Clinical Prediction Rules in Hospitalised Patients

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by

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SUMMARY

A significant number of clinical prediction rules (CPRs) have been developed for a wide range of medical conditions; however their routine clinical is limited due to lack of validation studies. Two CPRs were assessed for their predictive performance at Flinders Medical Centre (FMC): Wells and revised Geneva scores, used for assessing patients with suspected pulmonary embolism (PE), were assessed in an all-inclusive patient population; the Multidimensