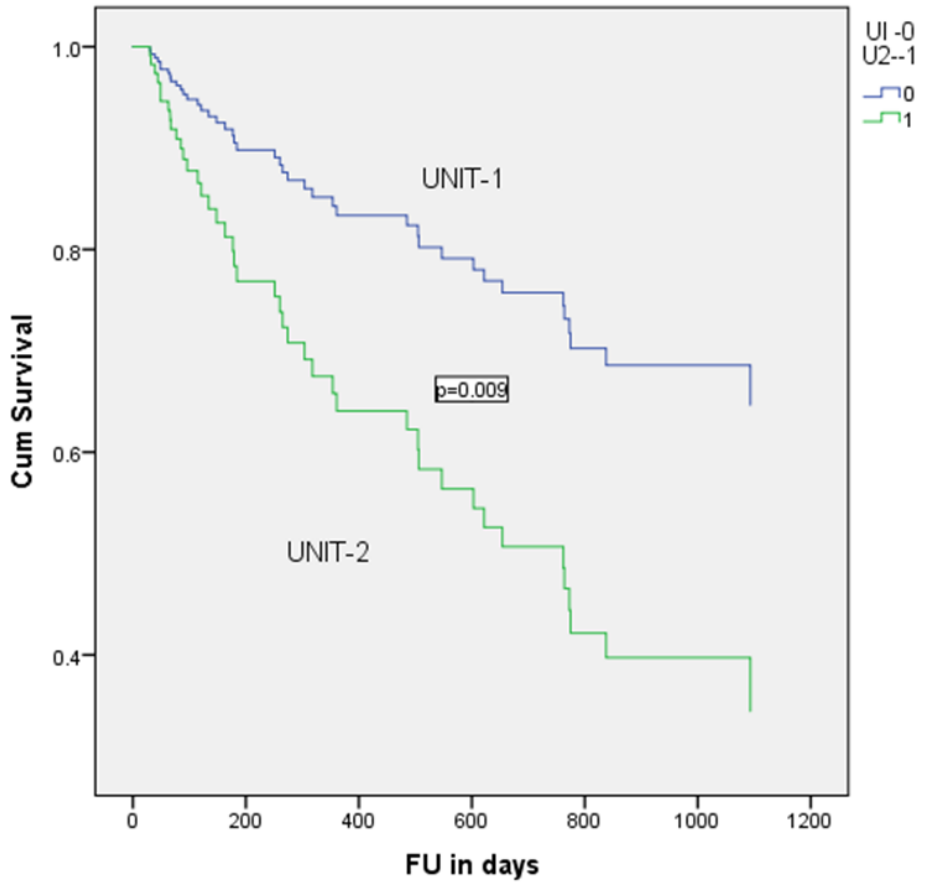
Bold indicates significant predictors of mortality.
LREA: liver-related emergency readmission; MELD: Model for End-stage Liver Disease.
*Full data available for 108 patients.

The following emerged as significant independent predictors of mortality:

- Unit 2 versus Unit 1 (HR = 2.54; 95% CI, 1.26–5.09; *p* = 0.009) ;
- LREA within 90 days of discharge (HR = 3.60; 95% CI, 1.87–6.92; *p* < 0.001);
- Charlson's comorbidity index (HR = 1.27; 95% CI, 1.05–1.54; *p* = 0.014).

The adjusted rates of transplant-free survival at 3 years were significantly different between units (67.7% and 37.2% in U1 and U2, *p* = 0.009) as shown in **Figure 6**.

Figure 6. Adjusted survival functions compared between U1 and U2 on Cox-regression analysis.



3.5 DISCUSSION

Decompensated cirrhosis is a complicated and resource-intensive chronic disease. With the increasing prevalence of cirrhosis and the persistent problem of recurrent readmissions, it is a healthcare priority to establish MOC that focus on effective delivery of the recent medical advances to this patient group.

In this study the long-term effects of managing decompensated cirrhosis using a coordinated MOC were evaluated, and key quality indicators were compared with another large hospital in the same metropolitan health region with routine care. A significantly reduced incident rate for LREA, in addition to reduced mortality, was found with the coordinated MOC. Reducing emergency admissions, some of which may represent high-value admissions, could have detrimental effects and lead to higher mortality.[12] It was, therefore, encouraging to observe that

the coordinated MOC with CLFP was associated with reduced mortality, in addition to reduced emergency admissions.

These findings appear to be in contrast to those of Kanwal et al. who reported the beneficial effects of early outpatient visits (within 7 days of hospital discharge) on survival (3.2% vs. 5.2%; HR = 0.60; 95% CI, 0.51–0.70) without a decrease in 30 day readmsision rates (15.3% vs. 13.8%; HR = 1.10; 95% CI, 1.02–1.19) in patients with cirrhosis after a hosptial discharge.[267] However, 35% of the primary and readmissions were not related to cirrhosis and 15% of early outpatient visits were to clinics unrelated to cirrhosis management. Unlike this study Morando et al. did not report any discordance between 30-day readmissions and mortality with improved post-discharge care.[127] The reduction in LREAs and mortality seen in U1 is consistent with the findings that adherence to quality indicators in the management of ascites, such as early paracentesis and commencement of diuretic therapy, reduced 30-day readmission and reduced 90-day mortality.[109]

Factors that could contribute to the differences between the two units were evaulated at the level of the patients, structural facilities and the care offered, as per current standards in clinical improvement literature.[268] With regard to patient factors, advanced age and nonalcoholic aetiology were found to be poor prognostic factors for mortality and 30-day readmission. Although these factors were more prevalent in U1, the clinical outcomes were better in U1. In addition, the disease severity was well matched between the two hosptials, ruling out patient-related factors as being responsible for the differences. As far as structural facilities were concerned, both hospitals had similar advantageous features, namely high cirrhosis volume, emergency departments, access to intensive care unit beds, teaching hospitals affiliated with universities and advanced endoscopic and radiological facilities.[268]

One key feature, namely the MOC, was distinctly different between the two hospitals. While the study cannot exclude other unknown factors that contributed to the important differences seen in LREA incidence and survival, it seems plausible that the coordinated MOC was a major driver of difference. However, it is difficult to dissect which specific aspects of the complex and multifaceted MOC were most likely to have contributed to the positive outcomes. The presence of a dedicated inpatient liver unit staffed by gastroenterologists with a special interest in hepatology and LT in U1 may be important, as the specialist care has been previously associated with reduced mortality.[269] Patients in U2 were cared for by a combination of

gastroenterologists with a special interest in hepatology, general gastroenterologists and general medicine specialists. In view of the rapid changes in knowledge in hepatology it may be difficult for general gastroenterologists and internists to offer the state-of-the-art care required for sick cirrhotic patients.[270]

It is also possible that the association of U1 with an LT unit could have positively influenced the outcomes. LT centres deal on a day-to-day basis with high volumes of patients with decompensated cirrhosis, and care in LT centres has previously been associated with less in-hospital mortality for cirrhosis.[268] However, attempts were made to correct for the direct effects of this potential bias by exclusion of all patients who were transplanted at U1 from the analysis. Despite exclusion of these patients, improved outcomes in terms of LREAs and survival persisted. Interestingly, being on a LT waiting list has been associated with increased LREAs, in contrast to the observation of fewer LREAs in U1.[3]

Although the influence of more specialised inpatient care cannot be excluded, the dedicated post-discharge monitoring programme, led by specialist hepatology nurses, was a likely critical driver of improved outcomes demonstrated in U1. These nurses greatly enhanced the post-discharge monitoring and were responsible for improved patient self-management, adherence to evidence-based care plans and conversion of emergency to elective-style admissions. The reduction in LREAs and mortality seen in U1 is consistent with the findings that adherence to quality indicators in the management of ascites, such as early paracentesis and commencement of diuretic therapy, reduced 30-day readmission and reduced 90-day mortality.[109]

Presence of comorbidities was associated with a higher mortality in the study cohort of patients with decompensated cirrhosis. This finding is similar to that reported by Powell et al. wherein cirrhotic patients with a Charlson's comorbidity index more than 3 had a signficiantly higher in-hospital mortality.[57] In this statewide study from Queensland, Australia, 40% of cirrhotic patients admitted to hospitals had evidence of associated comorbidites. This finding assumes importance with the increasing prevalence of nonalcoholic fatty liver disease (NAFLD) as a cause of CLD. NAFLD is associated with comorbidies, such as hypertension, diabetes mellitus, obesity and ischemic heart diseases.[46] Therefore, the impetus for coordinated MOC is more prounouced in the management of cirrhosis to reduce readmissions.

The vulnerability of the post-discharge period and need for a coordinated MOC to address this were confirmed by the findings of a recent study, which showed that medical advances in the past decade resulted in reduction of only in-hopsital mortality, without any change in mortality in the period up to 30 days after a hospital discharge in patients with decompensated liver cirrhosis.[7]. In this study the incidence of LREA within 30 days in U1 was only 13%. This figure compares favourably not only with U2 (24%) but also with published figures from other Australian and international centres. For example, Fagan et al. observed a 41% incidence of LREAs within 30 days in an Australian cohort of decompensated cirrhotic patients with ascites.[93] In a prospective multicentre study from the United States, 90-day readmissions occurred in 50% of patients with decompensated cirrhosis after a hospital discharge.[13] In a further retrospective study, readmissions within 30 days were noted in 37%, with 22% readmissions classified as preventable.[3]

Ascites-related admissions were the commonest cause for hospitalisation in this study, both at baseline and during follow-up. The frequency of ascites-related admissions was reduced at U1 but not at U2, during the study period. It seems likely, therefore, that the specific components of the coordinated MOC targeted at ascites were important and effective. An example of this included weekly nurse-led monitoring of electrolytes and weight among patients commenced on diuretics, which may have reduced admissions related to over-diuresis. A second example, in patients with more refractory ascites, was careful weight monitoring and nurse-facilitated elective paracentesis, which might have also prevented emergency presentations.

Hepatic encephalopathy was the other major cause of LREAs. Indeed, while both ascites and hepatic encephalopathy were associated with increased 30-day readmission, only hepatic encephalopathy was associated with increased 90-day readmissions. Despite the coordinated MOC, the occurrence of hepatic encephalopathy as an emergency admission was not reduced. Several key hepatic encephalopathy-specific interventions implemented by the coordinated MOC programme included education of patients and their carers concerning identification of early hepatic encephalopathy symptoms, escalating lactulose doses via action plans and enhancing adherence to rifaximin via education and adherence aids such as pill packs. Although these components of this care plan for U1 patients did not appear to reduce the frequency of hepatic-encephalopathy-related emergency presentation, they are still considered the key interventions. The possibility that they prevented increased numbers of hepatic-encephalopathy-related emergency admissions cannot be excluded. The only evidence for

interventions resulting in reduced hopsital admissions due to hepatic encephalopathycomes from a prospective study by Tapper et al.[128] Provision of electronic prompts for lactulose and rifaximin therapy for hepatic encephalopathy and appropriate treatment and antibiotic prophylaxis at discharge for patients with spontaneous bacterial peritonitis resulted in fewer 30-day readmissions with hepatic encephalopathy and shorter hospital stays. With a day-hopsital model for post-discharge care for cirrhotic patients, a lowering of 30-day readmissions and 12 month mortality were demonstrated in addition to lower costs of management of decompensated cirrhosis.[127]

The first limitation of the study is its retrospective design. Unmeasured variables could have influenced the results. The problem of nonrandomisation could have been reduced by propensity score matching of the two patient cohorts. Secondly, the relatively small sample size precludes us from making strong recommendations. Thirdly, all inpatients in U1 received speciality hepatology care unlike the practice in U2. The extent to which this difference influenced the final outcomes is difficult to quantify. However, the study highlights the variability of key quality indicators, such as mortality and LREAs, that can occur among patients with cirrhosis of the liver of similar severity managed within equivalent healthcare systems with different MOCs. In this perspective, there is a need for hospitals to monitor and report these indicators.

3.6 CONCLUSION AND FUTURE DIRECTIONS

Management of decompensated cirrhosis using a coordinated MOC demonstrated lower LREAs and better survival compared to standard care in this study. The study observations suggest that it is possible to achieve gains in these important quality indicators with relatively simple changes in care delivery and modest investments in outpatient-based hepatology nurses. The positive signals described in this study associated with a coordinated MOC with CLFP are clinically significant and encouraging. It suggests the feasibility of improving the care of this challenging patient group. However, verification of the clinical efficacy and cost-effectiveness of this MOC within a large multicentre prospective randomised controlled trial (RCT) is required.

Based on the information obtained from this retrospective study, a prospective multicentre RCT, The Australian Liver Failure trial (ALFIE), to study the effect of the CLFP in reducing

LREAs is underway. The sample size calculation for the trial was performed based on the assumption of an admission rate of three admissions per person per year in the usual care group (as was the case in U2), and a reduction of 20% in the treatment group, a sample size of 146 (50 per site) would be required to provide 80% power to detect a significant difference in event rates between the study arms at a type 1 error rate of $\alpha = 0.05$ with a median follow-up time of 18 months, and an allowance for a 20% attrition rate throughout the study period. The intervention will be along the lines described in the pilot study by Wigg et al.[11] The control arm will be the standard of care without any liver nurse initiated close follow-up. Both the study groups will be managed under speciality care in liver units. This study, which is currently in progress, includes the following patients:

1. Patients with cirrhosis of the liver.
2. Patients admitted to hospital with an episode of decompensation including any of the following:
    - ascites,
    - encephalopathy,
    - variceal bleeding,
    - spontaneous bacterial peritonitis,
    - hepatorenal syndrome.
3. Patients who have attended an outpatient liver clinic with a hospital admission in the past 6 months and a Child–Pugh B or C score.
4. Patients who are able to comprehend and willing to sign an Informed Consent Form (ICF) (West Haven Criteria = 0 or 1).
5. Patients with mild cognitive impairment, at the investigator's discretion.
6. Age ≥18 years.

Patients with active HCC, hepatic encephalopathy beyond grade1 and on LT waiting lists will be excluded. The study patients will be followed up for a total period of 24 months, death or LT. The CDM intervention will also be assessed for its cost-effectiveness and effect on quality of life in addition to its effects on LREA and survival. A qualitative analysis from patient, CLD nurse and gastroenterologist perspective will also form part of this study. The results of the RCT may provide more definitive evidence required to recommend widespread implementation of the coordinated MOC in the care of decompensated cirrhosis

4. VALIDATION OF A KNOWLEDGE QUESTIONNAIRE FOR PATIENTS WITH CIRRHOSIS OF THE LIVER

A major part of this chapter was published in the journal *Clinical Gastroenterology and Hepatology*, and the publication details are as follows:

> Validation of knowledge questionnaire for patients with liver cirrhosis. **Ramachandran J**, Woodman R, Muller K, Wundke R, McCormick R, Kaambwa B, Wigg A. *Clin. Gastroenterol. Hepatol*., **18(8)**:1867–1873, 2020.

Authors' contribution details are given below:

> **Jeyamani Ramachandran**: Conception and design of the study, analysis and interpretation of data, drafting of the manuscript and approval of the final version of the manuscript.
> **Rachel Wundke, Rosemary McCormick**: Generation of the data, assistance with study design and approval of the final version of the manuscript.
> **Kate Muller**: Revision of the manuscript and approval of the final version of the manuscript.
> **Billingsley Kaambwa**: Supervision and approval of the final version of the manuscript.
> **Richard Woodman**: Data analysis and interpretation, revision of the manuscript and approval of the final version of the manuscript.
> **Alan Wigg**: Overall supervision of the study, revision of the manuscript and approval of the final version of the manuscript.

4.1 SYNOPSIS

Background and aim: There is no validated questionnaire to assess disease knowledge and self-management among patients with cirrhosis of the liver. The aim of this study was to develop and validate a cirrhosis knowledge questionnaire (CKQ).

Methods: A preliminary CKQ with ten questions relevant to self-management of cirrhosis was administered to a pilot sample of 17 patients with decompensated cirrhosis, and its face validity was assessed. In consultation with experts, a second version of CKQ was developed with 14 multiple-choice questions. It was administered to 116 cirrhotic patients managed within a Chronic Liver Failure Program in Flinders medical Centre, Hepatology and Liver Transplant unit. Construct validity was assessed with an exploratory factor analysis (EFA) using maximum likelihood with varimax rotation, using MPlus software (version 8.0, Muthen & Muthen, California, USA). Known-group validity was assessed by comparing the performance of the CKQ in patients with and without active case management.

Results: One hundred and nine responses were obtained that included 42 patients with decompensated cirrhosis receiving case management. There were 69 men, and the mean (SD) age was 62 (13) years. A 3-factor EFA model with seven questions related to variceal bleeding/emergency situations, ascites and hepatic encephalopathy was the preferred model on the basis of model fit statistics. Internal consistency as measured by Cronbach's alpha was excellent at 0.82. The mean knowledge score (SD) was higher in 42 actively case managed patients than in 67 patients without case management [5.6 (1.1) vs. 4.3 (2.1), $p = 0.002$].

Conclusions: A CKQ was developed, and its face, construct and known-group validity were confirmed. Further confirmation of its dimensionality and assessment of its clinical predictive value are required.

4.2 INTRODUCTION

Advanced chronic liver disease (ACLD), otherwise known as cirrhosis of the liver, is an important cause of premature mortality in the Australian population.[1] Despite the medical breakthrough of hepatitis C virus (HCV) treatment, the burden of chronic liver disease (CLD) is estimated to be on an upward trend worldwide due to increased prevalence of harmful alcohol consumption and nonalcoholic fatty liver disease (NAFLD), the two major causes of cirrhosis-related mortality worldwide.[46,271] In Australia, it is projected that 8 million people will suffer from CLD by 2030 compared with 6 million in 2012.[99] Cirrhosis of the liver results in a multiple complications as it progresses from a compensated to a decompensated stage,[66] including variceal bleeding, ascites and hepatic encephalopathy, and is often accompanied by recurrent hospitalisations. The natural history of cirrhosis changes dramatically with the occurrence of emergency hospital admissions that are associated with high mortality.[98]

There is increasing evidence that careful monitoring of at-risk patients may be beneficial in preventing these hospitalisations.[3,13,15] There are also very helpful interventions that require patients' active involvement, such as salt restriction, monitoring of serum electrolytes to prevent diuretic-related complications and lactulose dose titration to prevent the occurrence of hepatic encephalopathy. In addition, lifesaving endoscopic and radiological surveillance measures require patients' active participation. These changes can be enhanced by appropriate patient education. Well-informed and actively participating patients have better health outcomes and behaviours.[16] Lack of educational support is increasingly recognised as an area of need in the management of patients with cirrhosis.[17] Randomised controlled studies have established the beneficial effects of patient education on quality indicators (such as readmissions) and mortality in other chronic diseases (such as ischemic heart disease, heart failure and asthma).[18-20] Educational interventions have been shown to be beneficial in achieving desired outcomes in the management of chronic diseases, even in patients with low health literacy.[130]

A validated knowledge questionnaire can be used not only to assess disease knowledge in patients but also to periodically examine the performance of chronic disease management (CDM) interventions that provide educational support. However, there is no validated instrument available for assessing knowledge among patients with cirrhosis. To fill this gap, a Cirrhosis Knowledge Questionnaire (CKQ) was developed and its validity assessed. The two

cornerstones in the evaluation of a measurement instrument are validity and consistency.[137] Validity refers to how well the instrument measures what it is meant to measure, whereas consistency indicates how consistently the measured results can be replicated.[138] Various types of validity exist including face validity, content validity, construct validity and criterion validity. In this study the stages of development of CKQ and its methods of validation including face validity, construct validity (using exploratory factor analysis, EFA) and known-group validity are discussed.

4.3 METHODS

This study was approved by the Southern Adelaide Human Research Ethics Committee reference number: HREC/15/SAC/6.

4.3.1 *Development of the Questionnaire*

4.3.1.1 *Initial Development Phase*

Backed by the literature review and clinical experience, a preliminary version of the questionnaire with 10 closed-ended questions involving a simple 'Yes' or 'No' response was developed (**Box 3**). The questions were related to the major complications of cirrhosis (ascites, variceal bleeding and hepatic encephalopathy), surveillance procedures and nutrition. It was administered to a pilot sample of 17 consecutive consenting patients with cirrhosis and decompensation managed at Flinders Medical Centre, Hepatology and Liver Transplant unit from February 2017 to May 2017. The questions were in English, related to the major complications of cirrhosis, surveillance procedures and nutrition. The exclusion criteria were any degree of overt hepatic encephalopathy or unwillingness to participate.

4.3.1.2 *Face Validity*

Patients were asked about the relevance, difficulty in understanding and answering the questions. The majority of the patients felt that the questions were relevant and did not have trouble in answering them. Two experienced CLD nurses also critically reviewed the questions.

Box 3. Preliminary version of the knowledge questionnaire.

Please circle the correct answer		
1	Emergency situations in cirrhosis include the following:	
	a) Variceal bleeding	Yes/No
	b) Confusion	Yes/No
	c) Fever	Yes/No
	d) Shortness of breath	Yes/No
2	As a patient with cirrhosis you may be asked to undergo an endoscopic examination to assess risk of variceal bleeding	Yes/No
3	The ascites action plan includes	
	a) Keep to a no salt added diet	Yes/No
	b) Measure your weight daily and record it	Yes/No
	c) Fluid tablets and drainage may be required	Yes/No
	d) Have to routinely restrict water intake	Yes/No
4	The most dangerous complication of ascites which demands early treatment is infection	Yes/No
5	The purpose of lactulose is	
	a) To prevent encephalopathy	Yes/No
	b) To prevent variceal bleeding	Yes/No
	c) To prevent ascitic fluid infection	Yes/No
	d) To treat fluid in the abdomen	Yes/No
6	You have to adjust daily dosing of lactulose according to your stool frequency and the risk of developing confusion	Yes/No
7	When you experience change in mood, memory, sleep or ability to concentrate, you might have hepatic encephalopathy	Yes/No
8	What actions are a part of good nutrition plan	
	a) Small frequent meals with nourishing snacks in between	Yes/No
	b) To eat high-protein, high-calorie food	Yes/No
	c) To avoid high-calorie food	Yes/No
	d) To avoid high-protein food	Yes/No
9	It is possible to detect liver cancers by periodic ultrasound exams of your liver	Yes/No
10	When detected early, it may be possible to treat liver cancers	Yes/No

During a subsequent review by a team of hepatology consultants, specialist nurses and a statistical consultant, the questions were revised from a simple 'Yes' or 'No' format to a multiple-choice format to reduce the impact of chance.

Thus, the initial 10 questions were retained and rephrased into 14 questions, and the CKQ was developed (**Box 4**).

Box 4. The CKQ: 14-item scale.

ASCQ1. What is the most important dietary measure that can help you with control of ascites (abdominal distention with fluid)?

a) Water restriction

b) Salt restriction

c) Regular lactulose therapy

d) High-protein diet

ASCQ2. What should you do at home to manage ascites?

a) Keep a record of your body weight on a regular basis

b) Eat low-fat diet

c) Have a large break between meals

d) Avoid constipation

ASCQ3. Monitoring the effects of fluid tablets

a) Involves regular blood tests to check salt levels

b) Needs regular checks of body weight

c) Can only be done by the GP

d) Both A and B

ASCQ4. When you are on fluid tablets what symptoms should you be concerned about?

a) Feeling of dizziness

b) Ongoing abdominal distention

c) Not passing enough urine

d) All of the above

SEPQ5. Increasing abdominal pain when you have ascites could mean a serious infection known as spontaneous bacterial peritonitis. This warrants medical attention:

Continued

a) Within a week

b) Immediately

c) At your next appointment with the doctor

d) Within the next 72 hours

VBQ6. As a patient with cirrhosis, you are asked to do an endoscopy (camera down the throat), which is helpful in checking for which of the following?

a) Varices (blood vessels) at risk of bleeding

b) Liver cancer

c) Fluid in the abdomen

d) Reflux symptoms

VBQ7. Warning signs of bleeding varices (blood vessels) include

a) Black-coloured stools

b) Vomiting of blood

c) Both A and B

d) None of the above

VBQ8. What treatment is given after a variceal bleed?

a) Only tablets are given

b) Regular frequent endoscopies are required

c) Both A and B

d) None of the above

HEPQ9. Change in the level of alertness, such as drowsiness or confusion, points towards hepatic encephalopathy (liver confusion), which is a common complication of advanced cirrhosis. This can be prevented by

a) Avoiding constipation and increasing dose of lactulose

b) Endoscopy

c) Salt-restricted diet

d) Fluid tablets

HEPQ10. If you are already on treatment with lactulose for hepatic encephalopathy, when are you supposed to increase the dose of lactulose?

a) If you feel like taking it

b) If you have diarrhoea

c) If you still feel more sleepy and confused

d) If the abdomen is distended with fluid

Continued

HEPQ11. Which among the following can make you (a patient with cirrhosis) drowsy?

a) Sleeping tablets

b) Constipation

c) Dehydration

d) All of the above

NUTQ12. Which of the following is the best dietary advice for you, a patient with cirrhosis?

a) Low-protein diet

b) Only vegetarian diet

c) High-calorie, high-protein diet taken at frequent intervals

d) Gluten-free diet

USGQ13. You are asked to undergo 6-monthly ultrasound to detect

a) Abdominal fluid

b) Bleeding varices

c) Liver cancers

d) Gall stones

EMERQ14. You should seek the help of your liver nurse or go to hospital when you have

a) Black stools

b) Drowsiness and irritability

c) Fever and abdominal pain

d) Any of the above

4.3.1.3 *Delivery Phase*

Two hundred and seventy-eight patients from the database of cirrhotic patients maintained in the hepatology unit as a part of a Chronic Liver Failure Program (CLFP) were approached for the study between September 2017 and May 2018. The CLFP is a chronic disease management (CDM) type of intervention as described in a previous study.[11] It is a multifaceted intervention covering four CDM domains, namely delivery system redesign, decision support, self-management support and clinical information systems. Specific interventions included case management for patients with decompensation of the disease with provision of protocol-based checklists and subsequent care plans for post-discharge care, post-discharge phone calls, home visits, self-management support with enhanced patient and carer education, patient action plans

for complications (ascites and encephalopathy), access to day case therapeutic large-volume paracentesis and a rapid access to care pathway for deteriorating patients. Patients with stable cirrhosis are followed up less intensively with 6-monthly clinic (community nurse-led clinics or hospital clinics) visits and ultrasound surveillance but did not receive any regular ongoing education. Two experienced hepatology nurses, both working approximately 0.6 full-time equivalents, support the CLFP, in close consultation with the hepatologists.

Since patients with diverse educational backgrounds were involved in the study, some of the questionnaires were administered in nurse-led clinics with assistance from nurses. Otherwise, CKQ and a consent form were posted to the patient and returned by pre-paid post. In the surveys completed at home, patients were encouraged to discuss with their carer and to refer to the information booklet provided as a part of the liver failure programme.

Participating patients were required to answer 14 multiple-choice questions related to knowledge of major complications of cirrhosis including ascites, variceal bleeding and hepatic encephalopathy, radiological surveillance, and nutrition. Correct response was allotted 1 point, a partially correct was given 0.5 points and an incorrect response was given 0 points. Unanswered questions were considered incorrect. If the entire questionnaire was not answered, it was excluded from analysis:

- *Inclusion criteria*: Patients with clinical diagnosis of cirrhosis confirmed by ultrasonography and/or liver biopsy with or without clinical manifestations of decompensation were included.
- *Exclusion criteria*: Patients with overt hepatic encephalopathy, who were unable to comprehend English and those unwilling to participate were excluded.

4.3.1.4 *Construct Validity*

Construct validity was assessed using maximum likelihood EFA with varimax rotation. The analysis was performed using Mplus software (version 8.0, Muthen & Muthen, California, USA).

Prior to EFA, suitability of the CKQ items for EFA was assessed using Kaiser–Meyer–Olkin (KMO) test and Bartlett's test of sphericity. KMO tests the degree that the variance in the data

is due to underlying factors and Bartlett's tests of sphericity evaluates the extent to which the items are unrelated to each other. A KMO value close to 1.0 and a *p*-value < 0.05 in Bartlett's test are indicative of appropriateness for factor analysis.

The EFA was run with solutions for CKQ models with two, three and four factors. Model fit statistics included the chi-squared (χ^2) test, root mean square error of approximation (RMSEA) and root mean square residual (RMSR). The acceptability criteria of model fit were chi-squared *p*-value > 0.05 and RMSEA < 0.05. The residual error and *R*-squared value for each item were estimated to determine the extent to which item was related to the knowledge factor scores.

Internal consistency was assessed using Cronbach's alpha. The acceptable range of values is from 0.70 to 0.90.

Known-group validity was assessed by comparing the mean of knowledge scores between patients expected to have better disease knowledge as a result of case management with those without case management using Student's *t*-test.

4.4 RESULTS

Seventeen patients with decompensated cirrhosis [median age (interquartile range) 57 (18) years; 88% men] participated in the first development phase of the study. Most patients reported no difficulty in understanding or responding and found the questions relevant.

Following the expert review, a second version, CKQ with 14 items was used for the second phase.

One hundred and sixteen responses were received from patients with cirrhosis managed through the CLFP. After excluding seven blank responses, 109 completed responses were analysed. There were 69 men, and the mean (SD) age was 62 (13) years. There were 42 patients who had either ongoing or history of case management with one or more features of hepatic decompensation (such as ascites, variceal bleeding and hepatic encephalopathy) and 67 patients without any prior case management or features of hepatic decompensation at the time of study.

Demographic features and mean knowledge scores were compared between the two groups as provided in **Table 7**.

Aetiology of liver disease was the only significant difference at baseline between the groups that received case management and the group that did not receive case management.

Table 7. Comparison between cirrhotic patients with and without active case management.

Demographic features	**Case management (*n* = 42)**	**No case management (*n* = 67)**	***p*-value****
Age in years, mean (SD)	60 (14)	63 (12)	0.228
Gender men, *n* (%)	30 (44)	39 (57)	0.221
Aetiology of liver disease, alcohol, *n* (%)	27 (64)	26 (39)	0.011
Ascites,* *n* (%)	30 (71)	1 (1.5)	<0.001
History of hepatic encephalopathy,* *n* (%)	13 (31)	0	<0.001
Variceal bleeding,* *n* (%)	10 (24)	4 (6)	0.016
Knowledge scores mean (SD)	5.6 (1.1)	4.3 (2.1)	0.002

*Number does not add up to 42 as multiple complications were coexistent in some.

**Independent *t*-tests and *chi-squared* tests of independence were used to calculate *p*-values.

4.4.1 *Validation of the Questionnaire*

4.4.1.1 *Construct Validity*

The overall measure of sampling adequacy by the KMO test for the 14 items was 0.84, and the median (range) for individual items (questions) was 0.85 (0.76–0.91). Bartlett's test of sphericity confirmed that there was an adequate degree of correlation among the 14 items [χ^2 = 489.202 (91 df), $p < 0.001$]. Thus, suitability of CKQ for EFA was confirmed.

Model fit statistics for EFA models that employed between two and four factors are shown in **Table 8**.

Both 3-factor and 4-factor models fulfilled the acceptability criteria of the chi-squared test of model fit (*p*-value > 0.05) and RMSEA < 0.05. Of these, the 3-factor model was chosen based on parsimony.

The EFA provided a 3-factor solution using varimax rotation and arrived at seven questions that had a loading each ≥0.6. At least two items loaded onto each of the factors in 3-factor model (with standardised factor loadings ≥0.6), whereas in the 4-factor model only one item was loaded onto two of the factors. Hence, the 3-factor model was chosen as the final model.

Table 8. Model fit statistics for EFA.

Model	**Chi-squared (df)**	***p*-value**	**RMSEA (90% CI)**	**RMSR**
1-factor	156.937 (77)	<0.001	0.097 (0.075–0.118)	0.086
2-factor	104.031 (64)	0.001	0.075 (0.047–0.101)	0.064
3-factor	67.161(52)	0.076	0.051 (0.000–0.084)	0.047
4-factor	45.393 (41)	0.2940	0.031 (0.000–0.074)	0.036

df: degrees of freedom; RMSEA: root mean square error of approximation; RMSR: root mean square residual.
Acceptability criteria of model fit were chi-squared *p*-value > 0.05, RMSEA < 0.05, RMSR < 0.05.

Table 9 provides factor loadings for the individual items in the 3-factor model.

The three factors in this model corresponded to questions related to the three most important complications of cirrhosis (variceal bleeding/emergency situations, ascites and hepatic encephalopathy), as provided in **Box 5**.

Figure 7 describes the relative frequency of correct responses for the 14 items in the CKQ. There were no questions for which all patients answered correctly, or for which all patients answered incorrectly. However, 89% of the cohort was aware of the need for 6-monthly ultrasound examinations suggesting a possible ceiling effect for this item. Conversely, 67% of

the cohort was not aware of the need to titrate lactulose for worsening symptoms of hepatic encephalopathy.

Figure 8 shows the scree plot of the eigenvalues from the EFA. The eigenvalues for the first three factors were 4.40, 0.89 and 0.56, respectively. The eigenvalue for all other factors were negligible (≤0.37).

Table 9. Standardised factor loadings for the individual items from EFA.

Items (questions)	Factor 1: VB	Factor 2: ASC	Factor 3: HEP
ASCQ1	0.456	0.460	–0.020
ASCQ2	0.253	0.437	0.028
ASCQ3	0.070	**0.781**	0.169
ASCQ4	0.189	**0.638**	0.407
SEPQ5	0.473	0.173	0.256
VBQ6	**0.628**	0.201	0.147
VBQ7	**0.562**	0.239	0.515
VBQ8	0.188	0.461	0.544
HEPQ9	0.204	0.158	**0.572**
HEPQ10	0.326	-0.047	0.396
HEPQ11	0.264	0.158	**0.794**
NUTQ12	0.395	0.133	0.217
USGQ13	0.379	0.131	0.269
EMERGQ14	**0.645**	0.159	0.360

Bold indicates items with standardised loadings ≥0.6 and are generally considered adequate for inclusion within a factor. These items were included in the final seven-item cirrhosis knowledge questionnaire (CKQ).

ASC: ascites; EMERG: emergency hospitalisation; EFA: exploratory factor analysis; HEP: hepatic encephalopathy; NUT: nutrition; SEP: sepsis; USG: ultrasonography; VB: variceal bleeding.

Box 5. Final seven-item knowledge questionnaire after factor analysis.

Factor 1*: *Variceal bleeding/emergency hospitalisation

VBQ6. As a patient with cirrhosis, you are asked to do an endoscopy (camera down the throat). Endoscopy is helpful in checking for which of the following?

a) Varices (blood vessels) at risk of bleeding

b) Liver cancer

c) Fluid in the abdomen

d) Reflux symptoms

VBQ7. Warning signs of bleeding varices (blood vessels) include

a) Black-coloured stools

b) Vomiting of blood

c) Both A and B

d) None of the above

EMERQ14. You should seek the help of your liver nurse or go to hospital when you develop

a) Black stools

b) Drowsiness and irritability

c) Fever and abdominal pain

d) Any of the above

Factor 2*: *Ascites

ASCQ3. Monitoring the effects of fluid tablets:

a) Involves regular blood tests to check salt levels

b) Needs regular checks of body weight

c) Can only be done by the general practitioner

d) Both A and B

ASCQ4. When you are on fluid tablets what symptoms should you be concerned about

a) Feeling of dizziness

b) Ongoing abdominal distention

c) Not passing enough urine

d) All of the above

Factor 3: *Hepatic encephalopathy*

HEPQ9. Change in the level of alertness, such as drowsiness or confusion, points towards hepatic encephalopathy (liver confusion), which is a common complication of

Continued

advanced cirrhosis. This can be prevented by

a) Avoiding constipation and increasing dose of lactulose

b) Endoscopy

c) Salt-restricted diet

d) Fluid tablets

HEPQ11. Which among the following can make you (a patient with cirrhosis) drowsy?

a) Sleeping tablets

b) Constipation

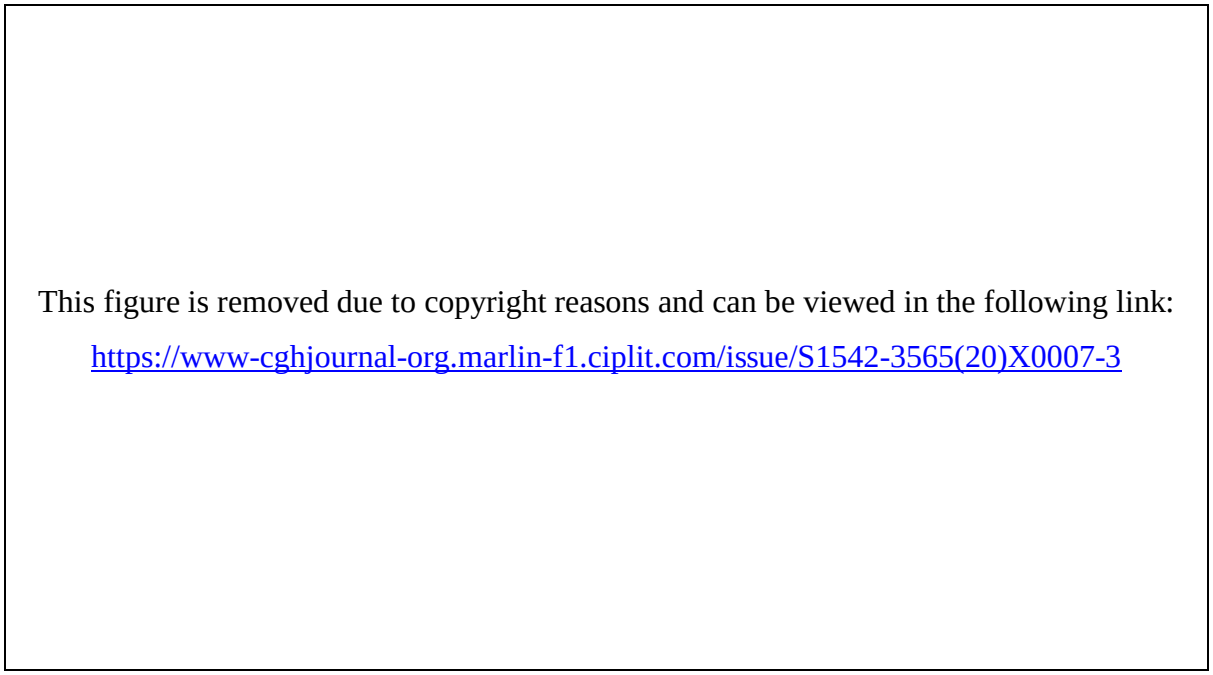
c) Dehydration

d) All of the above

Figure 7. Floor-ceiling effect: the relative frequency of correct and wrong responses for the 14 items in CKQ.

This figure is removed due to copyright reasons and can be viewed in the following link: https://www-cghjournal-org.marlin-f1.ciplit.com/issue/S1542-3565(20)X0007-3

Figure 8. The scree plot of the eigenvalues from the EFA.



4.4.1.2 *Internal Consistency*

The Cronbach's alpha for the 14 items was 0.85 demonstrating good internal consistency. Cronbach's alpha for the seven items in the revised CKQ after EFA was 0.82, thus confirming the internal consistency of the revised instrument as well.

4.4.1.3 *Known-Group Validity*

There was a statistically significant difference in the CKQ total knowledge score between patients case managed and those without case management (p = 0.002) (**Table 7**). This expected difference supports the validity of the instrument in evaluating knowledge of cirrhosis, given that case managed patients received ongoing patient education as a part of their case management.

4.5. DISCUSSION

There is currently no validated instrument available for assessment of disease knowledge among patients with cirrhosis of the liver. The educational needs of patients with CLD were determined to be infrequently met in a systematic review of studies that assessed the supportive care needs of patients with CLD.[17] As a quarter of readmissions are preventable in patients

with decompensated cirrhosis, patient education is of highest priority in this complex chronic disease.[3] Patient education is also a well-researched aspect of successful care given to many chronic diseases and an important component of CDM principles. Therefore, assessment of response to patient education with validated instruments is a vital component of quality measurement in the field of CDM. In this study a knowledge questionnaire (CKQ), for the examination of disease knowledge among patients with cirrhosis of liver, was developed and validated.

Face validity of the CKQ using a preliminary survey in a pilot sample was established. Subsequently, construct validity that establishes whether the questions are related to one or more constructs was assessed using EFA. The EFA revealed a 3-factor structure with seven items, corresponding to three established domains in cirrhosis, namely variceal bleeding, ascites and hepatic encephalopathy. The confirmation of good model fit with the EFA demonstrated that the questions within each factor were essentially unique to that factor, leaving a 'one-level' 3-factor model as the chosen structure for the questionnaire. The one-level structure of the model also suggests that the three domains were not part of a higher domain. They could be thought of as being quite independent, such that subjects can have knowledge in one domain without necessarily having knowledge in another domain. The significant difference in the knowledge scores between those patients with and without case management also demonstrated the known-group validity, as these two sets of patients might be expected to have different levels of knowledge. This higher level of knowledge might reflect the higher levels of educational support provided throughout the case management, or alternatively, a consequence of case managed patients with symptoms of hepatic decompensation being more receptive to the educational support provided.

This study cannot exclude the possibility that lower knowledge scores noted in patients with compensated cirrhosis may simply reflect less lived experience of decompensation events and their subsequent management.

Variceal bleeding is the most immediate, life-threatening complication of cirrhosis and its risk can be reduced by current prophylactic therapies. Crucial information on awareness of endoscopic surveillance and presentation of variceal bleeding were included in two questions within the first factor. An additional question on awareness of other emergency situations in cirrhosis including variceal bleeding also loaded onto the same factor. Ascites is the most

frequent complication of cirrhosis with 10% of patients with compensated cirrhosis developing this complication every year.[87] Self-management of ascites is facilitated by knowing the symptoms of over-diuresis and/or inadequate response. Questions on each of these aspects loaded onto the second factor. Hepatic encephalopathy is associated with recurrent hospital admissions accounting for significant morbidity and socioeconomic burden in patients with cirrhosis. In addition, it has detrimental effects on both physical and mental components of health-related quality of life in these patients.[272] Finally, the third factor included two questions related to symptom recognition, early management with lactulose and precipitants for hepatic encephalopathy. Thus, seven highly relevant questions in the management of patients with cirrhosis emerged in the final CKQ for the measurement of disease knowledge in these patients.

Using a knowledge survey prepared in-house, which was neither internally nor externally validated, Volk et al. showed that correct responses were obtained for only 53% of the 15 questions by cirrhotic patients followed up in their clinic.[139] The number of correct responses increased to 67% after intervening with an educational booklet. Limitations of the study, however, were that the survey had not undergone any form of validation, and did not include questions on variceal bleeding, the most lethal complication of cirrhosis. Moreover, the survey questions were related to a diverse range of knowledge, such as sodium content of sea salt, safety of surgery, cholesterol lowering medications and nonsteroidal anti-inflammatory drugs, and may have been too technical for many patients.

Goldsworthy et al. showed that disease knowledge was poor in a cohort of 52 cirrhotic patients attending a liver clinic in a tertiary-care centre.[140] The baseline score of 21% was improved significantly (to 60%) by multimedia interventions in the form of video presentations. While providing useful evidence for the widespread lack of knowledge among cirrhotic patients, a similar weakness of the study was the use of a questionnaire whose structure was not validated beyond face validity and content validity. Thus, while questions may have been relevant, their appropriate weighting and/or grouping had not been considered. In addition, the questionnaire had no mention of ascites, the commonest form of decompensation and the commonest cause of recurrent hospital admission in patients with cirrhosis. The survey consisted of a descriptive answer question, which many patients would find cumbersome.

The need for patient-centred education in cirrhosis was confirmed by a pilot study by Hayward et al. involving 50 patients with cirrhosis of the liver.[141] Nearly 60% of the study cohort

expressed a keen desire to receive education about the disease outcome and its complications. Patients were asked to answer 56 open-ended and closed-ended questions, following which they received a pilot educational booklet. Subsequently, they were asked to answer a survey of 13 questions that were also not validated. The baseline knowledge was poor, and improvement with the intervention was only marginal, possibly reflecting the poor sensitivity of the survey instrument and its lack of convergent validity. However, this study highlighted that patients with cirrhosis were ready to have disease education incorporated into their routine clinical care.

It might be argued that the knowledge assessment should be restricted to patients with decompensated cirrhosis in whom it would be most beneficial. However, as cirrhosis progresses from compensated to decompensated stage at a rate of 5–7% per year,[63] the complications could occur any time. Moreover, surveillance procedures are essential even in patients with compensated cirrhosis. Therefore, routine education of all cirrhotic patients about the disease and self-management seems warranted. The studies by Volk et al. and Hayward et al., which assessed the knowledge among patients with cirrhosis, also had predominantly patients with compensated cirrhosis, as in this study.[139,141] Nevertheless, in contrast to our findings of higher knowledge scores in patients with decompensated disease, no such difference was noted by them. This difference was likely explained by patients with decompensated cirrhosis in this study receiving education as a part of the case management in CLFP.

There are several limitations to the present study. Firstly, a relatively small number of items were retained in the final questionnaire (**Box 5**). It is unlikely that it fully captures all the relevant knowledge of patients regarding management of their disease. Therefore, before making a final recommendation for the use of the questionnaire to assess disease knowledge in patients with cirrhosis, it is planned to administer CKQ with additional items. In addition, the study did not assess the sensitivity of the CKQ to responding to improvements in knowledge. This can be assessed by measuring change in knowledge before and after educational intervention within a randomised controlled trial (RCT).

This study also did not establish the clinical relevance of using a CKQ. Therefore, a further prospective cohort study is necessary to determine whether knowledge, as assessed by CKQ, correlates with clinically relevant endpoints, such as readmission rates and mortality.

Test–retest was not done to assess the reliability of CKQ because of concerns about over-burdening patients. The response rate for study participation was only 42% (116 of 278), suggesting that most patients considered the study too demanding on their time or energy. Finally, the study only excluded those patients with overt hepatic encephalopathy and, therefore, cannot exclude the possibility that occult hepatic encephalopathy and cognitive dysfunction could have impaired performance in some patients.

4.6 CONCLUSION AND FUTURE DIRECTIONS

In summary, this study presents the first validated knowledge questionnaire for cirrhotic patients with confirmed face, construct and known-group validity. Use of this validated CKQ, with just seven questions, may improve assessment of patient knowledge and self-management of cirrhosis. Further confirmation of its dimensionality, sensitivity to clinical education and the clinical predictive value of disease knowledge require assessment in RCTs. Knowledge assessment before and after patient education using CKQ is likely to confirm the predictive value of the CKQ. Assessment of patient knowledge improvement with an educational intervention and its association with quality indicators, such as hospital readmissions and survival, will confirm the clinical predictive value of the scale. The ongoing Australian Liver Failure trial (ALFIE) RCT, with patient education provided as an intervention, will provide opportunities to evaluate the CKQ and develop it further.

5. PSYCHOMETRIC VALIDATION OF THE PARTNERS IN HEALTH SCALE AS A SELF-MANAGEMENT TOOL IN PATIENTS WITH CIRRHOSIS OF THE LIVER

A major part of this chapter is published in *Internal Medicine Journal*, and the details are as follows:

> Psychometric validation of the Partners in Health scale as a self-management tool in patients with liver cirrhosis.
> **Jeyamani Ramachandran**, Smith D, Woodman R, Muller K, Wundke R, McCormick R, Kaambwa B, Wigg A. *Intern. Med. J.* 24 August 2020; https://doi.org/10.1111/imj.15031.

Authors' contribution details are given below:

> **Jeyamani Ramachandran**: Conception, design of the study, analysis and interpretation of data, drafting and revision of the manuscript and approval of the final version of the manuscript.
> **David Smith**: Statistical analysis, manuscript editing and approval.
> **Rachel Wundke, Rosemary McCormick**: Generation of the data, assistance with study design and approval of the final version of the manuscript.
> **Kate Muller**: Revision of the manuscript and approval of the final version of the manuscript.
> **Billingsley Kaambwa**: Supervision and approval of the final version of the manuscript.
> **Richard Woodman**: Data analysis and interpretation, revision of the manuscript and approval of the final version of the manuscript.
> **Alan Wigg**: Conception, overall study supervision, revision of the manuscript and approval of the final version of the manuscript.

5.1 SYNOPSIS

Background and aim: Cirrhosis of the liver is a chronic disease that is complicated by recurrent hospital admissions. For optimal disease management, self-management skills are essential. At present, there is no validated instrument for measuring the self-management in these patients. To address this gap, the internal reliability and construct validity of the Partners in Health (PIH) scale, a chronic condition self-management tool, was evaluated in cirrhotic patients.

Methods: In this prospective cross-sectional cohort study, the PIH scale was administered to 133 consenting patients within a Chronic Liver Failure Program in Flinders Medical Centre, Hepatology and Liver Transplant Unit from February 2017 to May 2018. A Bayesian confirmatory factor analysis (BCFA) was used to evaluate an *a priori* 4-factor structure. Omega coefficients and 95% credible intervals (CrI) were used to assess the internal reliability. The known-group validity was assessed in patients receiving active case management (n = 60) versus those without (n = 73).

Results: The mean (standard deviation, SD) age of the participants was 62 (11) years. Model fit for the hypothesised model was adequate (posterior predictive *p-value* = 0.073) and all hypothesised factor loadings were substantial (>0.6) and significant (p < 0.001). Omega coefficients (95% CrI) for the PIH subscales of knowledge, partnership, management and coping were 0.88 (0.82–0.91), 0.68 (0.57–0.76), 0.92 (0.89–0.94) and 0.89 (0.85–0.92), respectively. The mean (SD) overall PIH score was higher in patients receiving active case management compared to those without case management [81 (12) vs. 73 (17); p < 0.001].

Conclusions: The dimensionality of the PIH and reliability for assessing self-management in patients with cirrhosis of the liver were confirmed in this study. The clinical predictive value of the PIH requires assessment in a prospective cohort.

5.2 INTRODUCTION

One of the major health issues facing Australia is the increasing prevalence of chronic diseases. About 50% of Australians suffer from one of the eight chronic diseases, namely heart disease, diabetes mellitus, arthritis, mental health conditions, asthma, chronic obstructive pulmonary diseases, backpain and cancer.[92] These chronic conditions contribute to increased hospitalisations, health-related costs, societal costs due to disability and poor quality of life (QoL). Cirrhosis is a frequent comorbidity encountered in patients with diabetes mellitus and ischemic heart disease due to a shared common cause, namely nonalcoholic fatty liver disease.[46] Cirrhosis is characterised by life-threatening and debilitating complications, such as ascites, bacterial infections, hepatic encephalopathy and variceal bleeding, as it progresses to a decompensated stage. Despite medical advances, recurrent hospital admissions ensue as a result of these complications and contribute significantly to direct medical costs and to poor QoL.[7]

As a quarter of the recurrent hospital admissions are deemed preventable, patient education and self-management assume priority in the care of these patients.[3] Examples of self-management interventions that could help include salt restriction, monitoring body weight while on diuretic therapy for ascites, adjusting lactulose dose according to the symptoms of hepatic encephalopathy, endoscopic surveillance for variceal bleeding, alcohol abstinence and medication adherence. Among patients with chronic diseases, those equipped with skills and self-management knowledge related to the disease were found to have improved health outcomes.[22] Self-management support is one of the most successful chronic disease management (CDM) interventions with consistent improvement in symptom control, QoL, hospitalisations and mortality rate in many chronic diseases.[10] Self-management support empowers patients with the knowledge and the behaviour required to cope with a chronic disease successfully. Self-management support, enabling patients to acquire knowledge and confidence required to manage chronic diseases, is an essential CDM principle.[10] Highly activated and engaged patients manage their chronic disease better, and experience positive health outcomes.[22]

The Partners in Health (PIH) scale is a generic tool that was developed for measuring self-management knowledge and behaviours in people with chronic illnesses, in response to the SA

Health Plus coordinated care trial.[23,24] The PIH scale was developed by Battersby et al. along the six major principles of chronic condition self-management[23] including

1. disease knowledge;
2. adherence to a treatment plan made in accordance with the healthcare provider;
3. playing an active role in the decision-making process;
4. awareness of warning symptoms and their management;
5. coping with the effects of the chronic illness in relation to the physical, mental and social aspects of life;
6. practice of a healthy lifestyle.

Its structural validity and internal reliability in the measurement of self-management in chronic diseases have been established.[155] In response to the changing definitions of health and self-management and supported by focus group discussions, the scale was revised to a 12-item scale with a 4-factor structure. The four factors are

1. partnership in treatment,
2. knowledge,
3. recognition and management of symptoms,
4. coping.[157]

This structurally sound tool has been used to measure self-management knowledge and behaviours in response to CDM interventions in the Flinders Chronic Condition Management Programme, Vietnam veterans with alcohol dependence, patients with osteoarthritis and dialysis patients.[156,158,159,273] However, a validation and application of this scale in patients with cirrhosis has not been performed till date.

Given the importance of self-management support in the optimal management of cirrhosis according to CDM principles, the structural validity, including dimensionality, and internal reliability of the PIH scale were assessed in this study in a cohort of cirrhotic patients.

5.3 METHODS

5.3.1 *Study Design*

This prospective cross-sectional study was approved by the Southern Adelaide Human Research Ethics Committee (reference number: HREC/15/SAC/6).

5.3.2 *Study Setting*

Two hundred and seventy-eight patients from the Chronic Liver Failure Program (CLFP) database of Flinders Medical Centre were approached for the study during the period from February 2017 to May 2018. The PIH scale (as in **Box 2**) was mailed to the patients within the CLFP together with the consent form and returned by either prepaid post or during their clinic appointments. A few patients required assistance from liver nurses to understand the questions, and, hence, these were administered in community nurse-led clinics.

The CLFP is a type of CDM intervention as described in a previous study.[11] In the CLFP, patients with decompensated cirrhosis receive active case management, which is a multifaceted intervention covering four CDM domains including self-management support, decision support, delivery system redesign and clinical information systems. Specific key interventions include provision of protocol-based checklists and subsequent care plans for post-discharge care, post-discharge phone calls, home visits, self-management support with enhanced patient and carer education, patient action plans for complications (ascites and hepatic encephalopathy), access to day case therapeutic large-volume paracentesis and a rapid access to care pathway for deteriorating patients. Patients with compensated cirrhosis receive reminders for appointments and surveillance procedures, in addition to rapid access care pathways for clinical deterioration. Two experienced hepatology nurses, both working 0.6 full-time equivalents support the CLFP in close consultation with five consultant gastroenterologists or hepatologists. The inclusion and exclusion criteria are as follows:

- *Inclusion criteria*: A diagnosis of cirrhosis, confirmed by a combination of clinical, biochemical, transient elastography and imaging criteria. Liver biopsy was not routinely performed for diagnosis, in keeping with current trends towards non-invasive diagnosis.

- *Exclusion criteria*: Patients with hepatic encephalopathy, those who were unable to comprehend English, and those unwilling to participate were excluded.

5.3.3 *Statistical Analysis*

Bayesian confirmatory factor analysis (BCFA) using MPlus software (version 8) was used to assess the structural validity of the PIH in patients with liver disease. A BCFA is similar to a standard confirmatory factor analysis (CFA), but does not rely on large-sample theory and performs better with small samples compared to maximum likelihood algorithms.[274] In addition to specification of the hypothesised major factors (that is, the dimensionality of the scale), it requires specification of informative small variance priors to allow for the possible inclusion of nonzero cross-loading of items between factors.[274]

A PIH factor model was first estimated using non-informative prior parameters for the hypothesised major loadings, and the factor cross-loadings constrained to zero. Then, the BCFA was repeated with the addition of informative priors for the cross-loadings. Each observed variable was standardised and given a suitable cross-loading prior variance in a range of increasing values (0.005, 0.01 and 0.02). Convergence of the models was assessed using the potential scale reduction (PSR), trace plots and histograms of the posterior parameter distributions. Model fit was evaluated using posterior predictive *p*-values (a PP *p*-value > 0.05 confirms model fit).[274] Differences in fit between models was assessed using deviance information criterion (DIC). Lower DIC values imply higher predictive accuracy.

To assess the internal consistency of the PIH, McDonald's omega coefficients and 95% Bayesian credible intervals were calculated using estimates from the final model.[275] For health status questionnaires, coefficient values between 0.70 and 0.95 are indicative of good internal consistency.[276] The known-group validity was assessed by comparing patients with and without active case management and self-management support. Independent *t*-tests and chi-squared (χ^2) tests of independence were used to compare patient characteristics between the two groups. The PIH total score and the individual domains were compared between case managed and non-case managed patients using an independent *t*-test. These tests were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA).

5.4 RESULTS

5.4.1 *Patient Characteristics*

Responses to the PIH scale were obtained from 135 consented patients with cirrhosis. After excluding duplicate responses, there were 133 responses from 60 patients within the case management group and 73 patients without case management. The mean (standard deviation) age was 62 (11) years, and 67% were men. The clinical details are provided in **Table 10.** The aetiology of cirrhosis was alcohol (*n* = 68, 51.1%), HCV (*n* = 23, 17.3%), nonalcoholic steatohepatitis (NASH; *n* = 27, 20.3%), mixed alcohol, HCV and NASH (*n* = 5, 3.75%) and miscellaneous (*n* = 10, 7.5%).

Table 10. Demographic features compared between cirrhotic patients with and without case management.

Demographic features	**Case management (*n* = 60)**	**No case management (*n* = 73)**	***p*-value****
Age in years, mean (SD)	60 (11)	62 (12)	0.228
Gender men, *n* (%)	45 (75)	44 (60)	0.09
Aetiology of liver disease (alcohol), *n* (%)	43 (71)	30 (41)	<0.001
Ascites,* *n* (%)	45 (75)	2 (3)	<0.001
Hepatic encephalopathy,* *n* (%)	17 (28)	0	<0.001
Variceal bleeding,* *n* (%)	9 (15)	4 (5)	<0.001

*Number does not add up to 60 as multiple complications were coexistent.

**Independent *t*-tests and χ^2 tests of independence were used to calculate *p*-values.

5.4.2 *Bayesian Confirmatory Factor Analysis Model*

Bayesian confirmatory factor analysis was performed on the PIH 12 items using all available data. **Table 11** presents the results from an exact BCFA 4-factor model comprised of non-informative priors for hypothesised major loadings and zero cross-loadings. This model

provided an acceptable fit of the data on the basis of PP *p*-value being close to the hypothesised threshold of 0.05 and the discrepancy between the observed and replicated chi-square values covered zero. Model fit for the PIH with non-informative priors and zero-cross loadings was acceptable based on the PP *p*-value (0.081) and the discrepancy between the observed and replicated chi-square values for the correlation matrix including zero. Models with increasing nonzero cross-loadings improved model fit as expected with PP *p*-values all >0.05.

The PSR values at the completion of the BCFA were <1.1 indicating that the model convergence was achieved. Trace plots for each posterior model parameter confirmed the convergence of chains to their stationary distributions and occurrence of good mixing. Histograms of Bayesian posterior parameter distributions were approximately normal.

Table 11. Model fit statistics for PIH 4-factor model using BCFA.

Prior values[a]	**95% Cross-loading limit**	**PP *p***	**Difference between observed and replicated χ^2 95% CI**		**DIC**
			Lower 2.5%	**Upper 2.5%**	
xload N (0, 0)	–	0.081	–10.92	57.93	3804
xload N (0, 0.005)	0.14	0.158	–16.54	53.20	3807
xload N (0, 0.01)	0.20	0.193	–19.18	52.56	3808
xload N (0, 0.02)	0.28	0.215	–20.64	52.98	3809

BCFA: Bayesian confirmatory factor analysis; DIC: deviance information criterion; PIH: Partners in Health scale; PP *p*: posterior predictive *p*-value; xload, cross-loading.

Table 12 depicts the factor correlation estimates for the BCFA 4-factor model. Non-informative priors were in the moderate to large range (all >0.6).[277] The results for the BCFA model with a 95% cross-loading limit equal to 0.28 are shown in **Table 13**.

Table 12. The PIH scale 4-factor Bayesian model: standardised estimates of major factor loadings and correlations between factors.

PIH Item	K	P	M	C
BCFA with zero cross-loadings				
1	**0.883***	0	0	0
2	**0.880***	0	0	0
3	0	**0.436***	0	0
4	0	**0.592***	0	0
5	0	**0.709***	0	0
6	0	**0.607***	0	0
7	0	0	**0.949***	0
8	0	0	**0.894***	0
9	0	0	0	**0.803***
10	0	0	0	**0.907***
11	0	0	0	**0.832***
12	0	0	0	**0.720***
Factor correlations				
K				
P	0.691*	–		
M	0.473*	0.506*	–	
C	0.392*	0.535*	0.587*	–

BCFA: Bayesian confirmatory factor analysis; C: coping; K: knowledge; M: recognition and management of symptoms; P: partnership in treatment; PIH: Partners in Health scale.

Standardised factor loadings are estimated correlations between the item and its factor. Zero loadings correspond to a simple structure confirmatory factor analysis model with prior distribution of mean zero and variance zero.

Values in bold indicate hypothesised major loadings.

*95% credibility interval does not cover zero.

Models with increasing nonzero cross-loadings improved model fit as expected, with PP *p*-values > 0.05. However, the smallest DIC values were obtained for the 4-factor model with non-informative priors, which was, therefore, the chosen model.

Table 13. The PIH scale 4-factor Bayesian model with cross loading: standardised estimates of factor loadings and correlations between factors.

Item	K	P	M	C
BCFA with 95% cross-loading limit 0.28				
1	**0.889***	0.055	–0.032	0.019
2	**0.947***	–0.009	0.016	–0.002
3	0.122	0.306	0.179	–0.102
4	0.000	**0.687***	–0.024	–0.043
5	0.038	**0.724***	–0.058	0.072
6	–0.035	**0.600***	0.032	0.043
7	0.033	0.002	**0.912***	0.048
8	–0.021	0.024	**0.976***	–0.002
9	–0.005	–0.027	0.082	**0.795***
10	0.043	–0.068	0.034	**0.950***
11	0.005	0.005	–0.116	**0.948***
12	–0.090	0.080	0.034	**0.721***
Factor correlations				
K				
P	0.641*	–		
M	0.455*	0.464*	–	
C	0.387*	0.534*	0.559*	–

BCFA: Bayesian confirmatory factor analysis; C: coping; K: knowledge; M: recognition and management of symptoms; P: partnership in treatment; PIH: Partners in Health scale.
Standardised factor loadings are estimated correlations between the item and its factor.
Values in bold indicate hypothesised major loadings.
*95% credibility interval does not cover zero.

To assess the reliability of subscale scores for the BCFA 4-factor model with non-informative priors, McDonald's omega coefficients were calculated. Coefficients (95% Bayesian credible intervals) for the PIH subscales of knowledge, partnership, management and coping were 0.88 (0.82–0.91), 0.68 (0.57–0.76), 0.92 (0.89–0.94) and 0.89 (0.85–0.92), respectively.

These values indicated that the reliability of the subscales in producing raw scores was in the acceptable range for knowledge, management of symptoms and coping. The coefficient for partnership was slightly below the conventional cutoff value, [276] while the credible interval suggested a moderate degree of uncertainty due to the smaller factor loadings and larger residual variances.

5.4.3 *Known-Group Validity*

The total PIH score and subscales were compared between patients with and without case management (**Table 14**). The mean total PIH score was significantly higher in case managed cirrhotic patients compared with those who were not case managed. The difference in mean subscale scores on 'knowledge and awareness of symptoms' and 'management of symptoms' between the two groups also achieved statistical significance. The findings in **Table 14** also suggest that cirrhotic patients reported lower coping capacity in the context of average sub-scale scores, as a proportion of maximum sub-scale scores (23/32).

5.5 DISCUSSION

The PIH scale was previously validated in patients suffering from a range of chronic diseases, such as diabetes mellitus and heart diseases, and found to be a dependable measure of self-management.[23,156,157] For the first time, in this study, the psychometric properties of the generic PIH scale have been evaluated in the specific setting of cirrhosis of the liver. Factor analysis confirmed the existence of four distinct factors that are theoretically underpinned by self-management principles relating to knowledge of illness, coping, management of the condition and adherence to the treatment.[155] Patients receiving case management, including self-management support, within the CLFP had higher self-management scores as measured by the PIH scale, confirming known-group validity in cirrhotic patients.

Table 14. The PIH total score and subscale scores of cirrhotic patients with and without active case management.

PIH Scale (max score)	Mean (SD)			*p*-value
	All patients with cirrhosis (*n* = 133)	**Active case management (*n* = 60)**	**No active case management (*n* = 73)**	
Total score (96)	77 (15)	81 (12)	74 (17)	0.006
Knowledge (16)	12 (3.5)	13 (3)	12 (4)	0.012
Partnership (32)	29 (4)	30 (3)	29 (5)	0.185
Management of symptoms (16)	13 (4)	14 (2)	12 (5)	<0.001
Coping (32)	23 (8)	23 (7)	22 (9)	0.227

PIH: Partners in Health scale.

**p*-value was assessed using independent *t*-test.

As disease education was also provided as a part of the CLFP, the subscales of 'knowledge' and 'awareness of symptoms' were also higher in the case managed group. The relatively low scores in the coping subscale in the entire cohort, irrespective of case management, underline the need for a model of care that addresses this need.

Self-management support is the foundation of a successful CDM programme. It empowers patients with the knowledge and behaviour required to cope with a chronic disease successfully. Self-management strategies include education about the disease, its complications, awareness of symptoms of worsening, and adoption of healthy lifestyle practices to cope with the disease and to enjoy a better QoL. An effective strategy acknowledges the pivotal role of patients in CDM to make decisions in partnership with the healthcare providers. It encourages patients to take responsibility for their own health by managing their chronic disease appropriately in tune with medical recommendations. Cirrhosis of the liver is associated with high morbidity and mortality. The total annual cost of CLD in Australia, inclusive of the burden of disease, was estimated to be AUD 50.7 billion in 2012.[278] With the estimated escalation of CLD burden to 8 million in Australia by 2030, the liability on the health system due to this incapacitating chronic disease will rise accordingly. As recurrent

hospital admissions in cirrhotic patients contribute significantly to this cost burden, self-management initiatives are important to supplement close monitoring of these patients for optimal disease management.

Health-related quality of life (HRQoL) is reported to be very poor in patients with cirrhosis, especially in those with ascites and encephalopathy.[272] However, there is a scarcity of literature on the impact of self-management programmes on HRQoL in cirrhosis. This contrasts with the Chronic Angina Self-Management Programmes, which were shown to improve the HRQoL and self-management of angina.[279]

In a pragmatic randomised controlled trial (RCT) of the Flinders Program of chronic condition management in community healthcare services, the utility of the PIH scale was assessed.[156] It was found useful both as a risk assessment tool at baseline and as a process metric to detect improvement in self-management ability over time, in response to an intervention. This study also highlighted a statistically significant association between PIH scores and other important measures of chronic disease outcomes, such as fatigue levels, HRQoL, self-efficacy score and health distress scores.[156]

Application of the PIH scale in cirrhotic patients has the potential to identify domains of care that need improvement and deliver support in a customised fashion. Estimation of supportive care needs of cirrhotic patients is an area of research that is frequently overlooked.[17] This was highlighted in a systematic review that found only three studies that addressed the supportive care (non-medical care) needs of patients with cirrhosis among 26 studies in patients with CLD.[144] This meta-analysis highlighted the unmet need for a standardised tool to assess supportive care needs to facilitate delivery of a holistic care that improves poor QoL in these patients. To bridge this gap, Valery et al. developed and validated the Supportive Needs Assessment tool for Cirrhosis (SNAC).[148] This 39-item scale with subscales ‘Psychosocial issues’, ‘Practical and physical needs’, ‘Information needs’, and ‘Lifestyle changes’ was shown to have excellent internal consistency and correlation with CLDQ. Since the PIH scale measures self-management knowledge and behaviours, it is best coupled with SNAC tool to optimise supportive care in patients with cirrhosis.

A liver-specific self-management questionnaire known as ‘self-management behaviour scale’ was developed by Wang et al, consisting of 24 items in four dimensions, as follows[149]:

1. daily life management (seven items);
2. dietary management (seven items);
3. illness-monitoring management (five items);
4. medication management (five items).

Although this tool was validated in 180 patients with predominantly HBV-related cirrhosis, the dimensionality was not confirmed by CFA. In contrast, the structure of both the original and revised PIH scales were validated by CFA and BCFA in different patient cohorts.[155,157] Using the self-management behaviour scale, factors influencing self-management behaviour were studied in a cohort of cirrhotic patients by Dong et al.[150] Disease severity, depression and lower self-management efficacy were found to adversely influence self-management behaviours. In contrast, the study found higher self-management scores in patients with hepatic decompensation and advanced liver disease. This could be due to the self-management support that the study patients with decompensated cirrhosis received as a part of CLFP. Although the scale used by Dong et al.[150] was specific to patients with cirrhosis, the lengthy questionnaire (20 items) could be a barrier to patient participation.

An RCT from Southern Iran measured the effect of self-management support on self-efficacy in patients with cirrhosis of the liver.[153] Self-efficacy was measured using the Strategies Used by People to Promote Health (SUPPH) questionnaire at baseline, soon after the intervention and 1 month after the intervention. In the intervention group, the total score and some subscales (stress reduction, decision making and positive attitude) improved significantly both immediately and 1 month after the intervention, relative to baseline scores. Although this study reiterated the feasibility of improving self-management efficacy with self-management training, the SUPPH questionnaire used in the study was not validated in cirrhosis.

The current study adds to the evidence base that the PIH scale is a useful tool to evaluate effectiveness of self-management support provided by CDM models. The PIH scale can be used in a comprehensive assessment of self-management behaviour without the need for multiple questionnaires both as a cross-sectional tool and as a tool to detect changes over a period of time in response to CDM interventions in patients with cirrhosis. However, there is no data currently available to support this. A few limitations of this study are acknowledged. The PIH scale is not a disease-specific tool. While the patients were asked to report the tool with respect to cirrhosis, it is possible that other concurrent comorbidities could have interfered

with the assessment. However, the PIH scale was well validated for measuring self-management across a range of chronic diseases.[155] Therefore, the impact of this is likely to be minimal. Even though patients with overt hepatic encephalopathy were excluded, this study cannot exclude the possibility of some study patients with less severe underlying cognitive dysfunction, such as minimal hepatic encephalopathy, and hence potential confounding related to this. Finally, the clinical predictive value of the PIH scale in cirrhosis with meaningful outcomes, such as reduced hospital readmissions, was not addressed in this study. However, the study provides good pilot data on the potential usefulness of the PIH scale and highlights the need for further studies in larger prospective cohorts and RCTs with CDM as the intervention.

5.6 CONCLUSION AND FUTURE DIRECTIONS

In conclusion, the first validation of the PIH scale, a self-management instrument, which was well studied in other chronic diseases, was described in patients with cirrhosis of the liver. Its dimensionality and reliability in measuring self-management in cirrhosis were confirmed. Consistent with the literature in other chronic diseases, provision of self-management support and disease knowledge, as part of case management within a CDM programme, resulted in better overall scores when measured by the PIH scale in cirrhosis. Measurement of self-management behaviours using the PIH scale in cirrhotic patients is likely to facilitate identification of areas that need improvement and enable subsequent delivery of support in a customised fashion.

The effect of providing self-management support as a CDM intervention on PIH scores will be studied in the ongoing multicentre RCT Australian Liver Failure trial (ALFIE). In addition, periodic measurement at 3, 6, 12 and 18 months during the intervention will test for the improvement in PIH scores on a longitudinal scale. The predictive value of PIH scores towards clinically relevant endpoints, such as hospital readmission rate and survival, which is also planned as a part of the ALFIE trial, will further define the usefulness of the PIH scale in cirrhosis.

6. EVALUATION OF NURSE-LED CIRRHOSIS CLINICS: QUALITATIVE AND COST-EFFECTIVENESS ANALYSIS

A major part of this chapter has been submitted to and is currently under review by the journal *Gastroenterology Nursing* and the details are as follows:

> Nurse-led cirrhosis clinics, a novel model of care for stable cirrhosis: a qualitative and cost-effectiveness analysis.
> **Jeyamani Ramachandran**, Sharon Lawn, Matilda Swee Sun Tang, Anuradha Pati, Luisa Wigg, Rachel Wundke, Rosemary McCormick, Kate Muller, Billingsley Kaambwa, Richard Woodman, Alan Wigg. *Aus. Health Rev.* (submitted).

Authors' contribution details are given below:

> **Jeyamani Ramachandran**: Conception, design, data collation, analysis, interpretation, manuscript writing, revision and finalisation of manuscript.
> **Sharon Lawn**: Expert advisor for qualitative analysis, editing and approval of final version of manuscript.
> **Matilda Swee Sun Tang**: Data collection.
> **Anuradha Pati**: Data collection, data analysis and assistance with mind maps.
> **Luisa Wigg**: Data collection and data analysis.
> **Rachel Wundke**, **Rosemary McCormick**: Assistance with data collection and study design.
> **Kate Muller**, **Billingsley Kaambwa**, **Richard Woodman**: Critical review of the manuscript and approval of the final version.
> **Alan Wigg**: Overall supervision, critical review of the manuscript and approval of the final version.

6.1 SYNOPSIS

Background and aim: Optimal care of patients with cirrhosis of the liver in the setting of increasing prevalence requires the implementation of innovative models of care (MOCs). Nurse-led cirrhosis clinic (NLCC) is one such novel model practised for patients with compensated cirrhosis in the Flinders Medical Centre, Liver unit. The study evaluated the experiences of patients and the medical staff involved in NLCCs to assist with understanding the acceptability, strengths, limitations and areas requiring improvement of the model. Cost-effectiveness of the model in terms of cost minimisation was also assessed.

Methods: A prospective, qualitative analysis of the model was performed using semi-structured interviews. Participants included eight patients attending NLCCs for at least a year with a past experience of attending specialists' clinics, four hepatologists who refer patients and three specialist nurses (SNs) who run the NLCC. Thematic analysis of the interview transcripts was performed. A cost-minimisation approach was used to assess the cost-effectiveness.

Results: The study patients expressed satisfaction and a good understanding of the model. They preferred it to hospital clinics for better accessibility and the unique nurse–patient relationship. Upskilling and provision of professional care in a holistic manner were important to the SNs. The hepatologists also expressed confidence and satisfaction, although they acknowledged lack of complete medical training of SNs. The potential greater availability of hospital clinic time for sick patients was welcomed. Increased SN staffing, regular discussion forums to promote their learning and formalisation of the referral process were the suggested improvements. No adverse experiences were reported by patients or staff. The mean medical costs per patient visit in the NLCC was significantly lower than hepatologists' clinics (AUD 59.44 vs. AUD 102.72; $p < 0.001$).

Conclusions: The NLCC model for compensated cirrhosis delivered by experienced SNs was cost effective and well received by patients, hepatologists and SNs without any adverse experiences. Management of increase in workload with increased number and hours of SNs and regular forums to provide professional development were some of the suggestions received. The model should be tested with appropriate training of SNs under close supervision of hepatologists in other settings before any recommendations for implementation can be made.

6.2 INTRODUCTION

The increasing health demands of an ageing population with multiple chronic comorbidities is challenging the traditional models of care (MOCs) in Australia.[25] In accordance with patients' preferences the management of chronic diseases is trending away from hospitals and towards care in the community.[25] Nurse-led clinics (NLCs) are an important part of the modern medical care delivery chain. Examples of speciality NLCs that care for patients with chronic diseases includes those for diabetes mellitus, mental health conditions, chronic constipation, eczema, rheumatoid arthritis, cancer chemotherapy and sexually transmitted diseases.[26] Overall, NLCs are well accepted by patients in view of improved access, satisfaction, affordability and convenience.[26]

In hepatology, the role and efficacy of NLCs are well established in the management of hepatitis C (HCV).[27,28,29] Chronic liver disease (CLD) is an important cause of premature mortality in the Australian population.[1] However, there is no evidence for the use of NLCs in the management of advanced CLD (ACLD) or cirrhosis of the liver. In its natural course, cirrhosis of the liver remains compensated without any clinical events for a variable period ranging from 10 to 12 years[63] during which time regular monitoring of liver functions and surveillance (endoscopic and radiological) are required, usually without any need for active medical intervention. With the prevalence of CLD, estimated to increase to 8 million by 2030 in Australia,[4] periodic review of these stable patients in addition to caring for sicker decompensated patients is likely to pose a significant burden on the healthcare system. Nurse-led cirrhosis clinics (NLCCs) is a model practised at Flinders Medical Centre since 2013, wherein stable patients with cirrhosis of the liver (Child–Pugh Class A) who require only monitoring and surveillance are reviewed 6-monthly by specialist nurses (SNs), under remote supervision of hepatologists. Such clinics have the potential to address the increasing disease burden of cirrhosis on healthcare workload and costs.

Given the novelty of the model, a qualitative study was performed to obtain insights into both patients' and providers' (hepatologists and SNs) views of these clinics in order to identify their strengths and potential areas for improvement. In addition, demonstration of cost benefits associated with these clinics may encourage wider implementation of this MOC. Hence, this study was conducted to provide a qualitative analysis and assessment of cost-effectiveness of NLCCs.

6.3 METHODS

An inductive, descriptive, semi-structured interview study design was chosen for this prospective qualitative process evaluation of NLCCs. This study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (HREC/18/SAC/316).

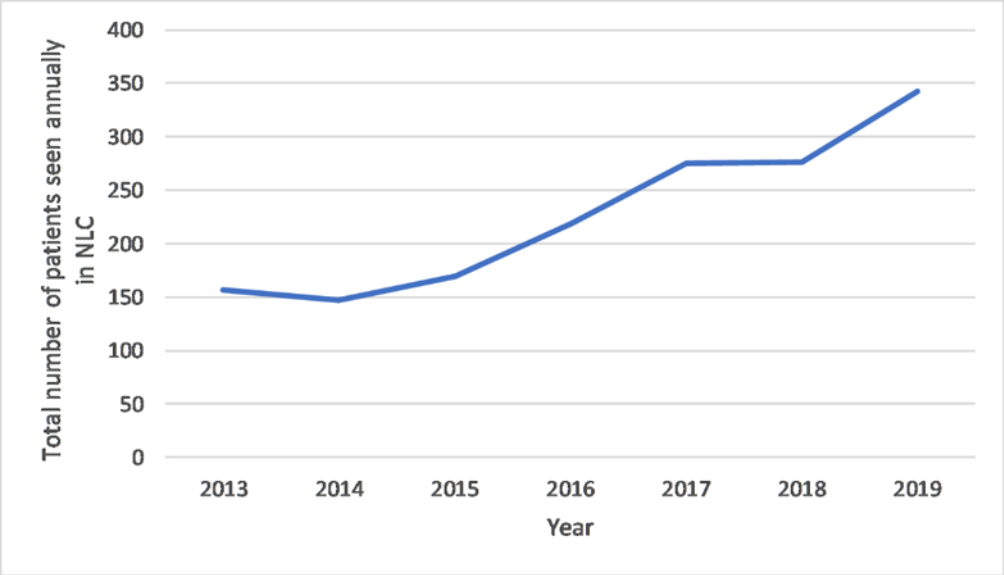
6.3.1 *Organisation of NLCCs*

The SNs who deliver outpatient care in NLCCs were trained on-the-job for nearly 10 years in the Liver Unit at Flinders Medical Centre. Funding for liver SN positions was initially sourced from a hospital avoidance programme within the Southern Adelaide Local Health Network in 2009. Since then, the SNs have been actively involved in the management of cirrhotic patients under close supervision of hepatologists as part of the Chronic Liver Failure Program (CLFP), a chronic disease management (CDM) initiative.[11,14,126] Their role involves case management for patients discharged from hospital following an admission for cirrhosis decompensation, and includes post-discharge phone calls, home visits, self-management support with patient and carer education, patient action plans for complications (ascites and hepatic encephalopathy), access to day care therapeutic large-volume paracentesis and a rapid access to care pathway for deteriorating patients. Furthermore, with the experience of observing hepatologists in clinics, their role subsequently expanded to outpatient management of stable patients.[181]

Since 2013, NLCCs that cater to compensated patients with cirrhosis have been an integral part of hepatology services at Flinders Medical Centre. Patients are referred to these clinics for monitoring and surveillance for cirrhosis by SNs after review by hepatologists, in the absence of any active liver-related medical issues. These NLCCs are co-located with primary health services near major transport and shopping hubs. Three such clinics are run fortnightly in which patients are reviewed every 6 months. Any active medical problems detected in these NLCCs are discussed with the hepatologists. In addition, the SNs provide disease education as well as evaluation and management of risk factors, such as alcohol and obesity, osteoporosis screening and vaccination for hepatitis A and B viruses. General practitioners (GPs) and hepatologists concerned receive regular communications from SNs about these visits, and thus have updated information on all developments. Any biochemical or clinical deterioration, as evidenced by symptoms of hepatic decompensation or worsening of Child–Pugh score (which is monitored biannually), results in referral back to the hepatologist's clinic. In contrast, there is only one consultant-run liver clinic (by four consultants) in the hospital every week. NLCCs cater

exclusively to stable cirrhotic patients, whereas the hospital consultant clinics must accommodate all other hepatology referrals including urgent appointments for hepatocellular carcinoma (HCC), decompensated liver disease and undiagnosed liver function test abnormalities. Thus, the NLC model enables the management of an expanding list of new and sick patients by hepatologists without compromising the ongoing care for chronic stable patients. Since its inception, the number of patients seen in NLCCs has increased from 150 in the year 2013 to 330 in 2019 as shown in **Figure 9**.

Figure 9. Trend of patient numbers reviewed in NLCCs over the years.



NLCC: Nurse-led cirrhosis clinic.

6.3.2 *Qualitative Exploration*

6.3.2.1 *Patients' Experiences*

The first arm of the study analysed patients' experiences in NLCCs. Given the focus of this qualitative analysis was to obtain a rich understanding of the patients' experience, rather than studying large numbers, a sample size of 10 patients was planned.[280] To achieve this, 16 patients were approached. Potential participants were identified from the electronic database of NLCC in March 2019 with a plan to interview participants in June 2019. Patients were included if they had at least two NLCC visits before their interview and at least two hepatologists' clinic visits prior to NLCC transfer. Non-English-speaking patients, those not completely transferred for nurse management (that is, alternate reviews with hepatologists), patients with a current unstable psychiatric diagnosis and/or cognitive impairment were

excluded. Of the sixteen consecutive eligible patients approached ten patients agreed to participate. However, only eight patients were interviewed (one cancelled the interview due to an acute diarrheal illness and the other declined participation later). Their demographic information is provided in **Table 15**.

After obtaining written consent, semi-structured interviews were conducted by a final year medical student, uninvolved in patient care, in a private space within the NLCCs for ease of attendance by the patients.

Interviews were conducted between July and August 2019. The interviews aimed to obtain a deep understanding of patients' experiences in these clinics using a variety of open-ended and occasional closed-ended questions (**Box 6**). Patients were prompted to expand on their answers when their responses were brief.

Box 6. Patient interview guide.

Tell me about your experience of seeing a Liver Nurse for your chronic liver disease.
What are the good things about the nurse clinic?
Anything you don't like?
Is there anything that would make the service better?
How is the nurse-led clinic different to seeing the Liver Specialist at the hospital?
How have you found the logistics (for example, reminders, parking, waiting time)?
How do the logistics compare to seeing the doctor at FMC?
What do you think about the quality of care at the nurse clinic?
Do you feel confident of receiving appropriate care?
What does the nurse discuss with you at your appointments?
Do you think the care is different or the same as seeing the liver specialist? If different, in what ways?
What would be your future preference given a choice?
Reasons for this preference?
Is there anything else we haven't discussed that you'd like to tell me about?

6.3.2.2 *Hepatologists' and specialist nurses' perspectives*

The study also explored the views and experiences of hepatologists and SNs involved in these NLCCs. For this, four hepatologists who organise NLCC referrals and three SNs who deliver care in NLCC were interviewed in December 2019. Demographics of the staff were as given in **Table 15**.

Two medical students conducted these interviews, guided by open-ended interview questions (**Box 7**). Written consent was obtained from the participating staff.

Table 15. Patient and staff demographics.

Study group	**Data**
Patients	*N* = 8
Age in years (median, IQR)	64 (20)
Male gender, *n*	6
Duration since diagnosis in years (median, IQR)	5.5 (3.8)
Duration of NLCC attendance in years (median, IQR)	2 (1)
Aetiology of cirrhosis (*n*)	
Alcohol	4
NAFLD	3
HCV	1
Hepatologists	*N* = 4
Age in years (median, IQR)	49 (14)
Male gender, *n*	3
Duration of practice in current role in years (median, IQR)	16 (12)
SNs	*N* = 3
Age in years (median, IQR)	46 (12)
Male gender, *n*	1
Duration of practice in current role in years (median, IQR)	11 (10)

HCV: hepatitis C virus; IQR: inter-quartile range; NAFLD: nonalcoholic fatty liver disease; NLCC: nurse-led cirrhosis clinic; SNs: specialist nurses.

Box 7. Medical practice staff interview guide.

FOR THE DOCTORS

Opening question

What is your opinion on nurses looking after stable cirrhotic patients who need monitoring?

Follow-up questions

What are the possible benefits?

Do you think there are any adverse implications? If so, please elaborate.

What is the kind of training required by the nurses to be able to run these clinics?

What are the key issues that need to be discussed by the nurse?

What do you see as the most important aspects of delivering this service to cirrhotic patients?

How can we install system checks?

How can this model be improved?

FOR THE SNS

How do you feel about your role in the nurse clinics for stable cirrhotic patients?

Do you think that you are well equipped with protocols and guidelines to perform your role?

When you run into problems how and from where or from whom do you seek support?

What is the referral pathway when patients become unstable?

How has this role helped you advance in your profession and career?

How are you supported and supervised?

Do you feel confident when you deliver the care?

How can this model of care be improved?

What do you need to improve in doing this job?

What do you see as the most important aspects of delivering this service to cirrhotic patients?

Were there any adverse implications?

6.3.3 *Cost-Effectiveness Analysis*

Cost minimisation is a unique type of CE evaluation that is undertaken when two types of treatments with equivalent outcomes are compared. In our case, the two models of care, namely, hepatologist clinics and the NLCCs, that render similar services were compared with respect to their cost for the period January to December 2019. This included costs for

hepatologists' visits in the public hospital clinic, time spent by nurses in NLCCs, administration of public hospital clinics and NLCCs, and minor costs, such as car parking fees.

Hepatologists' costs were calculated based on rates from Power Budgets Labour Template for all salary positions within South Adelaide Health Network as obtained from the hospital administration. Nurses' cost was calculated based on the South Australian Public Health Sector Enterprise Agreement. The total number of patients seen in NLCCs from January to December 2019 were obtained, and mean patient costs in both models were calculated and compared using Wilcoxon signed-rank test, IMB SPSS statistics for Windows, version 24. For this analysis, only the direct medical costs were calculated. Indirect costs, such as loss of wages, costs of carers and transport costs were not considered. The cost of investigations and medications were not compared as they would have been equivalent for both the models.

6.3.4 *Qualitative Analysis*

All interviews lasted between 15 and 30 minutes, were audio-recorded and professionally transcribed. The de-identified texts were imported into NVivo (a qualitative data analysis software package by QSR International, Melbourne, Australia) to facilitate coding and data management. Thematic analysis of the transcripts was guided by the six steps proposed by Clarke and Braun.[183] First, the lead author and a co-author reviewed interview texts and obtained a comprehensive overview. Provisional open codes were then applied to the texts in NVivo. The authors discussed, debated and added new codes, while constantly reviewing the texts. The codes were merged into tentative subthemes and themes. Final labels of subthemes and themes were subsequently determined. Thematic saturation was noted in the last two interviews in both sets. The draft themes and subthemes were then reviewed by a senior co-author, who also reviewed the interview transcripts. The senior author then interrogated and sought clarification on the codes and themes from the lead author as required, and thus the investigators reached an agreement on the thematic analysis. These discussions occurred over a series of face-to-face meetings, thus improving the strength of the analysis. Three investigators created mind maps to visually guide their discussions during the analysis process.[281]

This enhanced their decisions and parsimonious representation of main overarching themes and subthemes, and selection of quotes that best represented each theme or subtheme. These

findings were then presented to the rest of the research team for discussion, with any revisions made after deliberation and agreement by the research team before the writeup was finalised.

6.4 RESULTS

6.4.1 *Profile of the Patients*

Eight patients with cirrhosis of the liver participated in the qualitative study. Their clinical and demographic details are described in **Table 15**.

6.4.2 *Patients' Perspectives*

Four major themes that emerged in the analysis of patients' experiences include

1. accessibility;
2. nurse–patient relationship;
3. patient satisfaction;
4. understanding the MOC.

The subthemes and pivotal direct quotes to exemplify the themes are provided in **Table 16**. The relationship between the themes and subthemes are graphically represented in a mind map (**Figure 10**).

6.4.2.1 *Accessibility*

Easy access to the NLCCs in comparison to the usual specialist-run clinics was the most often noted and a universally acknowledged theme among the patients.

The clinic ambiance with shorter waiting times, less noise and greater privacy while waiting to see the nurse were cited as reasons to prefer NLCCs, compared with the large and often crowded specialist clinic waiting area. Patients also reported being less worried about acquiring infections and being less anxious concerning the NLCC visits; stating that it supported them in maintaining their compliance with clinic visits.

Patients stated that one of the important contributing factors to the improved accessibility of NLCCs was the approachability of the nurses that resulted in them feeling less anxious about the clinic visits.

6.4.2.2 *Nurse–Patient Relationship*

Patients felt that they were experiencing personalised care; they perceived the SN as friendly and warm, and felt that the SN took the time to convey genuine concern and care; knew them and their day-to-day disease management and related psychosocial needs better than the consultants. They described how this approach by SN supported their sense of hope and self-efficacy to manage their health and strengthened their sense of trust in the care provided and those who provided it. Many patients felt that these clinics were welcoming, non-judgemental and non-stigmatising. They were also more able to openly discuss nutrition and other issues relevant to their care, such as weight maintenance and alcohol, with the SNs, without fear, shame or embarrassment. The familiarity of seeing the same nurses rather than different doctors at the hospital clinics was important for many patient participants. They also described and appreciated nurse-led consultations as less formal and more relaxed.

6.4.2.3 *Patient Satisfaction*

Almost all the patients were confident that they were receiving a thorough, professional care from the SNs in NLCCs. Patients also felt that the SNs provided them with more detailed information about their illness than the doctors. They reported being happy with the way information was provided in simple terms, better matched to their level of health literacy and how they could readily apply it to their day-to-day self-management context. Since they were well informed of the developments in their disease process and periodic developments, they felt a sense of partnership in their care. This active participation is very vital in the management of chronic diseases because it fosters compliance in the long term.

6.4.2.4 *Understanding the Disease Process and the MOC*

One of the surprising themes that emerged was how well these patients understood the natural history of cirrhosis and the need for NLCCs. They were aware of the need to monitor their health and conscious of how precious doctors' time was. They emphasised that hospital clinics should be reserved for sicker patients, and well-trained nurses could manage stable patients

under the guidance of doctors. Most of the patients were also aware of the need for radiological tests and further confirmatory tests. It was encouraging to know that the patients considered NLCCs as a continuation of their hospital care in a less-intensive way. They did not view it adversely as being ignored or being offered a suboptimal option. All the eight patients expressed satisfaction with and a clear desire to continue their NLCC appointments rather than to change to specialist-run clinics.

Table 16. Important quotes, subthemes and themes of the experiences of patients.

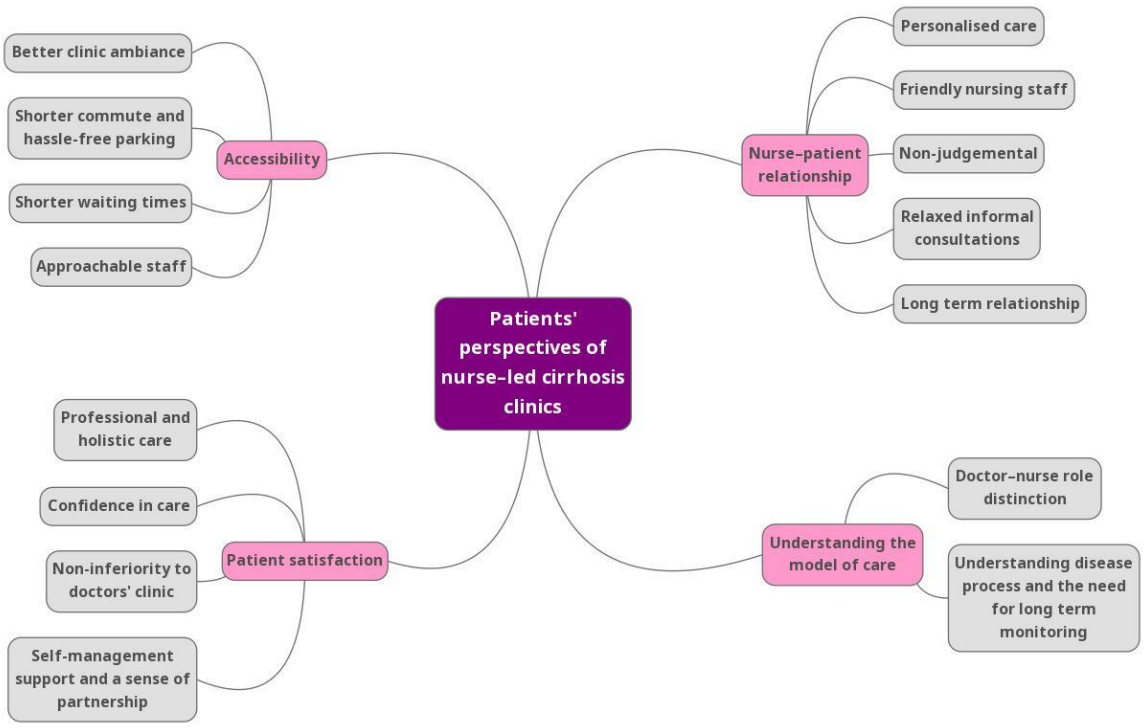
Themes and subthemes	**Quotes**
Accessibility	
Convenience	"That's about it really. It's just the time and the distance and parking."
Manageable logistics	"I certainly don't mind coming here. It's quicker and easier than going to Flinders." "No, parking's easy (NLCCs). I always get a park just across the road."
Better ambiance in the clinic with less crowd and low risk of infections	"Yeah, well I think the biggest bonus is having a liver condition you always worry about going into hospital and catching something or getting crook."
Organisation of the clinic with shorter waiting times	"Well, Flinders is a big waiting room with lots of people. Here it's usually you can find a nice, quiet spot, do some studying. That's the basic difference." "The waiting time at Flinders Medical Centre is longer. This here's quicker"
Accessible staff	"I never feel like I'm unwelcome. The one thing I've picked up on is that they know how to say things that give me a positive frame of mind." "I love coming here. The reason being, it's not the hospital, easy parking and R (one of the nurses) is very nice and good to get on with, so I'm more than happy to keep going this way."

Nurse–patient relationship	
Personalised care	"Distance, time and they're friendlier. You feel like a person, not just a name on a piece of paper."
Friendly nursing staff	"Extremely caring, understanding, patient-friendly yet professional and extremely helpful and supportive." "The content of the conversation with the liver nurse might be a little bit more personal or friendly or a bit more social perhaps in certain aspects, but I will always feel a very genuine sense of care from them. The specialists can be a bit more direct and perfunctory."
Non-judgemental, non-stigmatising, open communication	"Being an alcoholic, I didn't even think it was a disease, but it is a disease and we talk about the steps I'm taking and what I'm doing about it and it's very good, it's very casual, she's very supportive and that's what I like." "You're not getting lectured, so it's a very good experience, I love it."
Relaxed informal consultations	"So, it is nice to be able to have a chat with people who understand and who have been there from the start."
Long-term relationship	"It's more of a relationship than some clinics and I think because of the long-term relationship there's a bit more of an interest and personal care that goes into it." "They change doctors a lot which was frustrating because you didn't get a rapport."
Patient satisfaction	
Professional and holistic care	"I get exactly the same information that I was getting from the doctors." "I think taking a whole broad approach to what the blood tests entail." "They often touch on my weight, weight is an issue for me and their way of negotiating around that subject is always direct, positive and well meaning, bit more interest (than doctors) in my general well-being."

	"They often talk about what I'm eating. They ask me questions and my answers are important to them."
Confidence	"I'm confident that they know what they're doing." "Excellent, really good, Fantastic."
Non-inferiority to doctors' clinic	"I have always felt that the nurses have been up to date with what they ask and the things they want to know, and I don't see that there would be really any difference in speaking to a doctor." "They're very well informed and I believe that they know what they're doing." "I mean, obviously it's got the same outcome sort of thing."
Self-management support and a sense of partnership	"I need to keep an eye on how my liver is going which is why I have the MRIs." "But I know I'm looking after myself. And, the girls are aware that I'm doing the right thing." "And, then we get into the initial bloods and ultrasound results and depending on what those results show, any ideas or ways that I can help or improve." "Sort of run through what I've been doing for the last 6 months and say, you know, could that be a factor or is that a plus or a negative?"
Information update	"They've been really knowledgeable, and they've answered most of my queries and if they can't they've said, 'Look, leave it with me and I'll send you an email once I've talked to the doctors back at Flinders.' " "Yeah, they tell me a few things that the normal GP didn't have a clue of."
Understanding the model of care	
Doctor–nurse role distinction	"If it's just maintenance and routine follow-up, I'm happy with the liver nurse, but if it's to explore and discuss more serious issues that are coming out through the tests or if my general wellbeing and so on is not going so well, then I would probably prefer to see the specialist."

	"On a personal basis, I think what doctors they're do is the organiser and they give instructions to the nurses on how to treat people like me. So, really the liver nurses reflect the doctor's attitude and knowledge."
Understanding the disease process and the model of care	"I think it's important because it frees up resources so other people who have more need than me get to see the doctors, whereas I'm quite comfortable being monitored and I know that if something needs to be done that you guys will let me know."

Figure 10. Mind map of patients' experiences at NLCCs.



6.4.3 *Medical Care Providers' Perspectives*

Four hepatology consultants who refer patients to NLCCs and three SNs who run these clinics were interviewed. The three themes that emerged were

1. positive aspects,
2. concerns,
3. suggested areas of improvement.

The relationship between subthemes and themes are shown in a mind map in **Figure 11**. Exemplifying direct salient quotes are described in **Table 17**.

6.4.3.1 *Positive Aspects*

Both the doctors and nurses felt that care of stable cirrhotic patients in NLCCs would reduce waiting times in hepatologist clinics for new and sick patients awaiting consultant appointments. This would result in doctors being able to prioritise cirrhotic patients with urgent medical issues. At the same time, the stable patients were not lost to follow-up. Their care was continued in a less intense but a more holistic way. SNs were happy about being able to spend more time with patients focussing on issues, such as nutrition, alcohol and obesity, that could be neglected in a busy hospital hepatology clinic. One of the hepatologists felt that NLCCs had the potential to reduce emergency liver-related admissions by early detection of complications during the routine clinic visits. Bone health and surveillance are given a lot of importance in NLCCs. This was perceived as a major advantage of NLCCs by the hepatologists, as they could be missed in the busy doctor clinics. It was felt that NLCCs were ideally positioned to communicate between doctors and patients.

The SNs felt that a 30-minute appointment time helped them develop good rapport with patients and subsequently impart self-management skills, which was also cited by the doctors to be a valuable benefit of NLCCs. The easy access, shorter waiting times, convenience in booking appointments, attendance with shorter commuting times and improved parking in these NLCCs were also acknowledged. The hepatologists also expressed that NLCCs were cost-effective MOCs for compensated cirrhosis.

The SNs felt that the NLCCs expanded their clinical and communicative skill set. Liaising with GPs via the NLCCs was also appreciated by the SNs. Likewise, the hepatologists also appreciated the upskilling of nurses, resulting in almost independent management of stable patients.

The hepatologists seemed confident and supportive of the thorough care provided, which they thought was superior to the GP care for cirrhosis. The SNs seemed confident of managing patients with the provided protocols.

6.4.3.2 *Concerns*

The lack of full medical training by SNs and the potential risk of missing crucial medical events were potential concerns raised by the hepatologists. However, they mentioned that SNs could be trained with protocols to detect hepatic decompensation. One hepatologist observed it to be challenging to convince GPs and other hepatologists to accept the safety of this nontraditional model but believed that this could eventually be achieved via development in the confidence of the SNs' skills and their ability to report derangements.

The SNs felt that the role in stable cirrhosis was narrow and was not difficult to handle. Hence, they had no concerns about lack of formal medical training. However, they reported a risk of being overworked with the recent increase in patient numbers, which was agreed by the hepatologists.

The SNs suggested that expansion of their role with more time and personnel might avert the issue. In addition, the lack of onsite consultant support in the NLCCs was also cited as a concern by one of the SNs, as only remote supervision is provided. However, uninterrupted phone access to the on-call hepatologists could mitigate this concern.

6.4.3.3 *Suggested Improvements*

The SNs insisted that the referral process should be made more formal with clear written protocols on inclusion and exclusion criteria for review in NLCCs. They expressed ambiguity about some non-cirrhotic portal hypertension patients referred to them. It was thought that a more formal process would free up more spaces in consultant clinics. Improved staffing was suggested to increase the number of patients seen in NLCCs.

Most importantly, SNs felt the need for a regular forum to discuss NLCC patients instead of the impromptu discussions. Regular case presentations were thought to improve their learning. Training opportunities for SNs to observe doctors' clinics was proposed by a hepatologist to help them fine-tune their clinical skills.

Another potential innovative model that emerged from the study was the suggestion of a phone clinic alternating with physical clinics for very stable patients that could minimise the workload for the SNs.

Table 17. Themes, subthemes and important quotes of the hepatologists' and SNs' views.

Themes and subthemes	Quotes
Positives	
Potential reduction in waiting times for sicker patients	C: "From our perspective like waiting times in the doctor's clinic can be reduced by removing that group of patients from the clinic."
Enabling focus on sicker patients	C: "There are benefits to us for those patients to be seen elsewhere so we can concentrate on the sicker patients."
	SN: "It then frees up clinics here for our consultants to see sicker patients, new referrals and let that flow happen and it also works with our funding as well which is about out of hospital activity, so it has taken people out of the acute sector and seeing them in the community, so that works with our funding model as chronic liver disease nurses."
Patient convenience (accessibility)	SN: "They don't have to battle to get a car park, they like being closer to home."
	C: "They're going to turn up more if they can get there, if its' closer to their home."
Reduction in waiting times for stable patients	SN: "No real waiting time. We can generally slot them in when they're next due."
Holistic and improved care for stable patients	C: "The stable patients need sort of surveillance, you know, 6-monthly ultrasounds, blood tests, endoscopies, vaccinations, bone densities and the nursing staff are very good at making sure that happens and doctors are a bit forgetful, we're busy, we're rushed. So, it's been good for patient care."
	C: "GPs are a bit rushed, too busy to organise all the surveillance they need."
	C: "From the patient perspective, they get probably a more thorough review because the nurse can spend longer with them, talk through other issues, I think they have a lot more time to talk about social

	situation and other things that can impact on liver disease like alcohol use and things like that, so I think from the patients benefit; they can have a bit more intensive review."
	C: "They can keep patients from having to come into hospital for anything but serious deteriorations in their condition."
	SN: "Getting to know the patient and developing that rapport … that availability to look outside the square a little bit and get those people of a bit of a broader care."
Education of patient and enabling self-management	SN: "It's about just getting the patient to manage themselves and to know what's important for them because if they understand it, then they'll attend more, and I think our attendance rate is pretty good in NLCs compared to clinics here at Flinders."
	C: "One of the key roles they have is education of a patient."
	C: "Self-management, really trying to make patients manage themselves is a goal and I think the beauty of nurses is they generally have a lot more time and a lot more skills in that area and so that's a big advantage."
Well-coordinated care	SN: "Having good communication and rapport with the client and also feeding back to the general practitioner who really has been the key person for them in managing their general or overall health."
	SN: "We have good protocols, we have good education material, we've got a cirrhosis booklet now which we have developed which has got those care plans in."
	SN: "We are also well supported by the department here, but if we've got concerns, we know we've got the backup if we need it."
	C: "Easy access of nurses to either the patients specific hepatologist or the duty hepatologist who is on at any given time."
Professional development for nurses	C: "It has also been very good for upskilling the nurses that are looking after, you know, patients independently for years."
	C: "The role is quite a narrow one and I think we can train them up to a standard and using protocols."
	SN: "It's expanded my skillset."

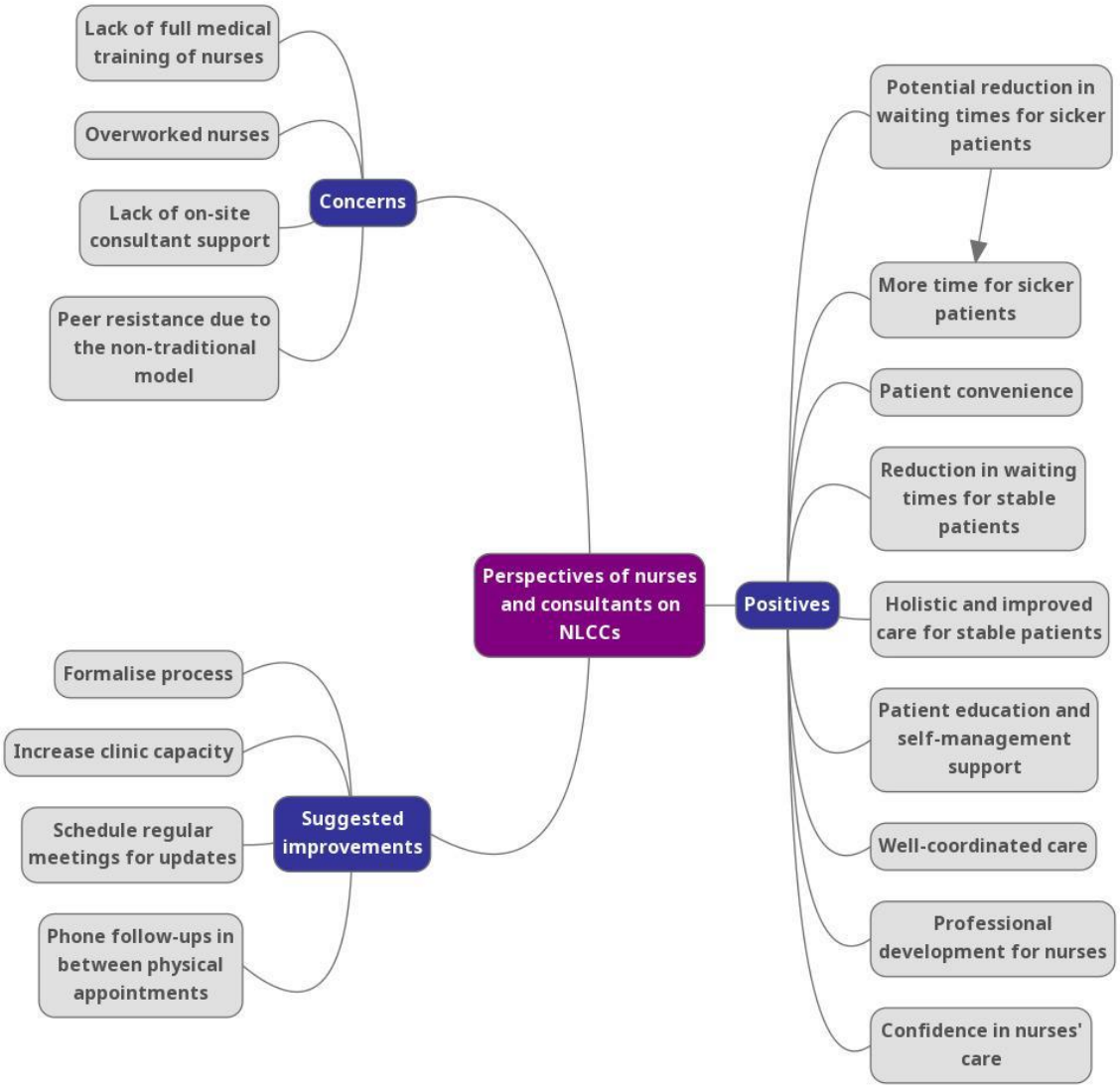
	SN: “We spent a lot more time in outpatients with the patient and the consultant, so I guess it was learning as we went, learning what people look for.”
	SN: “It’s given me skills to seek out other opportunities probably down the track.”
	SN: “It’s given me I guess, a little bit more scope to work in that community environment as well, to liaise with GPs and work closely with GPs with some of those clients.”
Confidence in nurses’ care	C: “The nurses also are quite protocol driven, so it makes sure that all the things get done; whereas I think sometimes doctors forget to order certain tests or do, you know, everything properly.”
	C: “They are very thorough, they know exactly what they are looking for, they are upskilled, so they are very good at looking after the cirrhotic patients and they know what sort of triggers would need to be checked with one of us.”
	C: “I think our nurses do a great job.”
	C: “I think there are very few downsides.”
	SN: “The actual delivery and I think the clinical component are quite satisfactory and very high class.”
	SN: “I feel very confident. Those protocols make it easy.”
	SN: “There is communication with the GP, so if there are other non-liver comorbidities or problems that occur outside of our context that the GPs are aware of who they can contact in an efficient way to discuss things.”
	C: “They can obviously communicate between patients and the doctors.”
	C: “All the correspondence is reviewed by us before it goes out, so if there is anything that’s a bit of a flag there, you know, if they’re getting a bit of ascites or anything like that, they let us know.”
Concerns	
Lack of full medical training of nurses	C: “Potentially that without full medical training the nurses might miss certain signs of things which might not be necessarily liver

	disease, but that are out of the scope of their area, so that could potentially be something that they miss."
	C: "Obviously the nurses do not have the clinical experience and the broad clinical experience the doctors do and that has to be acknowledged, but again, the role is quite a narrow one and I think we can train them up to a standard and using protocols."
	SN: "I think the role is not that hard which is why the specialists are referring them."
	SN: "Nurses in general, if this is done and sort of rolled out everywhere that nurses need to have a formal, proper training course to do, … on the job training is definitely something to do."
Overworked nurses	C: "Here it's just a matter of, you know, if the nursing staff are getting overwhelmed, making sure that there are extra resources so that they can do more clinics."
	C: "We have quite a large number of patients who are going to stay there for a long time and if we are continuing to refer, they are going to run out of capacity. So, I think more staffing to give them more capacity."
	SN: "I think one of the problems is the workload."
Lack of consultant support in the clinics (onsite)	SN: "And, support wise, … as support in the GP clinics, we don't have any, we're alone."
Need to gain trust of patients and doctors/ nontraditional model	C: "I think it's challenging for, you know, some people because it's not a traditional way of care. It does involve some clinical responsibility to nurses and I think one of the challenges is getting GPs and some consultants to understand that this is a necessity and that it's safe, but it does challenge traditional models of care and that is one of the adverse things, is trying to manage the push back from the GPs or consultants who don't quite understand the problem and getting them to buy in."
	C: "I think as long as your nursing staff are that you're comfortable with them and comfortable with their skills, and that you're confident that they will report major derangements, I think there are

	very few downsides. I think that once they gain the trust of patients, the patients accept them and value them as important as they value their consultants."
Improvements	
Formalise process	C: "The other thing is making sure that we have an electronic medical record that is visible to everyone involved in patient care."
	SN: "It's not written anywhere, and I think perhaps there could be some more written protocols, we're getting some patients that don't technically fit who we are especially looking after like patients with non-cirrhotic portal vein thrombosis."
Potential to increase clinic capacity	SN: "I think capacity is probably where we could look at improvement that we could see more patients."
	SN: "Availability and staffing is where we would look."
Schedule regular meetings for updates	SN: "Some sort of fairly regular review of cases would be important, so somebody who is responsible maybe on a weekly basis to discuss cases, make sure things are going in the right direction."
Phone follow-ups in between physical appointments	SN: "For some really stable patients, phone follow-up could improve the experience for them, so that we don't miss on any follow-ups."
	SN: "Even if it was just, you know, once in every 6 months, so they could have a face to face and then the next one could be on the phone in 6 months and if there was any changes obviously they would be coming back in, but sometimes I think patients are rocking up or travelling for long distances just to sit for 5 minutes and run through some results that could perhaps be done over the phone, that sort of thing just to make it easier for them."

C: consultant; SN: specialist nurse.

Figure 11. Mind map of medical care providers' perspectives of NLCCs.



NLCC: nurse-led cirrhosis clinics.

6.4.4 *Cost-Effectiveness Analysis*

Cost minimisation for the most recent year 2019 was calculated based on the number of patients who visited NLCC from January to December 2019. As these patients would have otherwise attended hepatologists' clinics in the hospital, those hypothetical costs were also calculated in addition to the costs of NLCCs, and comparisons were made between them (**Table 18**).

Table 18. Comparison of NLCC and hepatologists-run hospital clinic costs (mean costs in AUD).

Costs	NLCC	Hepatologists' clinic
Nurse or consultant cost	Per 30 minutes: 17.44	Per 20 minutes: 42.27
Car parking cost	0	7
Administrative and management	42.00	53.45
Mean total cost*	59.44	102.72

p-value calculated by ranked Wilcoxon signed-rank test, IMB SPSS statistics for Windows, version 24.
*$p < 0.001$.

As shown in **Table 18**, there was significant cost minimisation in NLCCs despite excluding hidden costs, such as carer costs and loss of wages and productivity. For the 336 patients reviewed in NLCCs during the year 2019, there was a cost minimisation of AUD 14 542.08.

6.5 DISCUSSION

An NLCC is a novel MOC in the management of compensated cirrhosis. This study provides an important first ever qualitative analysis of the patients' and healthcare providers' experiences in these clinics, thereby helping to identify the model's strengths and potential areas of improvement. In addition, the study demonstrated lower overall fixed costs per patient within the model as compared to the traditional hospital clinics.

Four major themes, namely accessibility, nurse–patient relationship, patient satisfaction and understanding the model encapsulated patients' experiences.

Patients consistently reported a preference for the NLCCs compared to the hospital clinics due to its community location, easier parking and shorter waiting time. It was not surprising that all the patients unanimously agreed on how easy it was to attend these clinics, without worrying about driving long distances or parking. This finding is supported by a randomised controlled trial (RCT) comparing nurse-led primary-care obesity clinics and hospital-based consultant-led clinics, in which the nurse-led clinics fared better in terms of access and convenience.[170] Proximity to home and accessibility of services were also reported as favourable features of

drop-in sexual health clinics run by nurses in South West England.[168] Shorter waiting times and hospital stays in a rural emergency clinic manned by nurse practitioner were met with patient satisfaction.[282] The improved accessibility of NLCCs might improve cirrhotic patients' compliance with clinic attendance, translating to better compliance with radiological and endoscopic surveillance, earlier intervention for complications, and improved long-term disease management. There are reports of adverse experiences, such as longer waiting times, uncomfortable waiting areas, inconveniences experienced at clinic appointments leading to poor compliance with clinic appointments, with the organisation of doctors' clinics.[134] Hence, it is very important that patients appreciate the convenient logistics of the NLCCs which is likely to foster compliance in the long run.

The style of engagement of the SNs and the time spent providing chronic condition self-management support appeared to be of importance to the cirrhotic patients treated in the NLCC model. There is evidence that self-management and self-efficacy are enhanced by effective communication between patient and care provider.[134] The sense of partnership with care providers reported in NLCC is very vital to the long-term management of cirrhosis. Lack of health-seeking behaviours and negative attitudes are not uncommon due to self-assumed stigma in patients with cirrhosis due to alcohol and HCV.[283] Instead, patients in NLCCs reported feeling less stigmatised and more receptive to information on alcohol abstinence and other aspects of lifestyle, such as diet and body weight. As alcohol and NAFLD are the most frequent causes of CLD, NLCCs are thus uniquely positioned to contribute towards optimal cirrhosis management by addressing these aetiological factors.[271] Successful risk factor modification has been reported in NLCs with different patient populations. For example, reduced substance abuse and improved health-related quality of life (HRQoL) were described following attendance in NLCs.[26,169] Ingram et al. reported adoption of safe sex practices and less risk-taking in the attendees of nurse-run youth sex clinic.[168] Two visits to a nurse-run respiratory clinic improved knowledge on chronic obstructive pulmonary disease, quality of life and, most importantly, decreased smoking significantly in comparison to standard care.[167] Nurse-run primary-care obesity clinics were found to be non-inferior to specialist-run hospital clinics in achieving reduction in body mass index, compliance with treatment and quality of life.[170]

Patient satisfaction as expressed by our patients on receiving a thorough professional care in the NLCCs is consistent with other studies.[26] NLCs have met national standards in healthcare effectiveness quality indicators and improved healthcare access to under-privileged patients.[284]

It was not surprising that all the patients in the study preferred being followed up in NLCCs. This is similar to the perceptions of patients served by Emergency Nurse Practitioners in the United Kingdom who preferred to attend the nurse-run emergency services.[282] Unlike the reports of 'feeling exposed', 'being controlled' and 'feeling disappointed' noted by Edwall et al. and Nymberg in diabetic clinics and lifestyle clinics, respectively, no negative feedback was reported with the NLCC model.[285,286]

From the analysis of healthcare providers' experiences, it was evident that potential shorter waiting times for new patients and continuous care of stable patients as achieved by the NLCC model were important. A more thorough and well-rounded approach by nurses with focus on radiological surveillance, education and self-management was appreciated by the doctors and the patients alike. The hepatologists saw SNs as complimenting the complex cirrhosis care and, hence, there was mutual respect for each other's role which contrasted with the traditional expectation of roles. There was a clear message from the study that a team care model delivered by SNs with remote supervision from specialists rather than a complete reliance on specialists is the way forward.

A pragmatic RCT study design to explore the effect of NLCs on physical and mental HRQoL was reported by Hjorth et al.[176] In this study the authors aimed to *compare* an organised nurse-led intervention in the form of clinic visits in addition to medical clinic visits *with* only medical clinic visits. The interventional visits varied according to the disease severity as follows:

- compensated cirrhosis – 12-monthly;
- current decompensation – twice a month;
- previous decompensation – every 3 months.

The primary outcome will be measured using RAND-36 at 0, 12, 24 months of enrolment. The study results will be available after its completion in 2020. Unlike our study, where patients with compensated cirrhosis of the liver were exclusively looked after by nurses, in this study nurse clinic was planned as an adjunct to the doctors' clinic.

The innovative NLCC model appears to be a good example of patient-centred interprofessional collaborative care.[287] Collaborative care is an increasingly recognised concept in the

management of complex patients where preventive, educational and healthcare needs are met by an interdisciplinary team of professionals. The common goal is improved outcomes for patients and collaborative practice thrives on respectful communication and coordination that was evident in the NLCC from the interviews. Cirrhosis of the liver, with its complex medical needs, appears to be an ideal choice for the employment of interdisciplinary collaborative practices.

A Cochrane Database Systematic Review commented on the effect of interventions that involved interprofessional collaboration between healthcare and social workers on three important outcomes: patient health, the model and behaviour.[288] Nine RCTs varying across different settings from primary to tertiary care reviewed different interventions, such as action plans, meetings, rounds and checklists between professionals. Morbidity or mortality outcomes were not discussed in any of the studies. The lack of convincing evidence in favour of interprofessional collaboration in this review could have been due to insufficient follow-up, shorter times for the intervention to be effective (described as acclimatisation periods) and lack of hard clinical endpoints. On the contrary, the NLCC model was analysed after an acclimatisation period of 6 years and was received with an overall positive feedback.

Although lack of medical training of nurses was mentioned as a downside of NLCCs, it was not considered unsafe. With their long association with the liver unit, the SNs were trained on the job with clear instructions and protocols to identify complications of advanced liver disease. Moreover, at each NLCC visit, the SNs evaluated patients from the point of view of cirrhosis decompensation with clinical symptoms, signs, blood tests and radiology, which should capture any hepatic worsening. The patients continued to see their GPs for other ailments and comorbidities which ensured ongoing medical care.

The study served its purpose of being a quality improvement initiative by providing suggestions for improvements of NLCC, such as regular SN meetings with hepatologists as opportunities for learning and extra personnel to cope with the increasing capacity of the clinics. The study also provided a new idea in the form of phone clinics for stable patients, which can be explored in the future.

As expected, NLCCs were also found to be cost saving from the healthcare providers' perspective. Moreover, from the patients' perspective, lack of parking costs, avoiding loss of

wages and carer costs were some of the other advantages. There have been very few studies on the cost-effectiveness of NLCs. Bicki et al. reported that a nurse-run free clinic in a low-income neighbourhood saved an estimated USD 1.28 million healthcare costs in emergency room visits by attending to 256 patients in 5 months.[180] However, Harrison et al. did not report any significant differences in resource utilisation between home and nurse clinic management of chronic ulcers.[179] However, unlike our study, costs were not comparted between hospital clinics and nurse clinics.

Patients with varying lengths of engagement with services for their liver care were interviewed only at one time-point in the study. Therefore, the study results cannot be generalised to all cirrhotic patients, or to other clinics and settings. Only a small sample of eight patients and seven staff were interviewed. However, qualitative analysis is meant to provide a deeper understanding, and achieving thematic saturation abrogated this problem. The NLCC model was delivered by SNs with considerable experience in cirrhosis management, and hence the study findings might therefore depend on this level of nursing experience. Crucial clinical outcomes, such as liver-related emergency hospitalisations, were not measured. Nevertheless, a recent Cochrane Review clarified that as yet no randomised trials of interprofessional collaboration interventions have demonstrated reductions in morbidity or mortality of the diseases, and their focus has been exclusively on the process delivery.[288] Hence, the effects of NLCC with clinical outcomes as endpoints could be planned as a further study. A limitation in the CEA was the calculation of only direct medical costs, excluding indirect costs, such as loss of wages, carer's cost, transport and parking costs.

The study had several strengths. It evaluated a well-established model after an acclimatisation period of 6 years, and the results are highly translational given its community setting. It also provides strong evidence for policy-makers that this MOC can be successfully implemented at a lower cost and is positively received by both patients and clinical staff.

A final strength of the study is the robust analytical methodology used, with two separate coders and subsequent review by an experienced investigator before finalising the themes. In-depth interviews of patients, SNs and hepatologists ensured that all aspects of care were considered.

6.6 CONCLUSION AND FUTURE DIRECTIONS

In conclusion, the NLCC model, delivered by experienced SNs, under remote supervision of hepatologists, yielded a positive feedback in the management of stable well-compensated cirrhosis, when reviewed from a qualitative and health economic perspective. It was well accepted and preferred by patients and the medical staff alike. This cost-effective model thus has the potential to meet growing health demands stemming from the increasing prevalence of cirrhosis of the liver. Future research requires replication of the model in larger settings and different areas, including regional areas, with appropriate nurse training and close supervision. Use of mixed methodology in the evaluation of this MOC, with measurement of clinical outcomes, such as saved hospital admissions, compliance with clinic appointments, adherence to radiological and endoscopic with surveillance and survival, in addition to patients' perspectives, will further enhance its role in the management of cirrhosis.

7. HEPATITIS C VIRUS INFECTION IN AUSTRALIAN PSYCHIATRIC INPATIENTS: A MICRO-ELIMINATION MODEL OF SCREENING AND TREATMENT

A major part of this chapter was published in the *Journal of Viral Hepatitis*, and the publication details are as follows:

> Hepatitis C virus infection in Australian psychiatric inpatients: a multicentre study of seroprevalence, risk factors and treatment experience.
> **Ramachandran J**, Budd S, Slattery H, Muller K, Mohan T, Cowain T, Tilley E, Baas A, Wigg L, Alexander J, Woodman R, Kaambwa B, Wigg A. *J. Viral Hepatitis*, **26(5)**:609–612, 2019.

Authors' contribution details are given below:

> **Jeyamani Ramachandran**: Literature search, study design, data analysis, interpretation and manuscript writing, revision and finalisation of the manuscript.
> **Silver Budd**: Study design, data collection and editing manuscript.
> **Hannah Slattery**: Study design and data collection.
> **Emma Tilley**: Data collection, patient follow-up and assistance in treatment collaboration.
> **Taryn Cowain, Titus Mohan, Andrea Baas, Laura Wigg**: Study design, data collection and study supervision.
> **Jacob Alexander**: Study design and data collection.
> **Kate Muller**: Data interpretation and manuscript supervision.
> **Richard Woodman**: Data analysis and manuscript supervision.
> **Billingsley Kaambwa**: Data interpretation and manuscript supervision.
> **Alan Wigg**: Study design, data interpretation, manuscript supervision and overall supervision of the study.

7.1 SYNOPSIS

Background and aim: HCV infection is a common cause of chronic liver disease and hepatocellular carcinoma managed with liver transplantation in Australia. Screening and treatment for hepatitis C virus (HCV) infection were not prioritised in psychiatric patients until recently, due to adverse neuropsychiatric effects of interferon therapy, despite reports of high prevalence. However, with the safe new antiviral drugs HCV eradication is a reality in these patients. The aim of this study was to evaluate HCV seroprevalence, risk factors and a multidisciplinary treatment model in an Australian cohort.

Methods: This prospective multicentre cohort study involved patients admitted to four inpatient psychiatric units, from December 2016 to December 2017 in metropolitan Adelaide. After pre-test counselling, consent and HCV testing, patients reported information on risk factors obtained.

Results: Two hundred and sixty patients (70% male) with a median age 44 years (IQR 24) were studied. HCV seroprevalence was 10.8% (28/260) with 95% confidence interval (95% CI) 7–15. Independent predictors of HCV positivity were

- injection drug use (OR = 44.05; 95% CI, 7.9–245.5; $p < 0.001$);
- exposure to custodial stay (OR = 7.34; 95% CI, 1.6–33.9; $p = 0.011$);
- age (OR = 1.09; 95% CI, 1.02–1.16; $p = 0.011$).

Of the 28 HCV antibody positive patients, 16 proved RNA positive. Eight of the sixteen HCV RNA-positive patients were treated. Hepatitis nurses liaised with community mental health teams for treatment initiation and follow-up under supervision of hepatologists. Seven patients achieved sustained viral response and one achieved end of treatment response. The remaining eight patients were difficult to engage with.

Conclusions: HCV prevalence was high in the study cohort of psychiatric inpatients. Although treatment uptake was achieved only in 50% patients, it was successfully completed by all of these patients as a result of a multidisciplinary model of care. These findings highlight the need to integrate HCV screening and linkage to treatment within psychiatry practice. The feasibility of achieving viral eradication with a sustainable multidisciplinary model was showcased in this study.

7.2 INTRODUCTION

Research worldwide has revealed that patients with significant mental illness are more susceptible to infection with bloodborne viruses, such as hepatitis B and C viruses (HBV and HCV, respectively) and human immunodeficiency virus (HIV).[212-214] This is due to the frequent prevalence of risk factors, such as injection drug use (IDU), high-risk sexual behaviour, sexual exploitation, social isolation and lower socioeconomic status. Despite higher prevalence, this population appears to be under-served with reported low rates of screening,[217] and there is poor knowledge of HCV infection and treatment methods within the mental health workforce.[218] Until the recent availability of direct-acting antivirals (DAAs), these patients were frequently a difficult-to-treat group due to the neuropsychiatric side effects of interferon therapy.

HCV infection is a common cause of chronic liver disease necessitating liver transplantation in Western countries. In view of the asymptomatic nature of the infection, less than 15% of chronically infected patients are aware of their infective status.[189,190] HCV eradication that can now be easily achieved with DAA drugs is curative and associated with reductions in both overall mortality and complications due to cirrhosis.[32] In addition, it has also been associated with improved quality of life and physical and social functioning.[33] The economic benefits of treating all HCV-positive patients, irrespective of the disease stage, have also been confirmed by multiple modelling studies.[41,260] Thus, the benefit of HCV treatment extends beyond the medical frontier into psychosocial and economic dimensions, which is very relevant to psychiatric patients. Moreover, screening and treatment of HCV assume specific importance in these patients, as it reduces the further spread of infection, especially among patients who continue the high-risk behaviour.

Australia is leading the world in HCV eradication with its unrestricted access to DAA therapy. To maintain good early progress in Australia it is important to identify previously neglected opportunities for treatment, by screening high-risk but marginalised populations such as patients with mental illness. With contraindications to prior interferon-based anti-HCV therapy, psychiatric patients have been a marginalised group with no incentive for proactive screening. Moreover, there are no well-conducted epidemiological studies estimating the burden of this now easily treatable infection among this population in Australia. The need to understand the magnitude of HCV infection in this under-served population and to explore models of care in treatment are crucial. Hence, the aim of this study was to perform a large

sero-survey of an Australian psychiatric inpatient population to determine the prevalence of HCV infection and its risk factors. A further aim was to describe the successful models used to treat HCV in this group.

7.3 METHODS

7.3.1 *Study Design*

This multicentre prospective observational period prevalence study was conducted over 12 months (December 2016 to December 2017), at four inpatient psychiatric units:

1. a metropolitan unit,
2. an outer suburban unit,
3. a war veterans' unit,
4. a unit dedicated to rural and remote area patients.

Due to administrative reasons, in centres 2 and 3 the study was discontinued during the 7th and 8th months, respectively. All patients admitted to participating psychiatric units during the study period were the potential study population and could be invited to participate after the treating psychiatry team ascertained the capability of the patient to consent for the study. Thus, patients who had the capacity and provided informed consent were included in the study. The study participants had blood drawn for HCV antibody after pre-test counselling and were asked to complete a questionnaire on possible risk factors (current or past injection drug use (IDU), exposure to custodial settings, prior or current sex work, tattoos or body piercing, blood transfusion or organ transplant before 1990, sexual partners of HCV-infected person, migrants from high-prevalence regions, Aboriginal Australians or Torres Strait Islanders, children born to HCV-positive mothers and occupational exposure). Reflex testing process was used when HCV serology was positive and HCV RNA testing was performed.[198] HCV RNA-positive patients were contacted by specialist hepatitis nurses, and treatment initiation was attempted through community and hospital clinics. HCV-negative patients and their general practitioners were informed of their status with advice on HCV prevention. For all patients, the socioeconomic index for areas (SEIFA) score of relative advantage and disadvantage was obtained from the Australian Bureau of Statistics (ABS) website using residential post codes.

7.3.2 *Sample Size Calculation*

Justification of sample size was as follows: assuming a prevalence of 10%, target width 0.06, actual width 0.06, proportion 0.100, and 95% confidence interval (95% CI) with lower limit 0.073 and upper limit 0.133 (if $p = 0.05$), the sample size was calculated to be 417. Since recruitment was lower than anticipated at the end of 12 months, a decision was made to conclude the study at that time. New sample size was calculated to be 254, assuming a prevalence of 12%, target width 0.08, actual width 0.08, proportion 0.120, and 95% CI with lower limit 0.08 and upper limit 0.160 (if $p = 0.05$).

7.3.3 *Statistical Methods*

Descriptive statistics were used for proportions to estimate HCV prevalence with 95% CI. IBM SPSS Statistics for Windows, version 23 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. For the univariate analysis, independent *t*-tests and one-way ANOVA (analysis of variance) test were used to compare continuous variables; chi-squared (χ^2) tests of independence were used to compare categorical variables. The CI for proportions and comparison between sample proportions for psychiatric diagnoses between groups were performed using Sergeant, ESG, 2018, Epitools Epidemiological Calculators, Ausvet (http://epitools.ausvet.com.au). Variables found significant ($p < 0.05$) on univariate analysis, age and gender were included in a multivariate binomial logistic regression model to look for independent risk factors for HCV seropositivity.

The study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (OFR #291.16 – HREC/16/SAC/232).

7.4 RESULTS

7.4.1 *Patient Characteristics*

Of the 1949 patients admitted to the mental health wards of the four units, 272 patients participated in the study.

Of the 272 patients consented to the study 12 were excluded as a blood sample could not be obtained. Fear of needles and anxiety about blood tests were the reasons cited in some patients.

Thus, the study population consisted of 260 patients. Their demographic characteristics, risk factors for HCV and psychiatric diagnoses are described in **Table 19.**

Table 19. Demographic profile, HCV risk factors and psychiatric diagnosis of the study cohort.

Demographic characteristics(n=260)	
Age in years, mean (SD)	44 (14)
Male, *n* (%)	182 (70)
Aboriginal ethnicity, *n* (%)	20 (8)
SEIFA score, mean (SD)	959 (73)
Risk factors	
Intravenous drug use, *n* (%)	74 (28)
Custodial stay, *n* (%)	54 (21)
Tattooing, *n* (%)	158 (61)
Sexual partners with HCV, *n* (%)	27 (10)
Children born to HCV-positive mothers, *n* (%)	17 (3)
Blood transfusion, *n* (%)	27 (10)
Migrants from high-prevalence areas, *n* (%)	22 (9)
Occupational exposure, *n* (%)	55 (21)
Primary psychiatric diagnosis	
Adjustment disorder, *n* (%)	7 (3)
Anxiety disorder, *n* (%)	27 (10)
Bipolar disorder, *n* (%)	27 (10)
Major depression, *n* (%)	67 (26)
Personality disorder, *n* (%)	8 (3)
Psychoactive substance use disorder, *n* (%)	21 (8)
Schizophrenia, *n* (%)	50 (19)
Others including PTSD, *n* (%)	53 (20)

HCV: hepatitis C virus; PTSD: post-traumatic stress disorder; SEIFA score: socioeconomic index for areas score.

Refusal to participate in the study was documented in 101 patients and reasons included patients' apprehension that participation would increase stress, strong feeling that they were unlikely to have HCV infection, lack of interest in completing questionnaires and more commonly the fear of undergoing a blood test.

7.4.2 *HCV Seroprevalence and RNA Prevalence*

Twenty-eight patients (10.8%; 95% CI, 7–15%) were HCV antibody positive. All these patients were cross-checked with the registry held by the National Notifiable Diseases Surveillance System (NNDSS). All had already been notified to this registry, and thus none were newly diagnosed.

Of these seropositive patients, 16 were HCV RNA positive, taking the HCV viraemic prevalence to 6.2%.

RNA-negative patients were reviewed, and clearance was attributed to successful prior treatment in five patients (two due to prior interferon therapy and three due to recent DAA therapy) and spontaneous clearance in seven patients, consistent with the natural history of the infection.

7.4.3 *Analysis of Factors Associated with HCV Seropositivity*

The demographic characteristics, HCV risk factors and primary psychiatric diagnoses were compared between HCV-positive and HCV-negative patients (**Table 20**). The socioeconomic status as assessed by the SEIFA score was not different between the two patient groups. Aboriginal ethnicity was the only significantly different demographic characteristic on univariate analysis. 50% of the study cohort reported more than one risk factor for HCV infection, 30% reported at least one risk factor and only 20% did not have any risk factor. Comparison of primary psychiatry diagnosis revealed a significantly higher proportion of persons with schizophrenia to be HCV positive in univariate analysis, but in multivariate analysis, it was not a significant predictive factor of HCV seropositive status.

Variables that were independently associated with HCV seropositive status on multivariate analysis were as follows:

- IDU (OR = 44.05; 95% CI, 7.9–245.5; $p < 0.001$),
- exposure to custodial stay (OR = 7.34; 95% CI, 1.6–33.9; $p = 0.011$),
- age (OR = 1.09; 95% CI, 1.02–1.16; $p = 0.011$).

7.4.4 *Treatment Model*

Of the 16 HCV RNA-positive patients, eight were initiated on DAAs: two in the hospital setting (tertiary-care centre and liver clinic), four by hepatitis nurses in community care settings and two by doctors in a rural clinic setting.

Initially, all patients were offered liver clinic appointments as per traditional model of care, but none of the patients attended. Subsequently, specialist hepatitis nurses coordinated care and made phone contact with both patients and mental health case workers and organised for them to attend community hepatitis nurse-run liver clinics. Thus, specialised hepatitis nurses played a central role in care coordination and follow-up of nonattending patients. They liaised with multiple teams including inpatient psychiatry teams, community mental health teams (including clozapine clinic coordinators), community pharmacists and primary-care physicians. Involvement of community pharmacists, who assisted in providing medication packs, was a crucial step that promoted adherence. Liaison with clozapine clinic nurse coordinators, who were involved with close monitoring of patients on antipsychotics, was another successful approach that assisted treatment initiation in some patients.

There were no adverse effects or worsening of underlying psychiatric illness reported in any of the patients during the DAA treatment period. Among the eight patients who commenced treatment, seven achieved a sustained virological response (SVR) and one patient achieved end of treatment response but was lost to follow-up.

However, despite multiple attempts, the remaining eight viraemic patients could not be engaged in treatment, highlighting the significant barriers and challenges that remain associated with treatment uptake of well-tolerated and highly effective DAA therapy. Reasons for lack of engagement were predominantly due to their unstable psychiatric comorbidity and lack of contact with mental health case workers or general practitioners. Hence, DAA therapy could not be initiated in these patients.

Table 20. Comparison of demographic characteristics, HCV risk factors and psychiatric diagnosis between HCV-positive and HCV-negative patients.

Factors	**HCV positive (*n* = 28)**	**HCV negative (*n* = 232)**	**Univariate analysis (*p*-value*)**	**Multivariate analysis OR (95% CI), *p*-value**
Demographic characteristics				
Age in years, mean (SD)	44 (13)	44 (10)	0.95	1.09 (1.02–1.16), *p* = 0.010
Male, *n* (%)	18 (64)	163 (70)	0.53	NS
Aboriginal ethnicity, *n* (%)	6 (22)	14 (6)	0.01	NS
SEIFA score, mean (SD)	964 (86)	959 (73)	0.95	–
Risk factors				
IDU, *n* (%)	22 (85)	52 (23)	<0.001	44.05 (7.9–245.5), *p* = <0.001
Custodial stay, *n* (%)	15 (58)	37 (16)	<0.001	7.34 (1.6–33.9), *p* = 0.011
Tattooing, *n* (%)	19 (73)	139 (60)	0.004	NS
Sexual partners with HCV, *n* (%)	5 (20)	22 (9.5)	0.005	NS
Children born to HCV-positive mothers, *n* (%)	1 (3.8)	16 (6.9)	0.01	NS
Blood transfusion, *n* (%)	2 (7.7)	25 (10.8)	0.011	NS
Migrants from high-prevalence areas, *n* (%)	1 (3.8)	21 (9.1)	0.008	NS
Occupational exposure, *n* (%)	4 (15)	51 (22)	0.316	NS
Primary psychiatric diagnosis				
Adjustment disorder, *n* (%)	0	7 (3)	0.325	–
Anxiety disorder, *n* (%)	1 (3)	26 (11)	0.18	–
Bipolar disorder, *n* (%)	3 (10)	24 (10)	1	–
Major depression, *n* (%)	5 (18)	62 (27)	0.32	–

Personality disorder, *n* (%)	1 (3)	7 (3)	1	–
Psychoactive substance use disorder including alcohol, *n* (%)	4 (14)	17 (7)	0.19	–
Schizophrenia, *n* (%)	10 (36)	40 (17)	0.01	NS
Others including PTSD, *n* (%)	4 (14)	49 (20)	0.44	–

CI; confidence interval; HCV: hepatitis C virus; IDU: intravenous drug use; NS: not significant; OR: odds ratio; PTSD: post-traumatic stress disorder; SEIFA: socioeconomic index for areas.
Independent *t*-tests and χ^2 tests of independence were used to calculate *p*-values.

7.4.5 *Comparisons among Study Centres*

As the study included patients from four different psychiatry units, HCV prevalence, risk factors for HCV and demographic characteristics were compared between these sites (**Table 21**). There was significant diversity among the four sites as evident from the differences in age, gender and significant risk factors for HCV. Although HCV prevalence was not statistically different across the four sites, the war veterans' unit, with an older population, had lower prevalence of HCV and the associated risk factors.

7.4.6 *Study Participation Rate and Exploration for Bias*

Of the 1949 patients admitted to the mental health wards of the four units, only 260 (13.4%) patients participated in the study. Reasons for this low participation rate were unclear, but in most cases was related to difficulties of junior medical staff prioritising the study over day-to-day clinical commitments on busy wards.

- refusal to participate in the study was documented in 101 patients and reasons included patients' apprehension that participation would increase stress,
- strong feeling that they were unlikely to have HCV infection,
- lack of interest in completing questionnaires,
- fear of undergoing a blood test.

Table 21. Comparison of demographic characteristics, HCV prevalence and significant risk factors among the four participating centres.

Factors	**Metropolitan unit (*n* = 103)**	**Outer suburban unit (*n* = 55)**	**Rural and remote unit (*n* = 31)**	**War veterans' unit (*n* = 71)**	***p*-value***
Age in years, mean (SD)	41 (12)	42 (12)	37 (11)	53 (15)	<0.001
Gender, male, *n* (%)	74 (72)	27 (49)	17 (55)	63 (89)	<0.001
Aboriginal ethnicity, *n* (%)	7 (7)	3 (6)	7 (22)	3 (4)	<0.001
HCV positivity, *n* (%)	15 (15)	6 (11)	5 (16)	2 (3)	0.067
IDU, *n* (%)	42 (42)	15 (27)	12 (39)	5 (7)	<0.001
Exposure to custodial stay, *n* (%)	29 (29)	7 (13)	10 (33)	6 (9)	0.010
Schizophrenia, *n* (%)	33 (32)	11 (20)	5 (16)	1 (1)	<0.001

HCV: hepatitis C virus; IDU: injection drug use.

**p*-value calculated using one-way ANOVA test and χ^2-tests of independence.

To explore for bias in the study cohort due to the low recruitment, comparison of age, gender and psychiatric diagnosis was made between participating and nonparticipating patients during the study period (**Table 22**). Comparison in socioeconomic status was made between an age and sex-matched cohort of 260 patients randomly selected from the entire admitted cohort against the study cohort. Although statistically significant differences were detected for age and gender, these were unlikely to be clinically significant. Most importantly, the two groups were well matched for socioeconomic status measured by SEIFA score. Diagnostic groups

traditionally associated with high risk for HCV (for example, schizophrenia and psychoactive substance abuse including alcohol misuse) were equally distributed in both the groups.

Table 22. Comparison between study participants and nonparticipants admitted in psychiatry wards.

Comparison parameters	**Study cohort (*n* = 260)**	**Admitted cohort (*n* =1677)**	***p*-value***
Age in years, mean (SD)	44 (14)	40 (13)	<0.001
Gender, men (%)	70	59	<0.001
SEIFA score, mean (SD)	959 (73)	963 (65)	0.5
Psychoactive substance abuse (%)	8	10	0.311
Schizophrenia (%)	19	20	0.078
Major depression (%)	26	14	<0.001
Personality disorder (%)	3	8	0.004
Bipolar disorder (%)	10	10	0.354
Anxiety disorder (%)	10	2	<0.001
Adjustment disorder (%)	3	11	<0.001
Post-traumatic stress disorder (%)	10	3	<0.001

SEIFA: socioeconomic index for areas; compared between 260 age-matched and sex-matched random controls from the admitted cohort and the study cohort.

**p*-values calculated using independent *t*-tests and Epitools Epidemiological Calculators, Ausvet (http://epitools.ausvet.com.au).

7.5 DISCUSSION

The main finding of this study was a high HCV antibody prevalence (10.8%) among a cohort of psychiatric inpatients. This is substantially higher than the prevalence of HCV in the Australian community, estimated at 1.2–1.8%.[190] This is the largest and only multicentre study performed to date in an Australian setting. Results from two smaller, single-centre Australian studies in this population have suggested variable HCV seroprevalence, with estimates ranging from 3.2% to 19%.[213,215] The study findings are consistent with seroprevalence surveys from other developed countries, which have estimated a pooled seroprevalence up to 17.4%, as reported in a recent meta-analysis.[214]

The reasons for this high prevalence relate to the frequent coexistence of multiple risk factors for HCV in this population including IDU, incarceration and other high-risk behaviours. The only surprising report of a HCV prevalence lower than the general population came from a Turkish study investigating 5227 mental health patients.[289] This was likely to be related to the exclusion of patients being treated for drug addiction in this study. However, another study by the same authors disclosed a high prevalence of HCV when it was assessed in an addiction treatment centre.[290]

The importance of this study relates to its definition of local HCV epidemiology in Australian psychiatric inpatients and the identification of this population as high risk. Indeed, the study demonstrates that only nine patients needed to be screened in this population to detect one HCV-positive patient. Recent European Association for the Study of the Liver (EASL) Guidelines have recommended screening for HCV in areas of intermediate prevalence (2–5%).[194] This data, therefore, provide the best available local evidence that the psychiatric inpatients represent a high-prevalence population of HCV and should be screened for this infection as a standard of care.

Therefore, there is a need to both educate and support the mental health workforce to embed HCV screening into routine patient care. Although data on cost-effectiveness of such a screening strategy was beyond the scope of this study, it is likely that screening and treatment of HCV infection would be beneficial, as supported by the cost-effectiveness of a one-time screening of all adults over 18 years of age in the United States.[221] In addition, cure serves as prevention of spread of infection by abolishing infectivity, thus supporting screening in this patient cohort.

This study did not reveal a high rate of undiagnosed infection, with all infections previously notified to the nationwide communicable diseases registry. It is possible that a larger study would have identified more cases, as a quarter of Australian HCV infections are estimated to be undiagnosed.[219] Of concern, however, was that despite notification, only 5 of the 21 patients with replicative virus were treated before the study. In the remaining 16 RNA-positive patients with notified infection, there was no evidence of any treatment plan. The lack of linkage among diagnosis and treatment demonstrates the multiple barriers confronting the treatment of HCV in patients with psychiatric illness. One such barrier is the inability to initiate antiviral treatment as inpatients due to the nonavailability of PBS funding in this scenario.

In addition to benefitting patients with a longer inpatient stay, patients at risk of poor engagement may be more likely to receive treatment, if the treatment could be initiated during inpatient admission.

In avoiding coercion to participate in the screening and by giving utmost importance to cultural sensitivity and confidentiality, the study adhered to the WHO recommendations on screening for HCV.[195] Immediate follow-up of results with confirmatory test and linkage to treatment were also some of the salient aspects of this study that were done in accordance with WHO recommendations that targeted screening for HCV should be accompanied by strategies for treatment to be clinically meaningful.

The inpatient admission offers a valuable screening opportunity for these patients, all of whom will have routine blood drawn as part of the admission process. It is possible that future strategies, using an 'opt out' screening model combined with rapid diagnostic tests on saliva or finger-prick blood could enhance the uptake and tolerability of screening in this population.

While this study focussed on inpatients, screening of outpatient populations at clinics monitoring toxicity of antipsychotic medications is another potential target that should be investigated in future studies. Indeed, patients in this setting may be less acutely unwell and more amenable to HCV screening and treatment.

The study also explored the problem of linking screening to care, in accordance with WHO recommendations that targeted screening for HCV should be accompanied by strategies for treatment to be clinically meaningful. All HCV RNA-positive patients were initially offered traditional care pathways with specialist follow-up at hospital clinics, with no patients attending. Subsequently, specialist hepatitis nurses played a central role in care coordination and follow-up of these nonattending patients. A report of a successful model detailing integration of HCV treatment with that of schizophrenia treatment by a community psychiatrist, with remote supervision by a hepatologist, has been described in the literature.[259] Successful screening and treatment uptake in psychiatric patients will involve a new and significant role for psychiatrists and their teams.[258]

This study is an attempt at micro-elimination of HCV in a marginalised group of psychiatric patients. As described by Lazarus et al., micro-elimination involves delivery of screening and

treatment of HCV to a focus group.[291] Some developed countries, such as the United Kingdom and the United States, practised micro-elimination by targeting patients with advanced liver disease due to HCV. Ireland achieved micro-elimination in patients with haemophilia infected with HCV via transfusion of infected blood products.[292] It is simpler to strategise case finding in smaller target groups by focussing on screening uptake and effective linkage to care.

Improving DAA access to a patient population, thus far excluded from the HCV treatment pathways due to inherent contraindications to interferons, qualifies as a successful plan at a micro-elimination strategy. Thus, a guideline has been provided for similar attempts at other mental health services in liaison with hepatology services.

The major limitation of the study was the relatively low recruitment (13% of the admitted patients) achieved during the study period, and inclusion of only inpatients. Lack of outpatient psychiatry clinics in public hospitals, and the labour-intensive process of pre-test counselling and consent mandated by the local ethics committee, precluded inclusion of psychiatric outpatients in the study. This limitation of convenience sampling was addressed by comparing the participating and nonparticipating groups for important characteristics including age, gender, psychiatric diagnosis and socioeconomic status.

This analysis did not reveal any clinically significant differences between the groups that would suggest bias, either positive (overestimation) or negative (underestimation), which provides greater confidence in the study results. In addition, the consistency of the seroprevalence rates between patients recruited from the three non-veterans sites adds further confidence to the prevalence estimate. The suboptimal recruitment rate reflects the difficulties of conducting real-world studies in this population. The ethics approval mandated a significant time burden on busy junior psychiatrists who were required to perform an elaborate consent process. It is likely that this process contributed to low uptake of the study across sites and some refusal in inpatients who were approached by these staff. This problem could be overcome in future studies with funding of dedicated trial coordinators at each site, with responsibilities for patient recruitment.

Despite this limitation the study had a number of strengths. It represents a large and methodologically robust sero-survey of HCV in an Australian psychiatric population and links screening to treatment. The large study sample size, the multicentre nature of the study and a

careful comparison of participating and nonparticipating patients increase confidence in the key finding surrounding the high prevalence of HCV in this group. A 'reflex testing' strategy was adopted in the study.

When the initial serum sample was found to be positive for HCV antibody, RNA testing was done in the same sample without a second phlebotomy. This has prevented the loss of confirmatory testing in up to 50% as reported by other investigators.[200]

The study was conducted along the strategic directions proposed in the WHO Global Health Sector Strategy on Viral Hepatitis.[231] Examples of this included identification of a focus group (screening psychiatric patients), planning and delivery of a high-impact intervention as a part of the health care (early RNA testing and linkage to care initiated during the psychiatry admission episode without the added cost of a separate study team), in a sustainable fashion (by nurse treatment in the community clinics), with plans for future innovation (a successful multidisciplinary model of care to increase treatment uptake in this challenging setting).

The study will achieve its true purpose if HCV screening can be performed at regular outpatient clinics, such as clozapine clinics (that monitor toxicity of antipsychotic medications) and community mental health clinics. As the testing involved venepuncture, it was challenging, and many found it worsening their anxiety. Testing of dried blood spot obtained from finger pricks, salivary testing with rapid diagnostic tests and point of care testing in mental health clinics are some of the strategies that can be employed to enhance case finding and treatment, minimising loss to follow-up.

In addition to HCV, psychiatric patients have a higher prevalence of obesity and are at risk for NAFLD, which is accentuated by weight gain secondary to commonly used antidepressants and antipsychotics.[293,294] A holistic approach addressing common aetiological factors of CLD, such as alcohol abstinence, HBV vaccination and lifestyle changes to prevent NAFLD, is required to reduce the morbidity due to CLD in these patients, in addition to HCV screening and treatment.

7.6 CONCLUSION AND FUTURE DIRECTIONS

This large multicentre study confirms the high prevalence of HCV in a cohort of psychiatric inpatients. The findings highlight the urgent need to educate the mental health sector about the necessity to embed HCV screening practices and to build effective linkages for their patients to HCV treatment in the current DAA era. Patients with mental illness represent an important reservoir of HCV infection in the Australian and other similar communities worldwide. Effective screening and treatment of this under-served population will be a key strategy towards meeting HCV elimination targets set by the WHO.

The study findings gave impetus for a statewide prospective study called ELIMINATE-C that involves HCV screening and linkage with treatment uptake at Rural and Remote mental Health Service in Adelaide. With the help of a study coordinator, inpatients and outpatients in these psychiatric units will be screened for HCV using RDTs. HCV positive patients will be referred to hepatitis nurses for further workup and treatment.

8. COST-EFFECTIVENESS OF TREATMENT MODELS OF CARE FOR HEPATITIS C VIRUS: THE SOUTH AUSTRALIAN STATEWIDE EXPERIENCE

A major part of this chapter was published in the *European Journal of Gastroenterology and Hepatology*, and the publication details are as follows:

> Cost-effectiveness of treatment models of care for hepatitis C: the South Australian state-wide experience.
> **Ramachandran J**, Kaambwa B, Muller K, Haridy J, Tse E, Tilley E, Altus R, Waddell V, Gordon D, Shaw D, Huynh D, Stewart J, Nelson R, Warner M, Boyd MA, Chinnaratha MA, Harding D, Ralton L, Colman A, Woodman R, Wigg AJ. *Eur. J. Gastroenterol. Hepatol.*, 31 December 2019. doi: 10.1097/MEG.0000000000001659 [Epub ahead of print].

Authors'contribution details are given below:

> **Jeyamani Ramachandran**: Study design, data analysis, interpretation and manuscript preparation.
> **Billingsley Kaambwa:** Data analysis and data interpretation, manuscript editing. and approval of the final manuscript.
> **Kate Muller, Richard Woodman**: Study design, manuscript editing. and approval of the final manuscript.
> **James Haridy, Edmund Tse**: Data collection and approval of the final manuscript.
> **Emma Tilley, Rosalie Altus, Victoria Waddell, David Gordon, David Shaw, Dep Huynh, Jeffrey Stewart, Renjy Nelson, Morgyn Warner, Mark Boyd, Mohamed A Chinnaratha, Damian Harding, Lucy Ralton, Anton Colman**: Data collection and approval of the final manuscript.
> **Alan Wigg:** Overall supervision, conception, study design, manuscript editing. and approval of the final manuscript.

8.1 SYNOPSIS

Background and aim: With unrestricted access to direct-acting antivirals (DAA), Australia is committed to eradicating hepatitis C virus (HCV) infection. The strategies used to augment treatment uptake include innovations in models of care (MOCs) and decentralisation of care. The aim of this research was to study the utilisation and long-term (lifetime) cost-effectiveness of four HCV treatment MOCs with DAA.

Methods: A Markov model-based probabilistic cost-effectiveness analysis (CEA) was undertaken extrapolating to up to 30 years from the cost and outcome data collected from a primary study involving a real-life Australian cohort. In this study, non-cirrhotic patients treated for HCV from 1 March 2016 to 28 February 2017 at four major public hospitals and liaising sites in South Australia were studied retrospectively. Depending on the person providing patient workup, treatment and monitoring, the MOCs were classified into

- MOC1 (specialist based);
- MOC2 (mixed specialist and hepatitis nurse based);
- MOC3 (hepatitis nurse based);
- MOC4 (general practitioner based).

Incremental costs were estimated from the Medicare perspective. Incremental outcomes were estimated based on the quality-adjusted life years (QALYs) gained by achieving a sustained virological response. A cost-effectiveness threshold of AUD 50 000 per QALY gained, the implicit criterion used for assessing the cost-effectiveness of new pharmaceuticals and medical services in Australia, was assumed. Net monetary benefit (NMB) estimates based on this threshold were calculated.

Results: A total of 1373 patients, 64% males, mean age 50 (SD ± 11) years, were studied. In the CEA, MOC4 and MOC2 clearly dominated MOC1 over 30 years with lower costs and higher QALYs. Similarly, NMB was the highest in MOC4, followed by MOC2.

Conclusions: Decentralised care using general practitioner and mixed consultant nurse models were cost-effective ways of promoting HCV treatment uptake in the setting of unrestricted access to new antivirals.

8.2 INTRODUCTION

Treatment with direct-acting antiviral (DAA) therapy has resulted in the evolution of hepatitis C virus (HCV) infection from the commonest cause of liver transplantation (LT) to an easily treatable cause of liver-related morbidity and mortality.[295] Australia is one of the first countries to provide unrestricted access to DAAs, supporting the World Health Organisation's goal of eradicating HCV by 2030.[187] The ease of administration of DAAs facilitates delivery of care in a nontraditional manner. Innovations in models of care (MOCs) and decentralisation of HCV care, to avoid bottlenecks associated with specialist tertiary care in hospitals, are two of the strategies that have contributed to Australia's leading position in HCV eradication.[232] Australia is currently witnessing an encouraging trend of increased community prescriptions for DAAs by general practitioners (GPs).[231] Multidisciplinary MOCs including the use of nurse consultants and shared care with GPs have been shown to be successful in achieving sustained virological response (SVR) in regional Australia.[246] The cost-effectiveness of DAAs over interferon therapy at any stage of liver disease is well known.[41,260] Similarly, the cost-effectiveness of providing HCV care in primary care has also been established in the project, Extension for Community Healthcare Outcomes (ECHO) in the United States.[263] However, the cost-effectiveness of nontraditional models that are unique to Australia, such as nurse-led care, shared care between specialists and nurses, and care by GPs, has not been evaluated to date. In this study, using real-life costs and SVR results of a non-cirrhotic Australian HCV patient cohort that received unrestricted access to DAAs throughout the state of South Australia (SA),[37] the lifetime cost-effectiveness of the four types of MOCs employed was evaluated. A Markov model-based cohort analysis of liver disease progression was used for the analysis.

8.3 METHODS

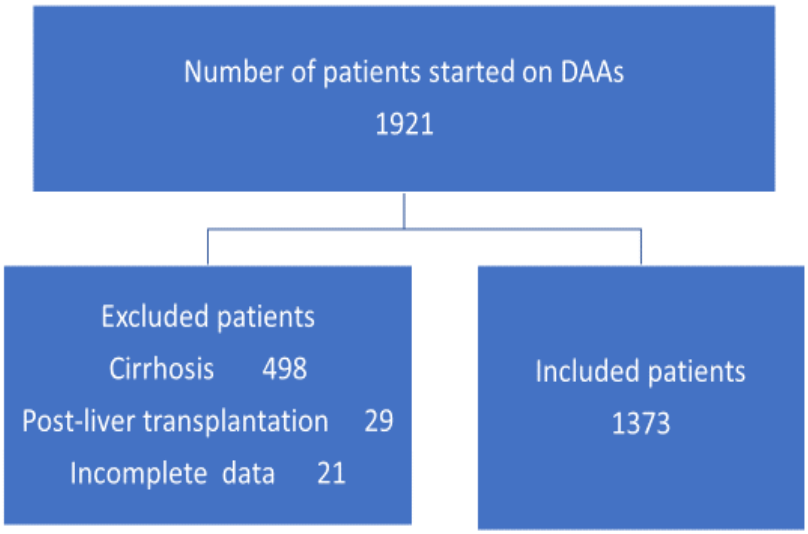
This economic evaluation was conducted and reported according to the best practice guidelines based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[296]

8.3.1 *Target Population*

A previous study examined the efficacy of DAAs in a real-life cohort of Australian patients initiated on DAA therapy from 1 March 2016 to 28 February 2017, during the first year of DAA initiation on the Australian Medicare Pharmaceutical Benefits Scheme in SA.[37] From this

(referred to henceforth as the primary study), the current study cohort was drawn. A total of 1921 patients were started on DAAs in all four major public hospitals and related sites in SA during the study period. Cirrhosis was diagnosed by biopsies when available, FibroScan® (>12.5 kPa) and/or aspartate transaminase to platelet ratio index (APRI) score (>1) as per the Australian recommendations for the management of HCV infection.[188] After excluding patients with cirrhosis (498 patients), those who had LTs (29 patients) and those without information on the treatment model (21 patients), 1373 patients were included in the study.The flowchart of study selection is as shown in **Figure 12.**

Figure 12. Flow chart of study cohort selection.



DAA: direct-acting antivirals.

The mean age of the study cohort was 50 (standard deviation, SD ± 11) years, and was comprised predominantly of men (64%). Evaluation for fibrosis was done in the setting of treatment unless previously completed. The APRI score was used when transient elastography was not available. 60% of patients were evaluated with FibroScan® (22% by specialists, 27% by nurses in tertiary care and 11% by nurses in community clinics). The mean (± SD) FibroScan® score was 6.45 (±2).

8.3.2 *Study Setting and Location*

The SA-based sites included the Royal Adelaide Hospital, the Queen Elizabeth Hospital, Flinders Medical Centre and Lyell McEwin Hospital, and other sites in liaison with these metropolitan public hospitals (namely, prisons, community clinics and country health hospitals). The study was approved by the Southern Adelaide Health Research Ethics Committee and those of the participating hospitals (Multisite LNR submission AU/15/571D215).

8.3.3 *Study Perspective*

The analysis was undertaken from the perspective of Medicare, the primary funder of universal healthcare insurance in Australia.

8.3.4 *Comparators*

Australia's response to the challenge of delivering hepatitis care to remote and rural communities has been via decentralised and multidisciplinary models with nurse-led clinics, remote consultations and shared care between GPs and specialists.[29] Under the Pharmaceutical Benefits Scheme, treatment initiation of DAAs by GPs is permitted under supervision of specialist physicians.

Nurse practitioners practising within defined protocols are actively involved in patient education, support, screening, diagnostic workup with FibroScan®, monitoring of HCV treatment in the community and supporting GPs. Nurse practitioners are also heavily involved with tertiary hospitals by sharing care with tertiary specialists. Therefore, in the Australian healthcare setting, nurse-led clinics and GP-led primary-care models operate in the delivery of DAA therapy, in addition to traditional specialist-delivered care.

As per the recommendations of the Australian Clinical Consensus Guidelines on the management of HCV infection,[188] four types of MOCs have been implemented in SA and were compared in this study. Allocation of patients to the different MOCs was not randomised, but dependent on the practice at each site, in accordance with the real-life design of the study.

The analysis was done in a retrospective fashion after patients were treated in a particular MOC. The MOCs were classified as follows:

1. *MOC1, Specialist model (in the public, community or private clinics)*: In this model patient workup, on-treatment monitoring and post-treatment monitoring were performed by a specialist. This is the usual MOC followed in most centres around the world, and hence used as the reference model.
2. *MOC2, Mixed specialist and viral hepatitis nurse model*: In this model, patient workup, on-treatment monitoring and post-treatment monitoring were shared between specialist and nurse, either in a tertiary-care setting or community setting. No more than one face-to-face specialist–patient contact occurred. An example would include a patient seen by specialist for initial visit, then subsequently managed by a nurse with no further specialist–patient contacts.
3. *MOC3, Viral hepatitis nurse model*: In this model, patient workup and treatment monitoring were performed by nurse either in a tertiary-care or in a community setting with remote specialist supervision only. No face-to-face specialist–patient contacts occurred. An example would include a nurse working in offsite clinics, such as GP Plus Health Care Centres or prison settings.
4. *MOC4, GP model*: In this model, patient workup and treatment monitoring were performed by GP in a community care setting with remote specialist/nurse supervision only. No face-to-face specialist–patient contacts occurred for the purposes of treatment.

The baseline characteristics of patients treated in the four MOCs and the uptake of MOCs are depicted in **Tables 23** and **24**, respectively.

The distribution of model uptake was different among the four hospitals studied (**Figure 13**). The SVR in the intention-to-treat (ITT) analysis was significantly different due to loss of follow-up found predominantly in MOC4. Although there were significant baseline differences among the MOCs, the SVR in per protocol (PP) analysis (after excluding patients with no SVR results) was not significantly different across the MOCs. The only factor that was significantly associated with lack of SVR in PP was genotype 3. Previous treatment, age or gender did not affect the SVR (data not shown).

Table 23. Comparison of baseline characteristics among four MOCs.

Baseline characteristics	**MOC1**	**MOC2**	**MOC3**	**MOC4**	***p*-value**
Number of patients treated	599	310	225	239	
Age in years, mean (SD)	51 (10)	52 (11)	50 (10)	47 (10)	<0.001
Gender male, %	69	60	54	73	<0.001
Genotypes 1 and 3, %	59 and 39	63 and 32	61 and 35	52 and 43	<0.001
Previous treatment, %	12 (*n* = 521)	18 (*n* = 238)	4 (*n* = 214)	5 (*n* = 193)	<0.001
SVR					
ITT, *n* = 1373	81%	82%	79%	70%	0.001
PP, *n* = 1130	96% (*n* = 509)	98% (*n* = 263)	95% (*n* = 186)	98% (*n* = 172)	0.09

ITT: intention to treat; PP: per protocol; SVR: sustained virological response.

MOC1: Consultant only model; MOC2: Shared care model with consultants and specialist nurses; MOC3: Specialist nurses only model; MOC4: General practitioner model.

Table 24. Estimates of probabilities of uptake in each MOC.

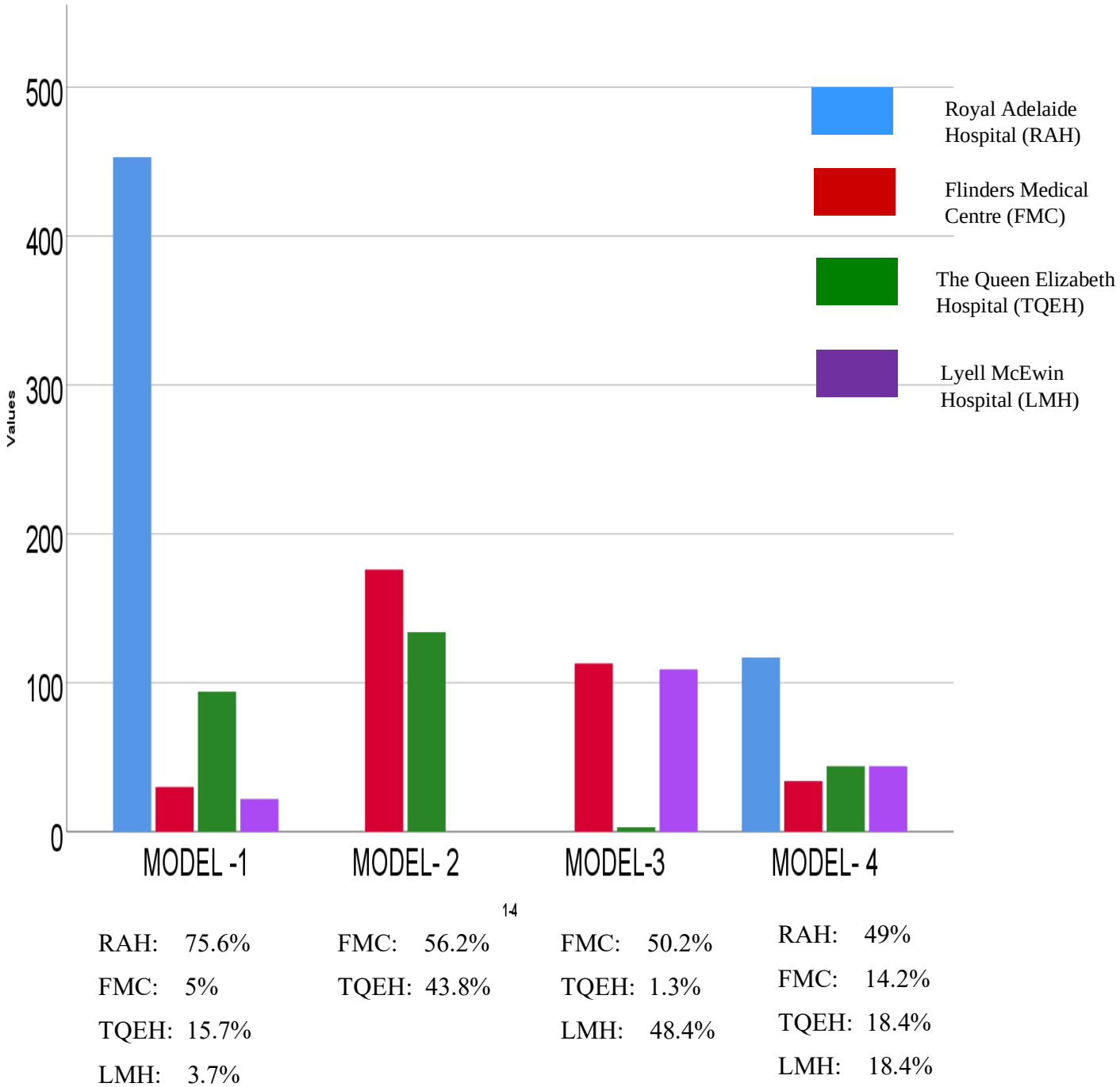
Description	**Estimate [SE]***	**Distribution****	**Source**
MOC1	0.436 [599, 1373]	Dirichlet	Study
MOC2	0.226 [310, 1373]		
MOC3	0.164 [225, 1373]		
MOC4	0.174 [239, 1373]		

*Figures in square brackets are occurrences (*r*) and population size (*n*) used to calculate probability.

**Distributions used in probabilistic sensitivity analysis.

MOC1: Consultant only model; MOC2: Shared care model with consultants and specialist nurses; MOC3: Specialist nurses only model; MOC4: General practitioner model.

Figure 13. Proportion of uptake of four MOCs in four major public hospitals.



8.3.5 *Time Horizon*

The time horizon for the base-case analysis was up to 30 years (lifetime). Sensitivity analysis estimated model outputs at 10 and 20 years after DAA therapy.

8.3.6 *Discount Rate*

For costs and outcomes, a 5% discount rate was applied in accordance with the recommendations of the Pharmaceutical Benefits Advisory Committee (PBAC), Australia.[297]

8.3.7 *Choice of Health Outcomes*

The primary outcome was the incremental cost per QALY gained in the four MOCs during a follow-up period up to 30 years after HCV treatment with DAAs. Where appropriate, the QALY estimates reflected cases of SVR achieved, based on data obtained from the primary study.[37] The probabilities of achieving SVR in each MOC are listed in **Table 25**.

8.3.8 *Measurement of Effectiveness*

Effectiveness was measured based on utility scores obtained from the literature.[260] Further, a utility score of 1 was assigned to indicate those who attained SVR and 0.88 to those who did not attain.[260]

8.3.9 *Estimating Resources and Costs*

Based on the real-life costs associated with the MOC in the primary study and that of managing long-term complications from the Australian literature,[223] long-term costs of up to 30 years post-treatment were estimated from the Markov model.

8.3.10 *Choice of Models and Assumptions*

A Markov model of liver disease progression (**Figure 14**) constructed using TreeAge Pro 2018 software was applied to this real-life cohort. Patients entered the model during the non-cirrhotic stage (F0 to F3) for HCV treatment in various MOCs and were followed over their lifetime. Those who achieved SVR were considered cured and not expected to have any further liver disease-related expenditure.

The possibility of reinfection and progression of liver disease due to cofactors, such as alcohol misuse or obesity, were excluded.

Those who did not achieve SVR progressed through the natural history into compensated cirrhosis (CC), which could lead to hepatocellular carcinoma (HCC) and/or decompensated cirrhosis (DC). Both these events could lead to liver transplantation (LT) or death. Non-liver-related causes of mortality were not considered.

Thus, five health states, namely chronic hepatitis C (CHC), CC, DC, HCC and LT, were considered. In line with similar models, a cycle length of 1 year was used in this model.[260]

8.3.11 *Model Parameters*

Model parameters are described in the following sections and the parameters are also summarised in **Tables 24–26.**

8.3.12 *Probabilities of MOC Uptake*

MOC1, the traditional and common type of MOC, was the most frequently employed. At the start of the Markov process, 44% of the cohort received HCV treatment by MOC1, 23% by MOC2, 16% by MOC3 and 17% received by MOC4 as shown in **Table 24**.

8.3.13 *Transition Probabilities*

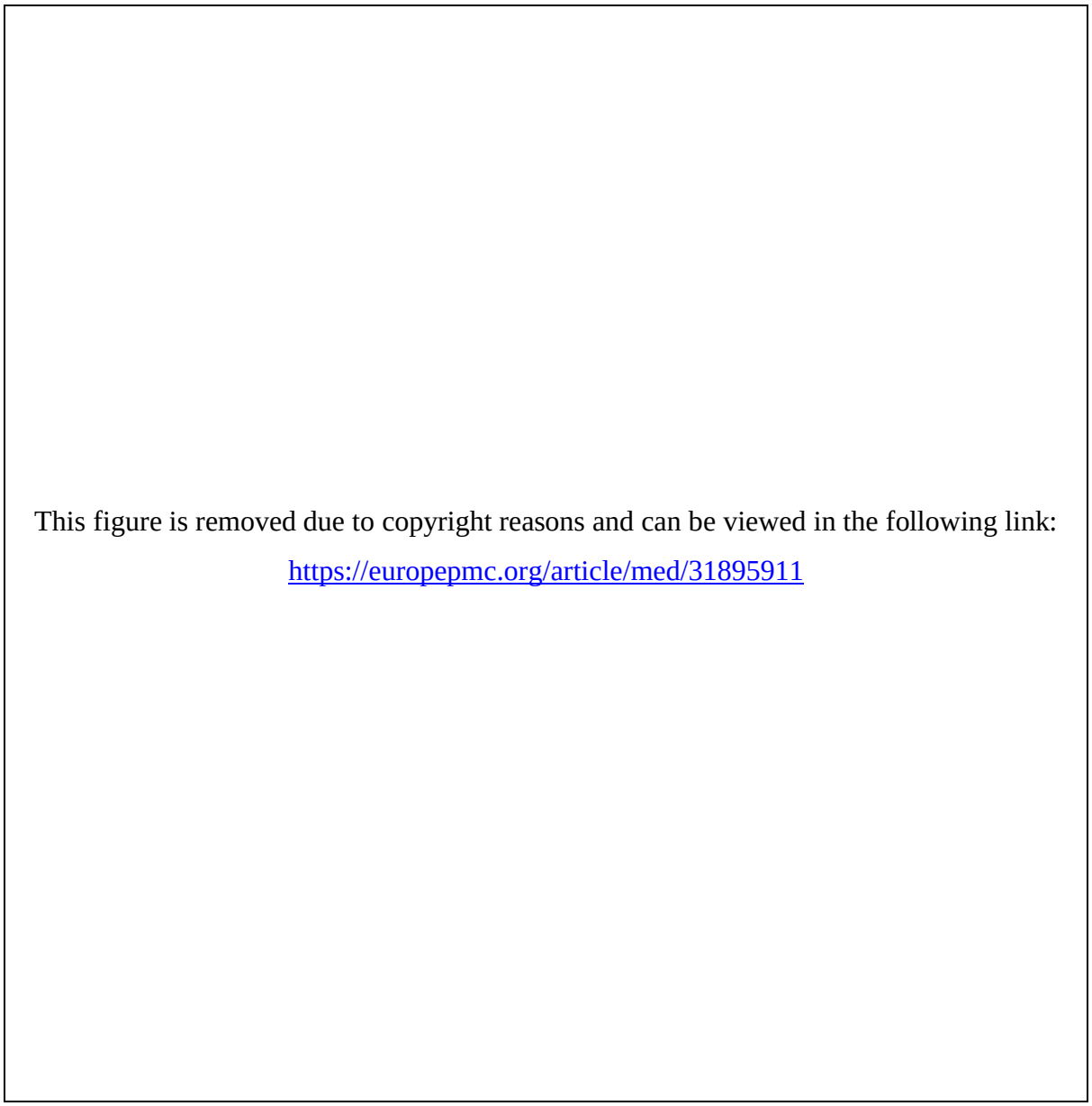
Table 25 provides the probability of achieving SVR in each MOC, based on data collected from the primary study.[37] The table also provides data on probabilities of transition to various health states based on the natural history of HCV obtained from the published literature.[260] As progression rates were only reported for patients without SVR, these estimates were calibrated to apply to only those who did not achieve SVR in each model.

8.3.14 *Costs*

Costs in the models were categorised into costs of the interventions (MOC) and those associated with each health state.

Intervention costs included those for specialists' visits (both in the public and in the private clinics), GP visits, nurse time, and for administration of public hospital and community (nurse-led) liver clinics.

Figure 14. Markov model of disease progression of chronic HCV infection.



Also included were costs of transient elastography (TE), blood tests for monitoring the success of therapy, costs of the DAA medications and travel costs for remote patients. Data calculation for costs was based on documentation from hospital clinical databases (for specialist visits and nurse clinics in public hospitals) and confirmed by discussions with the units on the model practised (for the frequency of nurse visits and phone calls) and Australian Liver Association (ALA) Guidelines on HCV Treatment (for visits to GPs and private specialists, and blood tests). To calculate the costs for the specialists' time in public hospitals, hospital administration provided costs from Power Budgets Labour Template for all salaried positions within Southern Adelaide Local Health Network (SALHN).

Table 25. Estimates of transition probabilities and distributions used in the reference case and sensitivity analyses.

Description	Estimate [SE]*	Distribution**	Source
Probability of moving between health states			
Probability of moving from CHC to SVR			
MOC1	0.965 [0.008]	Beta	Study
MOC2	0.987 [0.006]		
MOC3	0.960 [0.013]		
MOC4	0.987 [0.007]		
Probability of moving from CHC to CC	0.100 [0.070]	Beta	Kondili et al.[260]
Calibrated*** for MOC1	0.004 [0.002]		Kondili et al.[260] and Study
Calibrated*** for MOC2	0.001 [0.001]		
Calibrated*** for MOC3	0.004 [0.003]		
Calibrated*** for MOC4	0.001 [0.001]		
Probability of moving from CC to DC	0.030 [0.010]	Beta	Kondili et al.[260]
Probability of moving from CC to HCC	0.050 [0.010]		
Probability of moving from DC to LT	0.110 [0.010]		
Probability of moving from HCC to LT	0.200 [0.010]		
Probability of death for those who have suffered an event			
DC	0.090 [0.010]	Beta	Kondili et al.[260]
HCC	0.430 [0.010]		
LT	0.150 [0.010]		
Probability of death for all causes	0.020	Beta	ABS (2015)

*Estimates are mean [standard error].

**Distributions used in probabilistic sensitivity analysis.

***CHC to CC progression rate estimates from Kondili et al.[260] were for patients without SVR. Therefore, this estimate was calibrated to apply to only those who did not achieve SVR in each model (for example, 0.1 or 10% of 0.041 or 4% (1–0.959) = 0.004 or 0.4% of patients in MOC1).

ABS: Australian Bureau of Statistics; CC: compensated cirrhosis; CHC: chronic hepatitis C, no cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplantation; SVR: sustained virological response.

MOC1: Consultant only model; MOC2: Shared care model with consultants and specialist nurses; MOC3: Specialist nurses only model; MOC4: General practitioner model.

Based on the hourly rates, cost of each visit was calculated as follows: 40 min is considered long consultation and 20 min as short consultation and TE took 20 min. Similarly, based on the nurses' hourly rates obtained from the Nursing/Midwifery (South Australian Public Health Sector) Enterprise Agreement, 2016, the cost of each visit (40 min is long visit, 20 min is short visit, 20 min for phone consult and 20 min for TE by nurse) was calculated. Details of visits in terms of frequency and nature were available from the electronic nurse-maintained database at each site.

For the specialist visits at private hospitals costs and GP visits costs were calculated based on the Medicare item numbers. 'Medicare' is the name of the national government-funded universal health insurance scheme in Australia. Clinic maintenance costs were obtained from hospital administration data analysts. The costs of travel for remote patients were obtained from Patients Assistance Transport Scheme (PATS), SA Health. Costs of HCV medications and HCV testing were obtained from the Medicare Benefits Schedule (MBS). Costs for TE were calculated based on the nature of the proceduralist, namely specialist or nurse. Mean total costs per patient, combining cost estimates of these items for each MOC, were derived, and the incremental costs were compared within a cost-effectiveness analysis (CEA). An ITT approach was used to estimate the intervention costs with multiple imputations carried out to account for the missing data.[298]

Costs associated with health states in the model represented long-term costs for the management of CHC, cirrhosis and its complications including LT. These were obtained from a study that assessed the cost-effectiveness of HCV treatment with DAAs in intravenous drug users in Australia.[223] All costs were converted into Australian dollar (AUD) values during 2016 to 2017 and are provided in **Table 26**.

8.3.15 *Utility Scores*

Initial utility values for individuals in the model were obtained from Australian age-specific quality of life estimates as shown in **Table 26**.[299] Utility scores reflecting health-related quality of life (HRQoL) in a particular health state in the model were obtained from the literature.[260]

Multiplicative values of the Australian age-specific utility estimate and the utility score of each particular health state were used to model future health state utility scores. In addition, utility values for health states in the Markov model after completion of treatment were based on estimates from the literature as shown in **Table 26**.[260]

8.3.16 *Economic Evaluation*

Using the real-life costs and SVR outcomes as input from the primary study (**Tables 26**) a probabilistic Markov model-based analysis was undertaken with the primary outcome expressed in terms of incremental costs per QALY gained. An incremental approach was used to estimate the incremental cost-effectiveness ratios (ICERs), calculated as the incremental costs divided by incremental changes in QALYs. In line with reporting practice, no ICERs were presented where there was dominance (that is, where one model was both cheaper and more effective than the comparator).

8.3.17 *Base-Case Analysis*

The Markov model provided discounted lifetime costs and QALYs over a period of 30 years for each MOC. Probabilistic analyses were done based on 50 000 Monte Carlo simulations. Costs were modelled using the Gamma distribution, while Beta distributions were fitted to the transition probabilities and utility scores.

The parameters for these distributions are provided in **Table 26**. Following modelling good practice guidelines, a half-cycle correction factor was applied to both costs and outcomes in the first cycle.[300] Cost-effectiveness planes (CEPs) and cost-effectiveness acceptability curves (CEACs) were also reported. The model also provided net monetary benefit (NMB) estimates based on willingness-to-pay threshold of AUD 50 000 per QALY, which is the implicit cost-effectiveness criterion used in Australian studies.[301]

8.3.18 *Sensitivity Analyses*

Univariate sensitivity analyses were performed to address uncertainty in the modelling results. This involved varying the time horizon to present results at 10-year and 20-year post intervention. These time points were chosen to represent a plausible range within which the cost-effectiveness of the intervention could be assessed.

Table 26. Estimates of utilities, costs and distributions used in the reference case and sensitivity analyses.

Description	**Estimate***	**Distribution****	**Source**
*Age-related utilities****			
50–59 years	0.80 [0.24]	Beta	Hawthorne et al.[299]
60–69 years	0.80 [0.22]		
70–79 years	0.76 [0.23]		
80–85 years	0.70 [0.26]		
Utilities for health states			
CHC	0.88 [0.06]	Beta	Kondili et al.[260]
CC	0.83 [0.08]		
DC	0.73 [0.11]		
HCC	0.53 [0.40]		
LT	0.73 [0.18]		
SVR	1	–	
Costs for health states per patient			
Costs of treating HCV			
MOC1	77 211	Gamma	Study
MOC2	77 118		
MOC3	77 087		
MOC4	76 910		
Costs of managing HCV			
CHC	666	Gamma	Scott et al.[223]
CC	1094		
DC	17 788		
HCC	12 590		
One-off costs of transition between health states			
Transition to CC	662	Gamma	Scott et al.[223]
Transition to HCC	1135		
LT	170 326		

*Estimate means mean value.

**Distributions used in probabilistic sensitivity analysis.

***These estimates were based on age-related utility scores based on the assessment of quality of life (AQoL) figures (Hawthorne et al.)[299]

Figures in square brackets are standard deviations.

CC: compensated cirrhosis; CHC: chronic hepatitis C, no cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplantation; SVR: sustained virological response.

MOC1: Consultant only model; MOC2: Shared care model with consultants and specialist nurses; MOC3: Specialist nurses only model; MOC4: General practitioner model.

8.4 Results

8.4.1 *Base-Case Analysis*

8.4.1.1 *Mean Costs and QALYs*

Mean lifetime costs in AUD and QALYs per patient are provided in **Table 27**. MOC4 was associated with the lowest mean cost per patient, followed by MOC2, MOC3 and then MOC1. Mean QALY per patient estimates showed that MOC4 was the most effective closely followed by MOC2, whereas the QALYs for MOC1 and MOC3 were slightly lower. In comparison with MOC1, the usual care model, these results imply that both MOC2 and MOC4 dominated the former, as they were not only cheaper but also more effective.

While MOC3 was cheaper than MOC1, it was also less effective resulting in an ICER of AUD 3235/QALY. In terms of NMB (**Table 27**) MOC4 was associated with the largest NMB, followed by MOC2. NMB estimates for MOC1 and MOC3 were lower.

The difference in the NMB at a willingness-to-pay threshold of AUD 50 000 over 30 years was about AUD 1500 higher for every patient treated by GPs (MOC4) compared to traditional specialist care (MOC1). Similarly, it was possible to save AUD 1288 per patient in the long term by visiting the specialist just once and, subsequently, being monitored by nurses, as in MOC2.

Table 27. Results of CEA from the Markov model.*

Costs/QALY	**MOC1**	**MOC2**	**MOC3**	**MOC4**
Total healthcare costs in AUD (mean)	77 953	77 393	77 942	77 170
QALYs gained (mean)	12.51	12.53	12.51	12.53
NMB in AUD (mean)	547 715	549 003	547 560	549 242
ICER with MOC1 as reference	–	Dominant	3235/QALY	Dominant

Costs and outcomes are expressed per patient.

*Time horizon is 30 years for this analysis.

CEA: cost-effectiveness analysis; ICER: incremental cost-effective ratio; NMB: net monetary benefit.

MOC1: Consultant only model; MOC2: Shared care model with consultants and specialist nurses; MOC3: Specialist nurses only model; MOC4: General practitioner model.

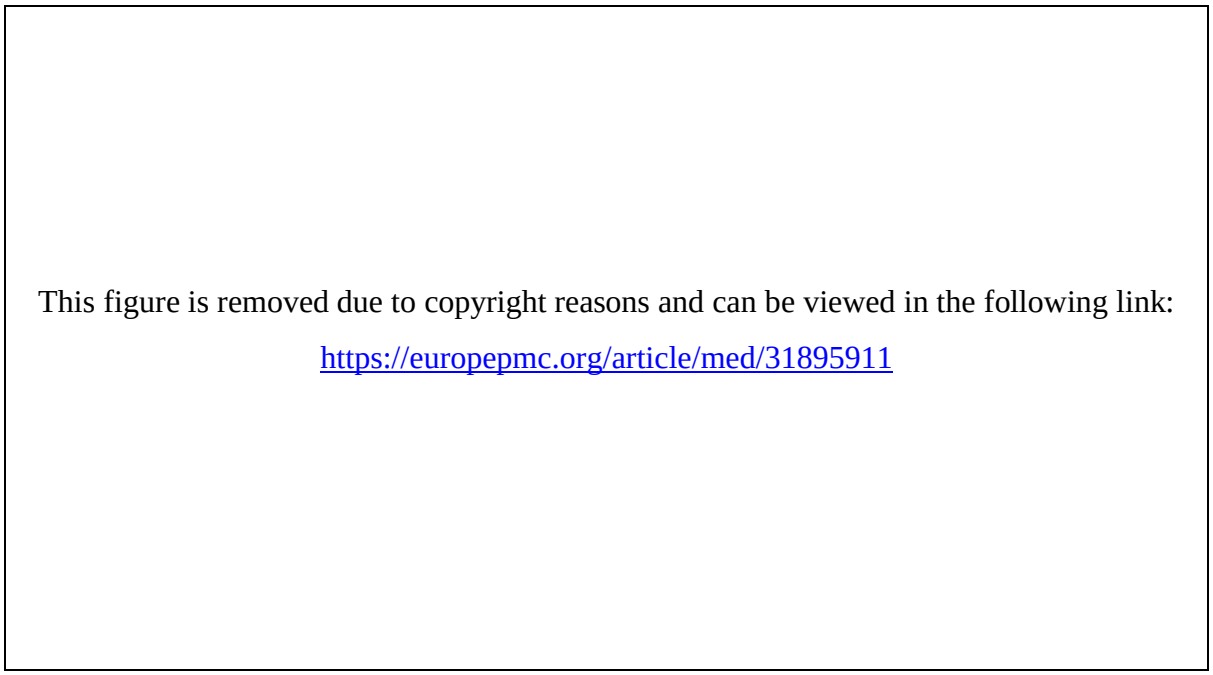
The CEPs and CEACs, all using MOC1 as the reference for the base-case analysis, are shown in **Figures 15** and **16**, respectively.

The joint distribution of the mean incremental costs and mean QALYs gained, presented in the CEPs (**Figure 15(a)** and **(c)**), show some degree of uncertainty with most results in the southeast and some in the northwest quadrants. In the case of MOC3, uncertainty was depicted by the ICERs being equally distributed in both the southeast and northwest quadrants (**Figure 15(b)**).

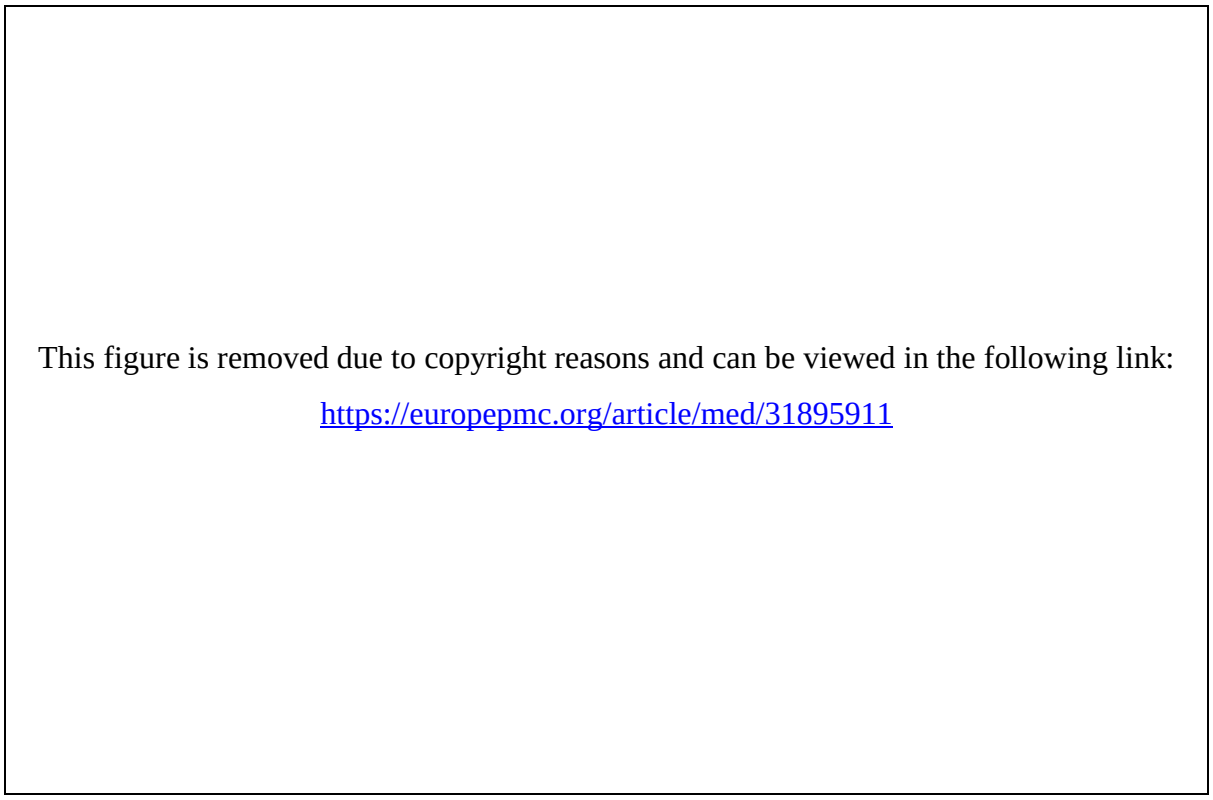
The CEACs show that, compared to MOC1, the probabilities of MOC2 and MOC4 being cost effective were, respectively, >0.8 (**Figure 16(a)**) and >0.9 (**Figure 16(c)**) at all willingness-to-pay thresholds. Below a threshold of AUD 20 000/QALY gained, MOC3 had a higher probability of being cost effective compared to MOC1, but a lower probability of being cost effective at thresholds greater than AUD 20 000/QALY (**Figure 16(b)**).

Figure 15. CEPs displaying incremental cost-effectiveness: (a) MOC2 over MOC1, (b) MOC3 over MOC1 and (c) MOC4 over MOC1.

(a)



(b)



(c)

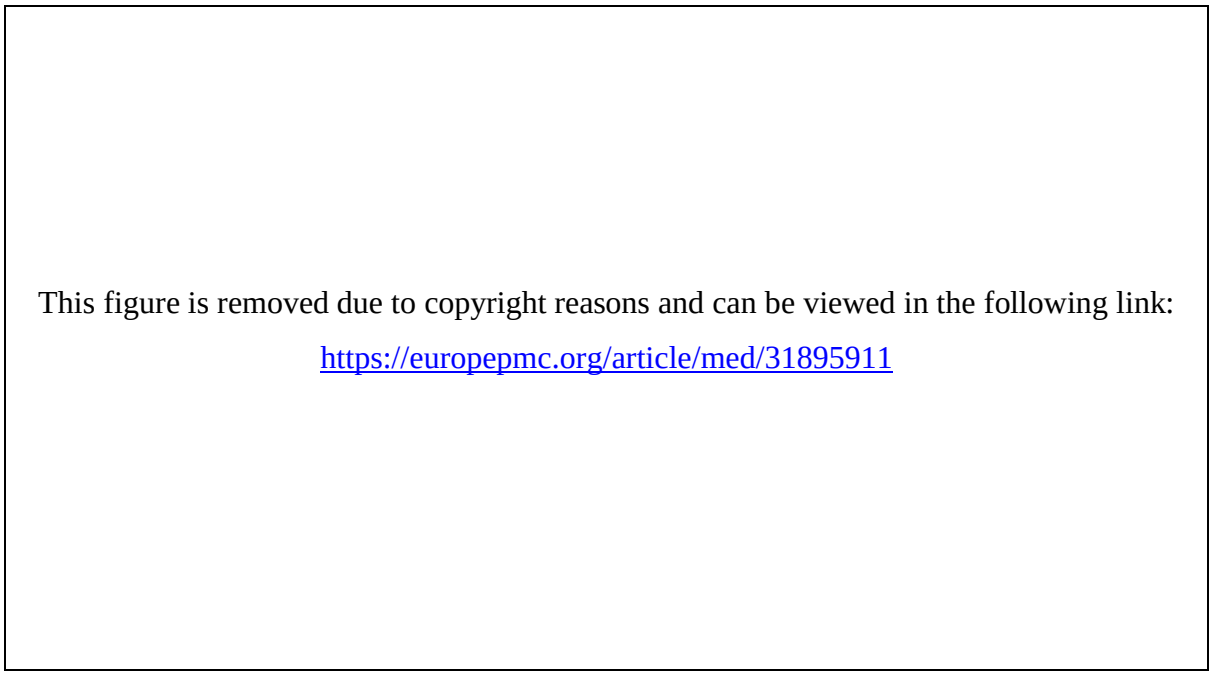
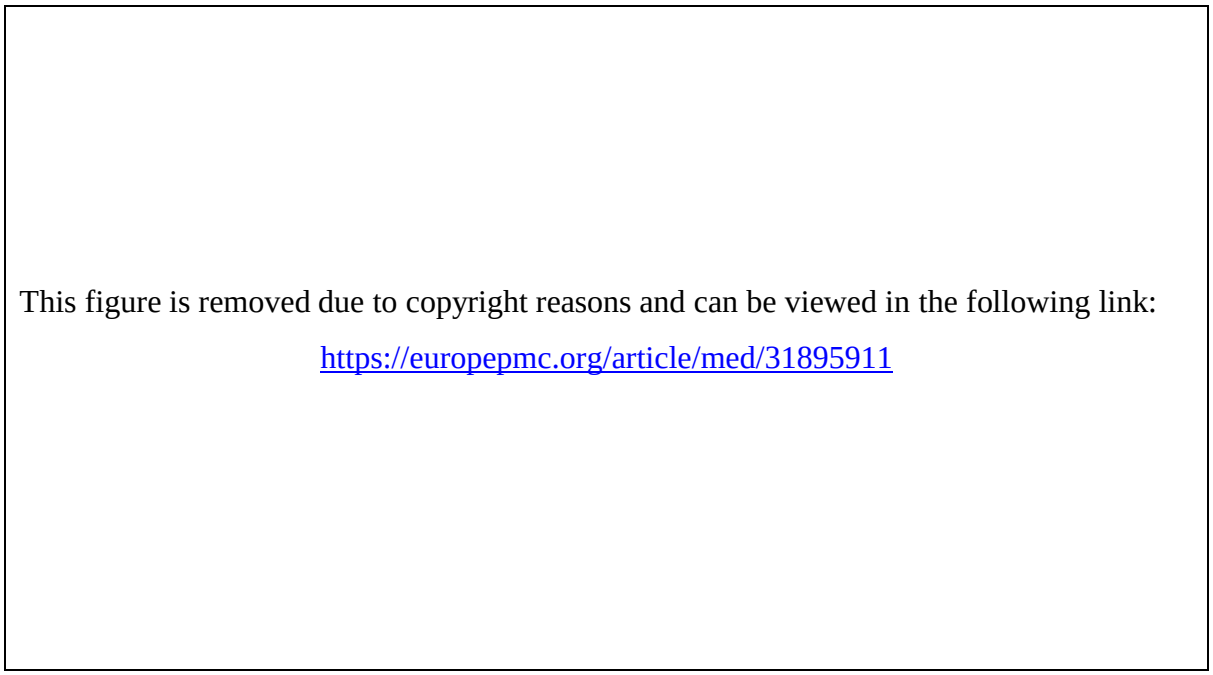


Figure 16. CEACs showing higher probability of different MOCs at various willingness-to-pay thresholds: (a) MOC2 compared to MOC1, (b) MOC3 compared to MOC1 and (c) MOC4 compared to MOC1.

(a)



(b)

(c)

8.4.2 *Sensitivity Analysis*

The results of changing the time horizon are given in **Table 28**. Similar to the base-case analysis, MOC4 was associated with the lowest mean cost per patient followed by MOC2, MOC3 and then MOC1 at the studied time points (10 and 20 years). Mean QALY per patient estimates also show that MOC4 was the most effective, followed by MOC2, MOC1 and MOC3.

The trend of NMB followed a similar pattern with the highest values in MOC4 followed by MOC2, both at 10 and 20 years. Although MOC3 was associated with a marginally higher NMB than MOC1 at 10 years, this was reversed at 20 years with the NMB of MOC1 exceeding that of MOC3.

8.5 DISCUSSION

Australia is a world leader in HCV treatment uptake and is on track towards achieving the WHO target of HCV elimination by 2030.[187] The recent increased uptake of HCV therapy in Australia has been driven largely by GPs and nonspecialists prescribing DAAs.[231] In this study the long-term economic benefits of four MOCs employed in an SA real-life cohort were compared using a Markov model-based cohort analysis of liver disease progression.

Table 28. Sensitivity analysis (based on probabilistic analysis and sensitivity analysis involving changing time horizons).

Time horizon	**Costs/QALY***	**MOC1**	**MOC2**	**MOC3**	**MOC4**
10 years	Total healthcare costs in AUD	77 479	77 217	77 395	77 003
	QALYs gained	6.3801	6.3856	6.3788	6.3857
	NMB in AUD	241 527	242 063	241 547	242 283
20 years	Total healthcare costs in AUD	77 812	77 341	77 779	77 121
	QALYs gained	10.2725	10.2830	10.2701	10.2833
	in AUD	435 812	436 811	435 725	437 043

Costs and outcomes are expressed per patient.

*Mean values.

MOC1: Consultant only model; MOC2: Shared care model with consultants and specialist nurses; MOC3: Specialist nurses only model; MOC4: General practitioner model.

NMB: net monetary benefit; QALY: quality-adjusted life year.

The CEA showed that MOC2 (where HCV care is shared between specialist and nurse) and MOC4 (GP-led MOC) were cost effective compared to MOC1 (consultant-led MOC). MOC3 was also cost effective when compared to MOC1, but only if the threshold was less than or

equal to AUD 20 000/QALY gained, after which MOC1 was the cost-effective option. Using an NMB approach, MOC4 was found to be the most beneficial way of delivering cost-effective HCV treatment followed by MOC2. MOC1 was the least value for money option. Sensitivity analyses demonstrated surprisingly minimal variance in per patient ICER across the four MOCs, although considerable NMBs were demonstrated at a population level.

MOC1 and MOC3 had lower SVR rates compared to MOC4 and MOC2. The reasons for the slightly poorer performance of these MOCs (although statistically not significant) are not clear. MOC1 could be cited as disadvantaged in having more treatment-exposed patients than MOC4. However, MOC2, which had the highest proportion of such patients, had a higher SVR rate, suggesting that previous treatment exposure did not have any association with SVR. Similarly, despite having predominantly more patients with genotype 3, which is usually associated with a lower SVR, MOC4 had the highest SVR. In spite of significant differences between the baseline characteristics of the four MOCs, SVR (per protocol) rates were not significantly different among them. Thus, decentralised models, such as MOC4, MOC3 and MOC2, were associated with similar SVR as MOC1, but with lower costs in our statewide cohort of non-cirrhotic patients.

This analysis of a real-life cohort of patients, treated in the first year of DAA availability in Australia, confirms long-term cost savings associated with delivering HCV care for non-cirrhotic patients in a decentralised fashion, sparing the valuable time and higher costs of specialists. Our research findings are consistent with recent results from Project ECHO (Extension for Community Healthcare Outcomes Project) confirming the cost-effectiveness of increasing case finding and treatment by primary-care providers.[263] In a prospective study from Cairns, Queensland, Australia, of the 734 HCV patients treated, nearly half of the patients were treated by non-gastroenterologists, such as GPs and sexual health physicians. Not surprisingly, the SVR rates were not different between gastroenterologists (92%) and other prescribers (94%).[246] Nevertheless, the study did not evaluate the economic aspects of treatment models.

The cost-effectiveness of DAAs over interferon therapy at any stage of liver disease has been established.[41,260] Cost-effectiveness of HCV therapy in any disease stage is supported by studies involving special populations, such as prison inmates,[302] people who inject drugs,[223] and in patients with decompensated cirrhosis and HCC listed for LT.[303] Interestingly, HCV treatment has also been shown to provide benefits to the government in the long term by

cancelling the direct healthcare costs incurred by saving on disability costs and by income generated from tax payment, in a study from United Kingdom.[304] However, the economic advantages of providing HCV care by GPs, nurses and shared care between specialists and nurses have not been previously reported.

In a systematic review of modelling approaches for the cost-effectiveness of DAA treatment for HCV, lack of use of real-world data has been stressed among the 36 cost-effective analyses published from 2011 to 2015.[35] This study is unique in establishing the real-life costs of a decentralised MOC over traditional specialist-led models. In addition to providing the cost of HCV treatment in a real-life scenario, this study also projected the long-term benefits of nontraditional MOC.

GP-based primary health care is the backbone of Australia's healthcare system.[25] There are many potential advantages in harnessing this workforce to assist with HCV elimination goals. Firstly, the GP is more likely to have an existing close and trusting relationship with their patient and be far more easily accessed relative to specialists. Secondly, the Australian GP workforce is numerically large, relative to the specialist workforce, and has a long history of rapid and flexible adjustments to new health requirements. With just 26% of HCV infections treated to date, reliance on primary-care providers for HCV treatment appears essential in Australia's journey towards the WHO target of HCV elimination by the year 2030.

Encouragingly, this is evident from the increase in prescriptions provided by GPs, which has risen to 540 prescriptions per month from November 2017, as reported by the Kirby Institute, New South Wales, Australia.[236] In addition to speeding up HCV eradication, this MOC has the potential to address other important cofactors in the progression of liver diseases, namely alcohol misuse and obesity. However, the loss to follow-up associated with the GP model (MOC4) is a limitation and needs to be addressed with GP education and support, perhaps by regional viral hepatitis nurses. Encouraging and empowering GPs with knowledge of HCV treatment and workup may also enable them to develop interest in identifying and managing advanced liver diseases, such as cirrhosis and HCC surveillance. Moreover, the use of these MOCs in non-cirrhotic patients will also diminish the burden on specialists so that their time can be better utilised for managing more complicated patients. Nontraditional MOCs, such as nurse-led care, are also crucial in facilitating treatment uptake in special situations, such as custodial settings[27,28] and mental health patients.[34] The tertiary healthcare system, already

challenged by an increasing burden of end-stage liver disease and liver cancer, may benefit from such potential improvements in efficiency.[25]

A few limitations of the study should be acknowledged. Firstly, the inclusion of non-health-related costs, such as loss of wages for the patients and carers, may have provided more comprehensive cost estimates but were beyond the scope of this study. Secondly, this study did not model for the minority of cases that would require retreatment for either reinfection or failure of initial treatment. However, these costs are unlikely to significantly affect the analyses in view of the small numbers reported in literature.[305,306]The possibility of progression of liver disease due to non-viral causes, such as alcohol misuse or obesity, was excluded, due to nonavailability of complete data. Transition rates used in the Markov model were based on an Italian population, which may not be totally representative of the Australian cohort. [260] However, these were the best available estimates in the literature. Nevertheless, robust real-life data underpinned the economic analysis of this study.

8.6 CONCLUSION AND FUTURE DIRECTIONS

This study has confirmed the cost-effectiveness of treating non-cirrhotic HCV patients with decentralised MOCs involving GPs and shared care between specialists and nurses. Thus, this study encourages the application of these nontraditional approaches with less reliance on specialists for HCV treatment uptake. Widespread use of these novel models is in alignment with the WHO global strategy of providing HCV care as a public health approach rather than a specialist service with restricted access.[187] However, loss of follow-up seen more frequently with the GP model poses challenges and needs to be managed with increased GP education and support.

9. CONCLUSIONS

The pivotal theme of this thesis was the role of innovative, multidisciplinary models of care (MOC) in the management of chronic liver disease (CLD), built along the principles of chronic disease management (CDM).[9] Cirrhosis, the advanced stage of CLD, is a complicated chronic disease associated with high morbidity (multiple hospital admissions and readmissions), poor quality of life, and mortality. Despite medical advances, management of decompensated cirrhosis of the liver continues to pose a significant burden on the healthcare system due to recurrent hospital admissions and the associated expenditure.[3,13] With the increasing prevalence of cirrhosis,[278] reliance on traditional care models is likely to add more strain on the already overburdened healthcare system. Innovative MOCs need to be implemented to tackle the growing demands. In this thesis, using diverse research methods, the performance of new MOCs were investigated across multiple domains, including clinical, economic, educational, supportive care and qualitative aspects of health care in the management of this complex condition. The evaluation of new MOCs was carried out across the entire spectrum of CLD from chronic hepatitis, through compensated cirrhosis to decompensated cirrhosis.

CDM interventions, proven to be successful in other similar chronic diseases, have not been well studied in cirrhosis.[10] Newer MOCs are required to provide continuous, ongoing care rather than infrequent physician appointments in order to provide clinical, educational and self-management support in the vulnerable post-discharge period.[7] A coordinated MOC, with specialist hepatology input during hospital admission and post discharge care within a Chronic Liver Failure Program (CLFP), based on CDM principles was tested for its effect on liver-related emergency readmissions (LREAs) and survival in patients with decompensated cirrhosis.[14] These principles included coordinated case management, home visits, weekly telephone reviews, rapid access to care pathways, education and self-management support, and patient action plans. In a retrospective fashion, this model was compared to standard care in the first study. Management of decompensated cirrhosis using a coordinated MOC was associated with significantly improved survival and lower LREAs in the studied cohort. Demonstration of survival benefit in addition to reduction in LREAs suggested that coordinated MOC was beneficial and did not reduce high-value admissions. Enhanced access to planned abdominal paracentesis and elective procedures was associated with fewer emergency presentations under a coordinated MOC. Thus, the study established the feasibility of achieving

lower LREA and improved survival with a coordinated MOC. The model should be evaluated in prospective trials before further recommendations can be made.

In the traditional management of cirrhosis, educational and self-management needs are not prioritised.[17] However, patient education is one of the salient and successful CDM interventions implemented in other chronic diseases.[10] Hence, to focus on the unmet educational needs of patients with cirrhosis, the lack of a validated patient knowledge questionnaire was addressed in the second study. A cirrhosis knowledge questionnaire (CKQ) was developed and validated in a prospective validation study of patients with cirrhosis, using an exploratory factor analysis.[21] A revised CKQ with seven items addressing the three most important complications of cirrhosis (variceal bleeding, ascites and hepatic encephalopathy), emerged as a useful tool in the assessment of disease knowledge. In patients receiving case management for decompensated cirrhosis, the knowledge scores were higher, thus confirming the utility of the questionnaire in evaluation of knowledge improvement with education.

Patient self-management, one of the most successful CDM interventions, is associated with consistent improvement in symptom control, quality of life, hospitalisations and mortality in many chronic diseases.[10] Acknowledging the vital role of patient participation in CLD, the Partners in Health (PIH) scale, a validated self-management measurement tool, was evaluated in patients with cirrhosis in the third study.[23] The structural validity of the scale was confirmed for its use in cirrhosis. Higher scores on the PIH scale were observed in patients receiving case management for decompensated cirrhosis. The PIH scale could be used to assess self-management, knowledge and behaviours at baseline, and hence enable provision of a more customised care. In addition, its application in monitoring improvement in self-management in response to CDM interventions was highlighted.

In the fourth study, qualitative and health economic aspects of another innovative multidisciplinary MOC, the nurse-led cirrhosis clinic (NLCC), was evaluated in the management of compensated cirrhosis. Two key principles of CDM namely, delivery system redesign and multidisciplinary care, were thus examined. This prospective study recorded the experiences of patients and the medical staff involved in NLCCs in order to understand the acceptability, strengths, limitations and ways to improve the model. Cost-effectiveness of the model in terms of cost minimisation was also assessed. Easy accessibility, unique nurse-patient relationship, patient satisfaction and understanding of the model encapsulated patients'

perspectives of the model. Potential to care for sick new patients without compromising care for stable cirrhotic patients was welcomed by the hepatologists. Upskilling and providing well-rounded continuous care with education and self-management support were appreciated by the specialist nurses (SN). The study identified potential areas for improvement that included the need for regular meetings between SNs and hepatologists and to increase staffing capacity of the SNs. The model was found to be well accepted by patients and healthcare providers, in addition to being cost effective. This study highlighted the expectations, beliefs and the supportive care needs of CLD patients and the need for providers to align care delivery accordingly, to maximise patient participation in their chronic disease management.

Prevention of development of chronic illness (cirrhosis) is an important CDM principle that was highlighted in the fifth study. Sustained viral eradication achieved by the new direct-acting antivirals is associated with prevention of cirrhosis, reductions in both overall mortality and complications due to cirrhosis in patients infected with HCV.[30,32]A high seroprevalence of HCV in psychiatric inpatients was demonstrated in a prospective fashion in the fifth study. This robust epidemiological exercise was integrated with antiviral treatment in a sustainable multidisciplinary model utilising specialist nurses, mental healthcare workers and community pharmacists. It was successful in achieving increased viral eradication, in this otherwise difficult-to-engage group.

Demonstration of economic benefits of novel MOCs is essential for their wider implementation. In the final study, a detailed economic analysis of the MOCs in the management of HCV, uniquely Australian, was performed to establish the sustainability of the models. Cost-effectiveness of HCV treatment models employing nurses, general practitioners and shared care between nurses and specialists was assessed using real-life statewide data and compared with traditional specialist-driven care. It was encouraging to note that these nontraditional MOCs were cost saving in the long term and were also more efficacious.

9.1 RECOMMENDATIONS AND FURTHER STUDIES

In advocating for innovative models to be delivered in a multidisciplinary fashion to meet the growing demands of CLD in a holistic way, this thesis also provides insights into future research in this field. Such studies will be important to facilitate the wider acceptance and implementation of CDM models as the standard of care of patients with CLD.

The efficacy of the coordinated MOC in meeting the quality of care indicators, namely lower LREA and improved survival in decompensated cirrhosis is best established with a prospective randomised controlled trial (RCT) of the model in a multicentre cohort. The results of the retrospective study[14] provided an important sample size estimate for the design of a National Health and Medical Research Council (NHMRC) funded multicentre prospective RCT, the Adelaide Liver Failure trial (ALFIE). This ongoing study is investigating the benefits of a CDM model in reducing the LREA rates in cirrhotic patients. The study results will provide information concerning the more widespread implementation of this CDM model for patients with decompensated cirrhosis of the liver. In addition to the assessment of LREAs, survival, cost-effectiveness of the model, and qualitative analysis of patients' and nurses' experience of participation are further endpoints that will be reported by this study. The study has completed recruitment and will report preliminary 1-year outcomes in mid-2021.

The result of the second study, the revised CKQ with seven items, to assess cirrhosis knowledge in patients, is likely to find application in the routine clinical management of cirrhosis. Measurement of CKQ performance at various time points during the CDM intervention as a part of the ALFIE trial, will provide further useful information on improvement in knowledge with education, provided as a part of CDM intervention. In addition, the ongoing RCT will provide valuable data for the much-needed external validation of the CKQ and confirmatory factor analysis to define its dimensionality.

The PIH scale was demonstrated to be reliable and valid in the measurement of self-management in cirrhosis. It can be used in the assessment of self-management behaviour in patients with cirrhosis in clinical practice and to customise the care delivery. It is planned to study this tool in a longitudinal fashion during the delivery of the CDM intervention in the ongoing ALFIE RCT. This will assess the degree of improvement in response to the self-management support delivered as a part of the CDM intervention.

The NLCC is a useful multidisciplinary model that can considerably reduce the clinical load of liver specialists when deployed with appropriate training and supervision of the nurses. The acceptability and cost savings demonstrated in this study should encourage policy-makers to fund the model and promote its widespread use.

In the fifth study psychiatric inpatients were identified as a high-risk population for HCV requiring defined pathways for screening and referral for treatment within the health network. In addition, the study created collaborative networks among psychiatrists, infectious disease specialists and hepatologists, which are being explored in a further statewide prospective study. The establishment of cost-effectiveness of nonspecialists MOC for HCV treatment with nurses and GPs, the subject of the sixth study, should encourage the wider use of these models worldwide.

Thus, the six studies in the thesis tested new MOCs incorporated with CDM principles:

1. coordinated care,
2. patient education,
3. self-management,
4. access to community care clinics,
5. cost-effective decentralised services,
6. multidisciplinary care

in patients with CLD and demonstrated positive outcomes across multiple domains.

Management of cirrhosis poses multiple challenges. Its growing burden warrants the use of new MOCs, very different from traditional models. High-quality evidence backed by randomised prospective studies are essential to facilitate the adoption of these new models into routine care and treatment guidelines. It is unlikely that one size will fit all, and a key challenge may be to customise interventions to individual patient and health care system needs. Standardization of care processes and subsequent training of care providers will be important future challenges of these models to ensure sustainability.

BIBLIOGRAPHY

1. *Australian Institute of Health and Welfare 2015. Leading cause of premature mortality in Australia fact sheet: liver disease. Cat. no. PHE 199. Canberra: AIHW.*
2. Ge PS, Runyon BA. Treatment of Patients with Cirrhosis. *The New England journal of medicine.* 2016;375(21):2104-2105.
3. Volk ML, Tocco RS, Bazick J, Rakoski MO, Lok AS. Hospital readmissions among patients with decompensated cirrhosis. *The American journal of gastroenterology.* 2012;107(2):247-252.
4. *Deloitte Access Economics; The economic cost and health burden of liver diseases in Australia.* 2013.
5. Agrawal K, Kumar P, Markert R, Agrawal S. Risk Factors for 30-Day Readmissions of Individuals with Decompensated Cirrhosis. *Southern medical journal.* 2015;108(11):682-687.
6. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology (Baltimore, Md).* 2013;57(4):1651-1653.
7. Kanwal F, Tansel A, Kramer JR, Feng H, Asch SM, El-Serag HB. Trends in 30-Day and 1-Year Mortality Among Patients Hospitalized With Cirrhosis From 2004 to 2013. *The American journal of gastroenterology.* 2017;112(8):1287-1297.
8. Benbassat J, Taragin MI. The effect of clinical interventions on hospital readmissions: a meta-review of published meta-analyses. *Israel journal of health policy research.* 2013;2(1):1.
9. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *The Milbank quarterly.* 1996;74(4):511-544.
10. Scott IA. Chronic disease management: a primer for physicians. *Internal medicine journal.* 2008;38(6):427-437.
11. Wigg AJ, McCormick R, Wundke R, Woodman RJ. Efficacy of a chronic disease management model for patients with chronic liver failure. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2013;11(7):850-858.e851-854.
12. Fan VS, Gaziano JM, Lew R, et al. A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial. *Annals of internal medicine.* 2012;156(10):673-683.
13. Bajaj JS, Reddy KR, Tandon P, et al. The 3-month readmission rate remains unacceptably high in a large North American cohort of patients with cirrhosis. *Hepatology (Baltimore, Md).* 2016;64(1):200-208.
14. Ramachandran J, Hossain M, Hrycek C, et al. Coordinated care for patients with cirrhosis: fewer liver-related emergency admissions and improved survival. *The Medical journal of Australia.* 2018;209(7):301-305.
15. Tapper EB, Volk M. Strategies to Reduce 30-Day Readmissions in Patients with Cirrhosis. *Current gastroenterology reports.* 2017;19(1):1.
16. Bodenheimer T. Helping patients improve their health-related behaviors: what system changes do we need? *Disease management : DM.* 2005;8(5):319-330.
17. Valery PC, Powell E, Moses N, et al. Systematic review: unmet supportive care needs in people diagnosed with chronic liver disease. *BMJ open.* 2015;5(4):e007451.
18. Kim YJ, Soeken KL. A meta-analysis of the effect of hospital-based case management on hospital length-of-stay and readmission. *Nursing research.* 2005;54(4):255-264.

19. Gwadry-Sridhar FH, Flintoft V, Lee DS, Lee H, Guyatt GH. A systematic review and meta-analysis of studies comparing readmission rates and mortality rates in patients with heart failure. *Archives of internal medicine.* 2004;164(21):2315-2320.
20. Gibson PG, Powell H, Coughlan J, et al. Self-management education and regular practitioner review for adults with asthma. *The Cochrane database of systematic reviews.* 2003(1):Cd001117.
21. Ramachandran J, Woodman R, Muller K, et al. Validation of Knowledge Questionnaire for Patients With Liver Cirrhosis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2019.
22. Hibbard JH, Greene J. What the evidence shows about patient activation: better health outcomes and care experiences; fewer data on costs. *Health Aff (Millwood).* 2013;32(2):207-214.
23. Malcolm W. Battersby AA, Marion M. Reece,Mignon J. Markwick and James P. Collins. The Partners in Health scale: The development and psychometric properties of a generic assessment scale for chronic condition self-management. *Australian Journal of Primary Health.* 2003;9(2&3):41-49.
24. Battersby M, Harvey P, Mills PD, et al. SA HealthPlus: a controlled trial of a statewide application of a generic model of chronic illness care. *The Milbank quarterly.* 2007;85(1):37-67.
25. *National primary health care strategic framework 2013.Department of Health, Australian Government.*
26. Randall S, Crawford T, Currie J, River J, Betihavas V. Impact of community based nurse-led clinics on patient outcomes, patient satisfaction, patient access and cost effectiveness: A systematic review. *International journal of nursing studies.* 2017;73:24-33.
27. Overton K, Clegg J, Pekin F, et al. Outcomes of a nurse-led model of care for hepatitis C assessment and treatment with direct-acting antivirals in the custodial setting. *The International journal on drug policy.* 2019.
28. Papaluca T, McDonald L, Craigie A, et al. Outcomes of treatment for hepatitis C in prisoners using a nurse-led, statewide model of care. *Journal of hepatology.* 2019;70(5):839-846.
29. Cheng W, Nazareth S, Flexman JP. Statewide hepatitis C model of care for rural and remote regions. *Journal of gastroenterology and hepatology.* 2015;30 Suppl 2:1-5.
30. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Direct-acting antiviral sustained virologic response: Impact on mortality in patients without advanced liver disease. *Hepatology (Baltimore, Md).* 2018;68(3):827-838.
31. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Impact of Sustained Virologic Response with Direct-Acting Antiviral Treatment on Mortality in Patients with Advanced Liver Disease. *Hepatology (Baltimore, Md).* 2019;69(2):487-497.
32. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2011;9(6):509-516.e501.
33. Younossi ZM, Birerdinc A, Henry L. Hepatitis C infection: A multi-faceted systemic disease with clinical, patient reported and economic consequences. *Journal of hepatology.* 2016;65(1 Suppl):S109-s119.
34. Ramachandran J, Budd S, Slattery H, et al. Hepatitis C virus infection in Australian psychiatric inpatients: A multicenter study of seroprevalence, risk factors and treatment experience. *Journal of viral hepatitis.* 2019;26(5):609-612.

35. Chhatwal J, He T, Lopez-Olivo MA. Systematic Review of Modelling Approaches for the Cost Effectiveness of Hepatitis C Treatment with Direct-Acting Antivirals. *PharmacoEconomics.* 2016;34(6):551-567.
36. Ramachandran J, Kaambwa B, Muller K, et al. Cost effectiveness of treatment models of care for hepatitis C: the South Australian state-wide experience. *European journal of gastroenterology & hepatology.* 2019.
37. Haridy J, Wigg A, Muller K, et al. Real-world outcomes of unrestricted direct-acting antiviral treatment for hepatitis C in Australia: The South Australian statewide experience. *Journal of viral hepatitis.* 2018;25(11):1287-1297.
38. Anthony PP, Ishak KG, Nayak NC, Poulsen HE, Scheuer PJ, Sobin LH. The morphology of cirrhosis. Recommendations on definition, nomenclature, and classification by a working group sponsored by the World Health Organization. *J Clin Pathol.* 1978;31(5):395-414.
39. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet.* 1997;349(9055):825-832.
40. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2015;13(4):643-654.e641-649; quiz e639-640.
41. Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. *Journal of hepatology.* 2014;60(3):530-537.
42. Kage M, Shimamatu K, Nakashima E, Kojiro M, Inoue O, Yano M. Long-term evolution of fibrosis from chronic hepatitis to cirrhosis in patients with hepatitis C: morphometric analysis of repeated biopsies. *Hepatology (Baltimore, Md).* 1997;25(4):1028-1031.
43. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nature reviews Gastroenterology & hepatology.* 2018;15(1):11-20.
44. Younossi Z, Stepanova M, Ong JP, et al. Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2019;17(4):748-755.e743.
45. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *Journal of hepatology.* 2016;64(6):1388-1402.
46. Younossi Z, Tacke F, Arrese M, et al. Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. *Hepatology (Baltimore, Md).* 2019;69(6):2672-2682.
47. Mahady SE, Adams LA. Burden of non-alcoholic fatty liver disease in Australia. *Journal of gastroenterology and hepatology.* 2018;33 Suppl 1:1-11.
48. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology (Baltimore, Md).* 2016;64(1):73-84.
49. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology (Baltimore, Md).* 2017;65(5):1557-1565.

50. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology (Baltimore, Md).* 2018;67(1):328-357.
51. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. *Hepatology (Baltimore, Md).* 2016;64(5):1577-1586.
52. Adams LA, Roberts SK, Strasser SI, et al. Nonalcoholic fatty liver disease burden: Australia, 2019-2030. *Journal of gastroenterology and hepatology.* 2020.
53. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *Journal of hepatology.* 2020;73(1):202-209.
54. Lin S, Huang J, Wang M, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. *Liver international : official journal of the International Association for the Study of the Liver.* 2020;40(9):2082-2089.
55. Rehm J, Shield KD. Global Burden of Alcohol Use Disorders and Alcohol Liver Disease. *Biomedicines.* 2019;7(4).
56. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. *Journal of hepatology.* 2013;59(1):160-168.
57. Powell EE, Skoien R, Rahman T, et al. Increasing Hospitalization Rates for Cirrhosis: Overrepresentation of Disadvantaged Australians. *EClinicalMedicine.* 2019;11:44-53.
58. Becker U, Deis A, Sorensen TI, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology (Baltimore, Md).* 1996;23(5):1025-1029.
59. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology.* 2011;141(5):1572-1585.
60. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. *Journal of hepatology.* 2018;69(1):154-181.
61. Hart CL, Morrison DS, Batty GD, Mitchell RJ, Davey Smith G. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. *BMJ (Clinical research ed).* 2010;340:c1240.
62. Singal AK, Anand BS. Mechanisms of synergy between alcohol and hepatitis C virus. *Journal of clinical gastroenterology.* 2007;41(8):761-772.
63. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *Journal of hepatology.* 2006;44(1):217-231.
64. Saunders JB, Walters JR, Davies AP, Paton A. A 20-year prospective study of cirrhosis. *British medical journal (Clinical research ed).* 1981;282(6260):263-266.
65. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *Journal of hepatology.* 2018;69(2):406-460.
66. D'Amico G, Morabito A, Pagliaro L, Marubini E. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Digestive diseases and sciences.* 1986;31(5):468-475.
67. Leung JC-F, Loong TC-W, Pang J, Wei JL, Wong VW-S. Invasive and non-invasive assessment of portal hypertension. *Hepatology International.* 2018;12(1):44-55.
68. Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *The New England journal of medicine.* 2005;353(21):2254-2261.
69. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology.* 2007;133(2):481-488.

70. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. *Hepatology (Baltimore, Md).* 2010;51(4):1445-1449.
71. de Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *Journal of hepatology.* 2015;63(3):743-752.
72. Krogsgaard K, Gluud C, Henriksen JH, Christoffersen P. Correlation between liver morphology and portal pressure in alcoholic liver disease. *Hepatology (Baltimore, Md).* 1984;4(4):699-703.
73. van Leeuwen DJ, Howe SC, Scheuer PJ, Sherlock S. Portal hypertension in chronic hepatitis: relationship to morphological changes. *Gut.* 1990;31(3):339-343.
74. Jung YK, Yim HJ. Reversal of liver cirrhosis: current evidence and expectations. *Korean J Intern Med.* 2017;32(2):213-228.
75. Grgurevic I, Bozin T, Madir A. Hepatitis C is now curable, but what happens with cirrhosis and portal hypertension afterwards? *Clin Exp Hepatol.* 2017;3(4):181-186.
76. Mandorfer M, Kozbial K, Schwabl P, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. *Journal of hepatology.* 2016;65(4):692-699.
77. Di Marco V, Calvaruso V, Ferraro D, et al. Effects of Eradicating Hepatitis C Virus Infection in Patients With Cirrhosis Differ With Stage of Portal Hypertension. *Gastroenterology.* 2016;151(1):130-139.e132.
78. D'Amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. *Alimentary pharmacology & therapeutics.* 2014;39(10):1180-1193.
79. D'Amico G, Morabito A, D'Amico M, et al. New concepts on the clinical course and stratification of compensated and decompensated cirrhosis. *Hepatol Int.* 2018;12(Suppl 1):34-43.
80. Kim TY, Lee JG, Sohn JH, et al. Hepatic Venous Pressure Gradient Predicts Long-Term Mortality in Patients with Decompensated Cirrhosis. *Yonsei medical journal.* 2016;57(1):138-145.
81. D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. *Gastroenterology.* 2006;131(5):1611-1624.
82. Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. *Liver international : official journal of the International Association for the Study of the Liver.* 2012;32(9):1407-1414.
83. Maurice JB, Brodkin E, Arnold F, et al. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. *Journal of hepatology.* 2016;65(5):899-905.
84. Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. *Hepatology (Baltimore, Md).* 2017;66(6):1980-1988.
85. Wundke R, Altus R, Sandford J, Wigg A. Improving management of oesophageal varices in patients with cirrhosis. *Quality & safety in health care.* 2010;19(6):536-541.
86. Infante-Rivard C, Esnaola S, Villeneuve JP. Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. *Hepatology (Baltimore, Md).* 1987;7(4):660-664.
87. Gines P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology (Baltimore, Md).* 1987;7(1):122-128.

88. Fleming KM, Aithal GP, Card TR, West J. All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study. *Liver international : official journal of the International Association for the Study of the Liver.* 2012;32(1):79-84.
89. Statistics ABo. 3303.0-Causes of Death in Australia 2015. . In: Statistics ABo, ed2016.
90. *Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101.Cat. no. CAN 100. Canberra: AIHW.*
91. AIHW National Hospital Morbidity Data. 2010. www.aihw.gov.au/hospitals/datacubes/index.cfm.
92. *Australian Institute of Health and Welfare 2018. Australia's health 2018. Australia's health series no. 16.AUS 221. Canberra: AIHW.*
93. Fagan KJ, Zhao EY, Horsfall LU, et al. Burden of decompensated cirrhosis and ascites on hospital services in a tertiary care facility: time for change? *Internal medicine journal.* 2014;44(9):865-872.
94. Bajaj JS, O'Leary JG, Reddy KR, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. *Hepatology (Baltimore, Md).* 2012;56(6):2328-2335.
95. Singal AG, Rahimi RS, Clark C, et al. An automated model using electronic medical record data identifies patients with cirrhosis at high risk for readmission. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2013;11(10):1335-1341.e1331.
96. Wong EL, Cheung AW, Leung MC, et al. Unplanned readmission rates, length of hospital stay, mortality, and medical costs of ten common medical conditions: a retrospective analysis of Hong Kong hospital data. *BMC health services research.* 2011;11:149.
97. Tapper EB, Halbert B, Mellinger J. Rates of and Reasons for Hospital Readmissions in Patients With Cirrhosis: A Multistate Population-based Cohort Study. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2016;14(8):1181-1188.e1182.
98. Ratib S, Fleming KM, Crooks CJ, Aithal GP, West J. 1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998-2009: a large population study. *Journal of hepatology.* 2014;60(2):282-289.
99. Roberts SE, Goldacre MJ, Yeates D. Trends in mortality after hospital admission for liver cirrhosis in an English population from 1968 to 1999. *Gut.* 2005;54(11):1615-1621.
100. Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology.* 2010;139(4):1246-1256, 1256.e1241-1245.
101. Fernandez J, Acevedo J, Castro M, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology (Baltimore, Md).* 2012;55(5):1551-1561.
102. Schultalbers M, Tergast TL, Simon N, et al. Frequency, characteristics and impact of multiple consecutive nosocomial infections in patients with decompensated liver cirrhosis and ascites. *United European gastroenterology journal.* 2020:2050640620913732.
103. Chalasani N, Kahi C, Francois F, et al. Improved patient survival after acute variceal bleeding: a multicenter, cohort study. *The American journal of gastroenterology.* 2003;98(3):653-659.

104. McCaughan GW, Munn SR. Liver transplantation in Australia and New Zealand. *Liver Transpl.* 2016;22(6):830-838.
105. Saab S, Nguyen S, Ibrahim A, Vierling JM, Tong MJ. Management of patients with cirrhosis in Southern California: results of a practitioner survey. *Journal of clinical gastroenterology.* 2006;40(2):156-161.
106. Kanwal F, Kramer J, Asch SM, et al. An explicit quality indicator set for measurement of quality of care in patients with cirrhosis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2010;8(8):709-717.
107. Kanwal F, Kramer JR, Buchanan P, et al. The quality of care provided to patients with cirrhosis and ascites in the Department of Veterans Affairs. *Gastroenterology.* 2012;143(1):70-77.
108. Ghaoui R, Friderici J, Desilets DJ, et al. Outcomes associated with a mandatory gastroenterology consultation to improve the quality of care of patients hospitalized with decompensated cirrhosis. *Journal of hospital medicine.* 2015;10(4):236-241.
109. Le S, Spelman T, Chong CP, et al. Could Adherence to Quality of Care Indicators for Hospitalized Patients With Cirrhosis-Related Ascites Improve Clinical Outcomes? *The American journal of gastroenterology.* 2016;111(1):87-92.
110. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. *Hepatology (Baltimore, Md).* 2010;52(1):132-141.
111. Hong TP, Gow PJ, Fink M, et al. Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study. *The Medical journal of Australia.* 2018;209(8):348-354.
112. Singal AG, Volk ML, Rakoski MO, et al. Patient involvement in healthcare is associated with higher rates of surveillance for hepatocellular carcinoma. *Journal of clinical gastroenterology.* 2011;45(8):727-732.
113. Wong CR, Garcia RT, Trinh HN, et al. Adherence to screening for hepatocellular carcinoma among patients with cirrhosis or chronic hepatitis B in a community setting. *Digestive diseases and sciences.* 2009;54(12):2712-2721.
114. Singal AG, Tiro JA, Marrero JA, et al. Mailed Outreach Program Increases Ultrasound Screening of Patients With Cirrhosis for Hepatocellular Carcinoma. *Gastroenterology.* 2017;152(3):608-615.e604.
115. Beste LA, Ioannou GN, Yang Y, Chang MF, Ross D, Dominitz JA. Improved surveillance for hepatocellular carcinoma with a primary care-oriented clinical reminder. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2015;13(1):172-179.
116. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodes J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology (Baltimore, Md).* 1988;8(5):1151-1157.
117. Caraceni P, Riggio O, Angeli P, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. *Lancet.* 2018;391(10138):2417-2429.
118. Hudson B, Round J, Georgeson B, et al. Cirrhosis with ascites in the last year of life: a nationwide analysis of factors shaping costs, health-care use, and place of death in England. *The lancet Gastroenterology & hepatology.* 2018;3(2):95-103.
119. McAlister FA, Stewart S, Ferrua S, McMurray JJJV. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. *J Am Coll Cardiol.* 2004;44(4):810-819.

120. Gonseth J, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. *Eur Heart J.* 2004;25(18):1570-1595.
121. Roccaforte R, Demers C, Baldassarre F, Teo KK, Yusuf S. Effectiveness of comprehensive disease management programmes in improving clinical outcomes in heart failure patients. A meta-analysis.[Erratum appears in Eur J Heart Fail. 2006 Mar;8(2):223-4]. *Eur J Heart Fail.* 2005;7(7):1133-1144.
122. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation.* 2009;119(14):e391-479.
123. Wigg AJ, McCormick R, Wundke R, Woodman RJ. Efficacy of a chronic disease management model for patients with chronic liver failure. *Clin Gastroenterol Hepatol.* 2013;11(7):850-858 e851-854.
124. Kanwal F. Coordinating care in patients with cirrhosis. *Clinical Gastroenterology & Hepatology.* 2013;11(7):859-861.
125. Mayorga CA, Singal AG. Can chronic disease management programs improve outcomes in patients with cirrhosis? *Gastroenterology.* 2013;145(5):1153-1155.
126. Wigg AJ, Chin JK, Muller KR, Ramachandran J, Woodman RJ, Kaambwa B. Cost-effectiveness of a chronic disease management model for cirrhosis: Analysis of a randomized controlled trial. *Journal of gastroenterology and hepatology.* 2018.
127. Morando F, Maresio G, Piano S, et al. How to improve care in outpatients with cirrhosis and ascites: a new model of care coordination by consultant hepatologists. *Journal of Hepatology.* 2013;59(2):257-264.
128. Tapper EB, Finkelstein D, Mittleman MA, Piatkowski G, Chang M, Lai M. A Quality Improvement Initiative Reduces 30-Day Rate of Readmission for Patients With Cirrhosis. *Clin Gastroenterol Hepatol.* 2016;14(5):753-759.
129. Hayward KL, Patel PJ, Valery PC, et al. Medication-Related Problems in Outpatients With Decompensated Cirrhosis: Opportunities for Harm Prevention. *Hepatol Commun.* 2019;3(5):620-631.
130. Eckman MH, Wise R, Leonard AC, et al. Impact of health literacy on outcomes and effectiveness of an educational intervention in patients with chronic diseases. *Patient education and counseling.* 2012;87(2):143-151.
131. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *The Cochrane database of systematic reviews.* 2008(2):Cd000011.
132. Haynes RB, Taylor DW, Sackett DL. Compliance in health care. 1979.
133. *First Report and Recommendations of the Commonwealth Fund's International Working Group on Quality Indicators, The Commonwealth Fund, June 2004.*
134. O'Brien MK, Petrie K, Raeburn J. Adherence to medication regimens: updating a complex medical issue. *Medical care review.* 1992;49(4):435-454.
135. Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *The American journal of cardiology.* 2001;87(7):819-822.

136. Singal AG, Yopp A, C SS, Packer M, Lee WM, Tiro JA. Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. *Journal of general internal medicine.* 2012;27(7):861-867.
137. Tavakol M, Dennick R. Making sense of Cronbach's alpha. *International journal of medical education.* 2011;2:53-55.
138. Bolarinwa O. Principles and methods of validity and reliability testing of questionnaires used in social and health science researches. *Nigerian Postgraduate Medical Journal.* 2015;22(4):195-201.
139. Volk ML, Fisher N, Fontana RJ. Patient knowledge about disease self-management in cirrhosis. *The American journal of gastroenterology.* 2013;108(3):302-305.
140. Goldsworthy MA, Fateen W, Thygesen H, Aldersley MA, Rowe IA, Jones RL. Patient understanding of liver cirrhosis and improvement using multimedia education. *Frontline gastroenterology.* 2017;8(3):214-219.
141. Hayward KL, Horsfall LU, Ruffin BJ, et al. Optimising care of patients with chronic disease: patient-oriented education may improve disease knowledge and self-management. *Internal medicine journal.* 2017;47(8):952-955.
142. Alavinejad P, Hajiani E, Danyaee B, Morvaridi M. The effect of nutritional education and continuous monitoring on clinical symptoms, knowledge, and quality of life in patients with cirrhosis. *Gastroenterology and hepatology from bed to bench.* 2019;12(1):17-24.
143. Beg S, Curtis S, Shariff M. Patient education and its effect on self-management in cirrhosis: a pilot study. *European journal of gastroenterology & hepatology.* 2016;28(5):582-587.
144. Zandi M, Adib-Hajbagheri M, Memarian R, Nejhad AK, Alavian SM. Effects of a self-care program on quality of life of cirrhotic patients referring to Tehran Hepatitis Center. *Health and quality of life outcomes.* 2005;3:35.
145. Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut.* 1999;45(2):295-300.
146. Rakoski MO, McCammon RJ, Piette JD, et al. Burden of cirrhosis on older Americans and their families: analysis of the health and retirement study. *Hepatology (Baltimore, Md).* 2012;55(1):184-191.
147. Bajaj JS, Wade JB, Gibson DP, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *The American journal of gastroenterology.* 2011;106(9):1646-1653.
148. Valery PC, Bernardes CM, Stuart KA, et al. Development and Evaluation of the Supportive Needs Assessment Tool for Cirrhosis (SNAC). *Patient Prefer Adherence.* 2020;14:599-611.
149. Qian Wang YW, Jian Gao, Jian-Tong Han Yan-Ping Li Development of a self-management behaviour scale for liver cirrhosis. *International Journal opf Nursing Sciences.* 2015;2(1):73-79.
150. Dong N, Chen WT, Bao M, Lu Y, Qian Y, Lu H. Self-Management Behaviors Among Patients With Liver Cirrhosis in Shanghai, China: A Cross-Sectional Study. *Clinical nursing research.* 2018:1054773818777914.
151. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. *Effective clinical practice : ECP.* 2001;4(6):256-262.
152. Frei A, Svarin A, Steurer-Stey C, Puhan MA. Self-efficacy instruments for patients with chronic diseases suffer from methodological limitations--a systematic review. *Health and quality of life outcomes.* 2009;7:86.

153. Mansouri PM, Ghadami MM, Najafi SSM, Yektatalab SP. The effect of Self-Management Training on Self-Efficacy of Cirrhotic Patients Referring to Transplantation Center of Nemazee Hospital: A Randomized Controlled Clinical Trial. *International journal of community based nursing and midwifery.* 2017;5(3):256-263.
154. Lev EL, Owen SV. A measure of self-care self-efficacy. *Research in nursing & health.* 1996;19(5):421-429.
155. Petkov J, Harvey P, Battersby M. The internal consistency and construct validity of the partners in health scale: validation of a patient rated chronic condition self-management measure. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2010;19(7):1079-1085.
156. Battersby M, Harris M, Smith D, Reed R, Woodman R. A pragmatic randomized controlled trial of the Flinders Program of chronic condition management in community health care services. *Patient education and counseling.* 2015;98(11):1367-1375.
157. Smith D, Harvey P, Lawn S, Harris M, Battersby M. Measuring chronic condition self-management in an Australian community: factor structure of the revised Partners in Health (PIH) scale. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2017;26(1):149-159.
158. Brand CA, Amatya B, Gordon B, Tosti T, Gorelik A. Redesigning care for chronic conditions: improving hospital-based ambulatory care for people with osteoarthritis of the hip and knee. *Internal medicine journal.* 2010;40(6):427-436.
159. Chan JM, Helene; Bell, Lee. A pilot study to assess the efficacy of the Flinders Program of Chronic Condition Self-management on the health and wellbeing of haemodialysis patients. *Renal Society of Australasia Journal.* 2014;Volume 10(Issue 2):66-74.
160. Reed RL, Roeger L, Howard S, et al. A self-management support program for older Australians with multiple chronic conditions: a randomised controlled trial. *The Medical journal of Australia.* 2018;208(2):69-74.
161. Hatchett R. *Nurse-led Clinics: Practice Issues,The emergence of the modern nurse-led clinic.* Routledge, London, UK,.
162. Horrocks S, Anderson E, Salisbury C. Systematic review of whether nurse practitioners working in primary care can provide equivalent care to doctors. *BMJ (Clinical research ed).* 2002;324(7341):819-823.
163. Edwall LL, Hellstrom AL, Ohrn I, Danielson E. The lived experience of the diabetes nurse specialist regular check-ups, as narrated by patients with type 2 diabetes. *Journal of clinical nursing.* 2008;17(6):772-781.
164. Whitehouse M, Clark J. Earmarked for success. Interview by Alison Handley. *Nursing standard (Royal College of Nursing (Great Britain) : 1987).* 2010;24(30):18-19.
165. Schadewaldt V, Schultz T. Nurse-led clinics as an effective service for cardiac patients: results from a systematic review. *International journal of evidence-based healthcare.* 2011;9(3):199-214.
166. Bentley M, Stirling C, Robinson A, Minstrell M. The nurse practitioner-client therapeutic encounter: an integrative review of interaction in aged and primary care settings. *Journal of advanced nursing.* 2016;72(9):1991-2002.
167. Efraimsson EO, Hillervik C, Ehrenberg A. Effects of COPD self-care management education at a nurse-led primary health care clinic. *Scand J Caring Sci.* 2008;22(2):178-185.
168. Jenny Ingram DS. `No worries!': Young people's experiences of nurse-led drop-in sexual health services in South West England. *Journal Of research In Nursing.* 2007;Volume: 12(issue: 4):page(s): 305-315.

169. Savage CL, Lindsell CJ, Gillespie GL, Lee RJ, Corbin A. Improving health status of homeless patients at a nurse-managed clinic in the Midwest USA. *Health Soc Care Community.* 2008;16(5):469-475.
170. Banks J, Sharp DJ, Hunt LP, Shield JP. Evaluating the transferability of a hospital-based childhood obesity clinic to primary care: a randomised controlled trial. *Br J Gen Pract.* 2012;62(594):e6-12.
171. Marshall B, Floyd S, Forrest R. Clinical outcomes and patients' perceptions of nurse-led healthy lifestyle clinics. *Journal of primary health care.* 2011;3(1):48-52.
172. Mutsekwa RN, Canavan R, Whitfield A, Spencer A, Angus RL. Dietitian first gastroenterology clinic: an initiative to reduce wait lists and wait times for gastroenterology outpatients in a tertiary hospital service. *Frontline gastroenterology.* 2019;10(3):229-235.
173. Biddle ML, Adler NR, Heath M, Streat S, Wardrop M, Watson JP. Nurse-led clinic: effective and efficient delivery of assessment and review of patients with hepatitis B and C. *Internal medicine journal.* 2014;44(6):581-585.
174. El-Gohary M, Moore M, Roderick P, et al. Local care and treatment of liver disease (LOCATE) - A cluster-randomized feasibility study to discover, assess and manage early liver disease in primary care. *PloS one.* 2018;13(12):e0208798.
175. Nazareth S, Leembruggen N, Tuma R, et al. Nurse-led hepatocellular carcinoma surveillance clinic provides an effective method of monitoring patients with cirrhosis. *International journal of nursing practice.* 2016;22 Suppl 2:3-11.
176. Hjorth M, Sjoberg D, Svanberg A, Kaminsky E, Langenskiold S, Rorsman F. Nurse-led clinic for patients with liver cirrhosis-effects on health-related quality of life: study protocol of a pragmatic multicentre randomised controlled trial. *BMJ open.* 2018;8(10):e023064.
177. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Annals of medicine.* 2001;33(5):350-357.
178. Wilde B, Starrin B, Larsson G, Larsson M. Quality of care from a patient perspective--a grounded theory study. *Scand J Caring Sci.* 1993;7(2):113-120.
179. Harrison MB, Graham ID, Lorimer K, et al. Nurse clinic versus home delivery of evidence-based community leg ulcer care: a randomized health services trial. *BMC health services research.* 2008;8:243.
180. Bicki A, Silva A, Joseph V, et al. A nurse-run walk-in clinic: cost-effective alternative to non-urgent emergency department use by the uninsured. *Journal of community health.* 2013;38(6):1042-1049.
181. Wundke R, McCormick R, Narayana SK, Sorensen L, Wigg A. The Chronic Liver Disease Nurse Role in Australia: Describing 10 Years of a New Role in Cirrhosis Management. *Gastroenterology nursing : the official journal of the Society of Gastroenterology Nurses and Associates.* 2020;43(1):E9-e15.
182. http://www.uk.sagepub.com/books/Book233059.
183. Clarke V, Braun V. Thematic Analysis. In: Teo T, ed. *Encyclopedia of Critical Psychology.* New York, NY: Springer New York; 2014:1947-1952.
184. Mahomed R, St John W, Patterson E. Understanding the process of patient satisfaction with nurse-led chronic disease management in general practice. *Journal of advanced nursing.* 2012;68(11):2538-2549.
185. Reinson T, Bradbury K, Moore M, Sheron N. Healthcare practitioners' experiences of an intervention to detect and treat patients with liver disease (the LOCATE intervention): a qualitative process evaluation. *BMJ open.* 2019;9(5):e028591.

186. Lim CY, Berry ABL, Hirsch T, et al. Understanding What Is Most Important to Individuals with Multiple Chronic Conditions: A Qualitative Study of Patients' Perspectives. *Journal of general internal medicine.* 2017;32(12):1278-1284.
187. Report WHO. *Global health sector strategy on viral hepatitis 2016–2021, towards ending viral hepatitis.*
188. Gastroenterological Society of Australia. *Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement (January 2017). Melbourne*:.
189. Mathurin P. HCV burden in Europe and the possible impact of current treatment. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver.* 2013;45 Suppl 5:S314-317.
190. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *Journal of hepatology.* 2014;61(1 Suppl):S45-57.
191. Gravitz L. Introduction: a smouldering public-health crisis. *Nature.* 2011;474(7350):S2-4.
192. Lauer GM, Walker BD. Hepatitis C virus infection. *The New England journal of medicine.* 2001;345(1):41-52.
193. Guidelines for the screening care and treatment of persons with chronic hepatitis C infection Updated version, April 2016, World health organization.
194. EASL Recommendations on Treatment of Hepatitis C 2018. *Journal of hepatology.* 2018.
195. WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. In.
196. *Hepatitis C Virus Infection Consensus Statement Working Group. Australian Recommendations for the managment of heaptitis C infection: a consensus statement.* Melbourne: Gastroenterological Society of Australia;September 2018.
197. Schillie S WC, Osborne M, Wesolowski L, Ryerson AB. . *CDC Recommendations for Hepatitis C Screening Among Adults — United States, 2020. MMWR Recomm Rep 2020;69(No. RR-2):1–17.*
198. Chapko MK, Dufour DR, Hatia RI, Drobeniuc J, Ward JW, Teo CG. Cost-effectiveness of strategies for testing current hepatitis C virus infection. *Hepatology (Baltimore, Md).* 2015;62(5):1396-1404.
199. Parr JB, Lodge EK, Holzmayer V, et al. An Efficient, Large-Scale Survey of Hepatitis C Viremia in the Democratic Republic of the Congo Using Dried Blood Spots. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2018;66(2):254-260.
200. Iversen J, Grebely J, Catlett B, Cunningham P, Dore GJ, Maher L. Estimating the cascade of hepatitis C testing, care and treatment among people who inject drugs in Australia. *The International journal on drug policy.* 2017;47:77-85.
201. Soulier A, Poiteau L, Rosa I, et al. Dried Blood Spots: A Tool to Ensure Broad Access to Hepatitis C Screening, Diagnosis, and Treatment Monitoring. *The Journal of infectious diseases.* 2016;213(7):1087-1095.
202. Poiteau L, Soulier A, Rosa I, et al. Performance of rapid diagnostic tests for the detection of antibodies to hepatitis C virus in whole blood collected on dried blood spots. *Journal of viral hepatitis.* 2016;23(5):399-401.
203. Khuroo MS, Khuroo NS, Khuroo MS. Diagnostic accuracy of point-of-care tests for hepatitis C virus infection: a systematic review and meta-analysis. *PloS one.* 2015;10(3):e0121450.

204. Tang W, Chen W, Amini A, et al. Diagnostic accuracy of tests to detect Hepatitis C antibody: a meta-analysis and review of the literature. *BMC infectious diseases.* 2017;17(Suppl 1):695.
205. Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. *Liver international : official journal of the International Association for the Study of the Liver.* 2011;31(8):1090-1101.
206. Butler T S, M. . *Nation Prison Entrants' Blood-borne Virus Survey Report* Kirby Institute (UNSW Sydney). 2017 ISBN-13: 978-0-7334-3772-4. ;2004, 2007, 2010, 2013, and 2016.
207. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *The Lancet Global health.* 2017;5(12):e1192-e1207.
208. Iversen J, Wand H, Gonnermann A, Maher L. Gender differences in hepatitis C antibody prevalence and risk behaviours amongst people who inject drugs in Australia 1998-2008. *The International journal on drug policy.* 2010;21(6):471-476.
209. Larney S, Peacock A, Leung J, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. *The Lancet Global health.* 2017;5(12):e1208-e1220.
210. Sievert W, Altraif I, Razavi HA, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. *Liver international : official journal of the International Association for the Study of the Liver.* 2011;31 Suppl 2:61-80.
211. *The Kirby Institute. Hepatitis B and C in Australia Annual Surveillance Report Supplement 2016.*: The Kirby Institute, UNSW Australia, Sydney NSW 2052;2016.
212. Kakisi OK, Grammatikos AA, Karageorgopoulos DE, Athanasoulia AP, Papadopoulou AV, Falagas ME. Prevalence of hepatitis B, hepatitis C, and HIV infections among patients in a psychiatric hospital in Greece. *Psychiatric services (Washington, DC).* 2009;60(9):1269-1272.
213. Lacey C, Ellen S, Devlin H, Wright E, Mijch A. Hepatitis C in psychiatry inpatients: testing rates, prevalence and risk behaviours. *Australasian psychiatry : bulletin of Royal Australian and New Zealand College of Psychiatrists.* 2007;15(4):315-319.
214. Hughes E, Bassi S, Gilbody S, Bland M, Martin F. Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness: a systematic review and meta-analysis. *The lancet Psychiatry.* 2016;3(1):40-48.
215. Gunewardene R, Lampe L, Ilchef R. Prevalence of hepatitis C in two inpatient psychiatry populations. *Australasian psychiatry : bulletin of Royal Australian and New Zealand College of Psychiatrists.* 2010;18(4):330-334.
216. Sanger C, Hayward J, Patel G, et al. Acceptability and necessity of HIV and other blood-borne virus testing in a psychiatric setting. *The British journal of psychiatry : the journal of mental science.* 2013;202(4):307-308.
217. Trager E, Khalili M, Masson CL, Vittinghoff E, Creasman J, Mangurian C. Hepatitis C Screening Rate Among Underserved Adults With Serious Mental Illness Receiving Care in California Community Mental Health Centers. *American journal of public health.* 2016;106(4):740-742.
218. Rose G, Cama E, Brener L, Treloar C. Knowledge and attitudes towards hepatitis C and injecting drug use among mental-health support workers of a community managed organisation. *Australian health review : a publication of the Australian Hospital Association.* 2013;37(5):654-659.

219. Hajarizadeh B, Grebely J, McManus H, et al. Chronic hepatitis C burden and care cascade in Australia in the era of interferon-based treatment. *Journal of gastroenterology and hepatology.* 2017;32(1):229-236.
220. Rein DB, Smith BD, Wittenborn JS, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Annals of internal medicine.* 2012;156(4):263-270.
221. Eckman MH, Ward JW, Sherman KE. Cost Effectiveness of Universal Screening for HCV Infection in the Era of Direct-Acting, Pangenotypic Treatment Regimens. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2018.
222. Opstaele L, Bielen R, Bourgeois S, et al. Who to screen for hepatitis C? A cost-effectiveness study in Belgium of comprehensive hepatitis C screening in four target groups. *Acta gastro-enterologica Belgica.* 2019;82(3):379-387.
223. Scott N, Iser DM, Thompson AJ, Doyle JS, Hellard ME. Cost-effectiveness of treating chronic hepatitis C virus with direct-acting antivirals in people who inject drugs in Australia. *Journal of gastroenterology and hepatology.* 2016;31(4):872-882.
224. Yoshida EM, Sulkowski MS, Gane EJ, et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. *Hepatology (Baltimore, Md).* 2015;61(1):41-45.
225. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. *Annals of internal medicine.* 2017;166(9):637-648.
226. Ioannou GN, Feld JJ. What Are the Benefits of a Sustained Virologic Response to Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection? *Gastroenterology.* 2019;156(2):446-460.e442.
227. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2015;61(5):730-740.
228. Younossi ZM, Park H, Saab S, Ahmed A, Dieterich D, Gordon SC. Cost-effectiveness of all-oral ledipasvir/sofosbuvir regimens in patients with chronic hepatitis C virus genotype 1 infection. *Alimentary pharmacology & therapeutics.* 2015;41(6):544-563.
229. Younossi ZM, Stepanova M, Nader F, Lam B, Hunt S. The patient's journey with chronic hepatitis C from interferon plus ribavirin to interferon- and ribavirin-free regimens: a study of health-related quality of life. *Alimentary pharmacology & therapeutics.* 2015;42(3):286-295.
230. Younossi ZM, Stepanova M, Racila A, et al. Long-term Benefits of Sustained Virologic Response for Patient-Reported Outcomes in Patients With Chronic Hepatitis C Virus Infection. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2020;18(2):468-476.e411.
231. Hajarizadeh B, Grebely J, Matthews GV, Martinello M, Dore GJ. Uptake of direct-acting antiviral treatment for chronic hepatitis C in Australia. *Journal of viral hepatitis.* 2018;25(6):640-648.
232. The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 9). The Kirby Institute US, Sydney, NSW, Australia, July 2018. *The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 9). The Kirby Institute, UNSW Sydney, Sydney, NSW, Australia, July 2018.*

233. Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. *The New England journal of medicine.* 2011;364(23):2199-2207.
234. Baker D, Alavi M, Erratt A, et al. Delivery of treatment for hepatitis C virus infection in the primary care setting. *European journal of gastroenterology & hepatology.* 2014;26(9):1003-1009.
235. Bloom S, Kemp W, Nicoll A, et al. Liver stiffness measurement in the primary care setting detects high rates of advanced fibrosis and predicts liver-related events in hepatitis C. *Journal of hepatology.* 2018;69(3):575-583.
236. *The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 10). The Kirby Institute, UNSW Sydney, NSW, Australia, June 2019 (available online at: https://kirby.unsw.edu.au/report/monitoring-hepatitis-c-treatment-uptake-australia-issue-10-june-2019).*
237. *Department of Health, Western Australia. Hepatitis C Virus Model of Care. Perth, WA: Health Networks Branch, Department of Health,Western Australia, 2009. .*
238. Nazareth SP, Carol; Tibbet, Patricia and Cheng, Wendy. Innovative practice in the management of chronic Hepatitis C: introducing the nurse practitioner model. *Australian Journal of Advanced Nursing, The, Vol 25, No 4, June/Aug 2008: 107-113* 2008.
239. Grogan A, Timmins F. Patients' perceptions of information and support received from the nurse specialist during HCV treatment. *Journal of clinical nursing.* 2010;19(19-20):2869-2878.
240. Hashim A, O'Sullivan M, Williams H, Verma S. Developing a community HCV service: project ITTREAT (integrated community-based test - stage - TREAT) service for people who inject drugs. *Primary health care research & development.* 2018;19(2):110-120.
241. Sims OT, Melton PA, Ji S. A Descriptive Analysis of a Community Clinic Providing Hepatitis C Treatment to Poor and Uninsured Patients. *Journal of community health.* 2018;43(4):725-730.
242. O'Sullivan M, Jones AM, Gage H, et al. ITTREAT (Integrated Community Test - Stage - TREAT) Hepatitis C service for people who use drugs: Real-world outcomes. *Liver international : official journal of the International Association for the Study of the Liver.* 2020.
243. Phillips C, Schulkind J, O'Sullivan M, et al. Improving access to care for people who inject drugs: Qualitative evaluation of project ITTREAT-An integrated community hepatitis C service. *Journal of viral hepatitis.* 2020;27(2):176-187.
244. Tait JM, Wang H, Stephens BP, et al. Multidisciplinary managed care networks-Life-saving interventions for hepatitis C patients. *Journal of viral hepatitis.* 2017;24(3):207-215.
245. Scott N, Hainsworth SW, Sacks-Davis R, et al. Heterogeneity in hepatitis C treatment prescribing and uptake in Australia: a geospatial analysis of a year of unrestricted treatment access. *Journal of virus eradication.* 2018;4(2):108-114.
246. Lee A, Hanson J, Fox P, Spice G, Russell D, Boyd P. A decentralised, multidisciplinary model of care facilitates treatment of hepatitis C in regional Australia. *Journal of virus eradication.* 2018;4(3):160-164.
247. Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2013;57 Suppl 2:S80-89.

248. Hellard M, Rolls DA, Sacks-Davis R, et al. The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. *Hepatology (Baltimore, Md).* 2014;60(6):1861-1870.
249. Jeffrey GP, MacQuillan G, Chua F, et al. Hepatitis C virus eradication in intravenous drug users maintained with subcutaneous naltrexone implants. *Hepatology (Baltimore, Md).* 2007;45(1):111-117.
250. Alavi M, Grebely J, Micallef M, et al. Assessment and treatment of hepatitis C virus infection among people who inject drugs in the opioid substitution setting: ETHOS study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2013;57 Suppl 2:S62-69.
251. Keats J, Micallef M, Grebely J, et al. Assessment and delivery of treatment for hepatitis C virus infection in an opioid substitution treatment clinic with integrated peer-based support in Newcastle, Australia. *The International journal on drug policy.* 2015;26(10):999-1006.
252. Grebely J, Alavi M, Micallef M, et al. Treatment for hepatitis C virus infection among people who inject drugs attending opioid substitution treatment and community health clinics: the ETHOS Study. *Addiction (Abingdon, England).* 2016;111(2):311-319.
253. Fragomeli V, Weltman M. Addressing viral hepatitis in the opiate substitution setting: an integrated nursing model of care. *Journal of gastroenterology and hepatology.* 2015;30 Suppl 2:6-11.
254. Bruneau J, Zang G, Abrahamowicz M, Jutras-Aswad D, Daniel M, Roy E. Sustained drug use changes after hepatitis C screening and counseling among recently infected persons who inject drugs: a longitudinal study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2014;58(6):755-761.
255. Caven M, Malaguti A, Robinson E, Fletcher E, Dillon JF. Impact of Hepatitis C treatment on behavioural change in relation to drug use in people who inject drugs: A systematic review. *The International journal on drug policy.* 2019;72:169-176.
256. Caven M, Robinson EM, Eriksen AJ, Fletcher EH, Dillon JF. Hepatitis C diagnosis and treatment, impact on engagement and behaviour of people who inject drugs, a service evaluation, the hooked C project. *Journal of viral hepatitis.* 2020.
257. Raison CL, Borisov AS, Broadwell SD, et al. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. *The Journal of clinical psychiatry.* 2005;66(1):41-48.
258. Chasser Y, Kim AY, Freudenreich O. Hepatitis C Treatment: Clinical Issues for Psychiatrists in the Post-Interferon Era. *Psychosomatics.* 2017;58(1):1-10.
259. Herold S, Freudenreich O. Hepatitis C Virus and Schizophrenia: Expanding the Role of the Community Psychiatrist. *Psychosomatics.* 2016;57(6):634-637.
260. Kondili LA, Romano F, Rolli FR, et al. Modeling cost-effectiveness and health gains of a "universal" versus "prioritized" hepatitis C virus treatment policy in a real-life cohort. *Hepatology (Baltimore, Md).* 2017;66(6):1814-1825.
261. Sievert W, Razavi H, Estes C, et al. Enhanced antiviral treatment efficacy and uptake in preventing the rising burden of hepatitis C-related liver disease and costs in Australia. *Journal of gastroenterology and hepatology.* 2014;29 Suppl 1:1-9.
262. Martin NK, Vickerman P, Grebely J, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology (Baltimore, Md).* 2013;58(5):1598-1609.
263. Rattay T, Dumont IP, Heinzow HS, Hutton DW. Cost-Effectiveness of Access Expansion to Treatment of Hepatitis C Virus Infection Through Primary Care Providers. *Gastroenterology.* 2017;153(6):1531-1543.e1532.

264. Ruggeri M, Romano F, Basile M, et al. Cost-Effectiveness Analysis of Early Treatment of Chronic HCV with Sofosbuvir/Velpatasvir in Italy. *Applied health economics and health policy.* 2018;16(5):711-722.
265. Ward Z, Reynolds R, Campbell L, et al. Cost-effectiveness of the HepCATT intervention in specialist drug clinics to improve case-finding and engagement with HCV treatment for people who inject drugs in England. *Addiction (Abingdon, England).* 2020.
266. Wigg AJ, Chinnaratha MA, Wundke R, Volk ML. A chronic disease management model for chronic liver failure. *Hepatology (Baltimore, Md).* 2015;61(2):725-728.
267. Kanwal F, Asch SM, Kramer JR, Cao Y, Asrani S, El-Serag HB. Early outpatient follow-up and 30-day outcomes in patients hospitalized with cirrhosis. *Hepatology (Baltimore, Md).* 2016;64(2):569-581.
268. Mathur AK, Chakrabarti AK, Mellinger JL, et al. Hospital resource intensity and cirrhosis mortality in United States. *World journal of gastroenterology.* 2017;23(10):1857-1865.
269. Bini EJ, Weinshel EH, Generoso R, et al. Impact of gastroenterology consultation on the outcomes of patients admitted to the hospital with decompensated cirrhosis. *Hepatology (Baltimore, Md).* 2001;34(6):1089-1095.
270. Bini EJ. Hepatology training during gastroenterology fellowship: are we getting to the core of the curriculum? *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2008;6(6):608-609.
271. Cotter TG, Charlton MR. The Triumph of Bacchus: The Emergence of Nonalcoholic Steatohepatitis and Alcoholic Liver Disease as the Leading Causes of Mortality From Cirrhosis. *Hepatology (Baltimore, Md).* 2019;69(3):931-933.
272. Arguedas MR, DeLawrence TG, McGuire BM. Influence of hepatic encephalopathy on health-related quality of life in patients with cirrhosis. *Digestive diseases and sciences.* 2003;48(8):1622-1626.
273. Battersby MW, Beattie J, Pols RG, Smith DP, Condon J, Blunden S. A randomised controlled trial of the Flinders Program of chronic condition management in Vietnam veterans with co-morbid alcohol misuse, and psychiatric and medical conditions. *The Australian and New Zealand journal of psychiatry.* 2013;47(5):451-462.
274. Muthén B, Asparouhov T. Bayesian structural equation modeling: a more flexible representation of substantive theory. *Psychol Methods.* 2012;17(3):313.
275. Geldhof GJ, Preacher KJ, Zyphur MJ. Reliability estimation in a multilevel confirmatory factor analysis framework. *Psychol Methods.* 2014;19(1):72.
276. Terwee CB, Bot SDM, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol.* 2007;60(1):34-42.
277. Cohen J. A power primer. *Psychol Bull.* 1992;112(1):155.
278. *Deloitte Access Economics; The economic cost and health burden of liver diseases in Australia. 2013.*
279. McGillion MH, Watt-Watson J, Stevens B, Lefort SM, Coyte P, Graham A. Randomized controlled trial of a psychoeducation program for the self-management of chronic cardiac pain. *Journal of pain and symptom management.* 2008;36(2):126-140.
280. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qual Health Res.* 2016;26(13):1753-1760.
281. Wheeldon J. AM. Mind Maps in Qualitative Research. In: P L, ed. *Handbook of Research Methods in Health Social Sciences.* Singapore: Springer,; 2019.

282. McDevitt J, Melby V. An evaluation of the quality of Emergency Nurse Practitioner services for patients presenting with minor injuries to one rural urgent care centre in the UK: a descriptive study. *Journal of clinical nursing.* 2015;24(3-4):523-535.
283. Vaughn-Sandler V, Sherman C, Aronsohn A, Volk ML. Consequences of perceived stigma among patients with cirrhosis. *Digestive diseases and sciences.* 2014;59(3):681-686.
284. Coddington J, Sands L, Edwards N, Kirkpatrick J, Chen S. Quality of health care provided at a pediatric nurse-managed clinic. *Journal of the American Academy of Nurse Practitioners.* 2011;23(12):674-680.
285. Edwall LL, Danielson E, Ohrn I. The meaning of a consultation with the diabetes nurse specialist. *Scand J Caring Sci.* 2010;24(2):341-348.
286. Nymberg P, Drevenhorn E. Patients' experience of a nurse-led lifestyle clinic at a Swedish health centre. *Scand J Caring Sci.* 2016;30(2):349-355.
287. Bridges DR, Davidson RA, Odegard PS, Maki IV, Tomkowiak J. Interprofessional collaboration: three best practice models of interprofessional education. *Medical education online.* 2011;16.
288. Reeves S, Pelone F, Harrison R, Goldman J, Zwarenstein M. Interprofessional collaboration to improve professional practice and healthcare outcomes. *The Cochrane database of systematic reviews.* 2017;6:Cd000072.
289. Karabulut N. Prevalence of HBV, HCV and HIV in Inpatients of a Mental Health Hospital in Turkey, 2011-2013. *Iranian journal of public health.* 2015;44(7):1026-1028.
290. Karabulut N, Bulut Y, Telo S. Frequency of Hepatitis B and C Viruses, and HIV Among Drug Addicts in the Eastern Anatolia, Turkey. *Jundishapur journal of microbiology.* 2015;8(8):e19698.
291. Lazarus JV, Wiktor S, Colombo M, Thursz M. Micro-elimination - A path to global elimination of hepatitis C. *Journal of hepatology.* 2017;67(4):665-666.
292. Hepatitis C 'effectively eradicated' in haemophilia patients who were given contaminated blood.https://www.thejournal.ie/hepatitis-c-3154653-Dec2016/?utm_source=twitter_self. Published Dec 22, 2016. Accessed 4 th March, 2020.
293. Gurpegui M, Martínez-Ortega JM, Gutiérrez-Rojas L, Rivero J, Rojas C, Jurado D. Overweight and obesity in patients with bipolar disorder or schizophrenia compared with a non-psychiatric sample. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012;37(1):169-175.
294. Tek C, Kucukgoncu S, Guloksuz S, Woods SW, Srihari VH, Annamalai A. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. *Early Interv Psychiatry.* 2016;10(3):193-202.
295. Chung RT, Baumert TF. Curing chronic hepatitis C--the arc of a medical triumph. *The New England journal of medicine.* 2014;370(17):1576-1578.
296. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2013;16(2):e1-5.
297. Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Department of Health 2008.
298. StataCorp. *Stata 15 Base Reference Manual. College Station, Stata Press.* 2016.

299. Hawthorne G, Korn S, Richardson J. Population norms for the AQoL derived from the 2007 Australian National Survey of Mental Health and Wellbeing. *Australian and New Zealand journal of public health.* 2013;37(1):7-16.
300. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2012;15(6):796-803.
301. Harris AH, Hill SR, Chin G, Li JJ, Walkom E. The role of value for money in public insurance coverage decisions for drugs in Australia: a retrospective analysis 1994-2004. *Medical decision making : an international journal of the Society for Medical Decision Making.* 2008;28(5):713-722.
302. Tan JA, Joseph TA, Saab S. Treating hepatitis C in the prison population is cost-saving. *Hepatology (Baltimore, Md).* 2008;48(5):1387-1395.
303. Ahmed A, Gonzalez SA, Cholankeril G, et al. Treatment of patients waitlisted for liver transplant with all-oral direct-acting antivirals is a cost-effective treatment strategy in the United States. *Hepatology (Baltimore, Md).* 2017;66(1):46-56.
304. Connolly MP, Kotsopoulos N, Ustianowski A. Modeling the fiscal costs and benefits of alternative treatment strategies in the United Kingdom for chronic hepatitis C. *Journal of medical economics.* 2018;21(1):19-26.
305. Falade-Nwulia O, Sulkowski MS, Merkow A, Latkin C, Mehta SH. Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era. *Journal of viral hepatitis.* 2018;25(3):220-227.
306. Dore GJ, Altice F, Litwin AH, et al. Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. *Annals of internal medicine.* 2016;165(9):625-634.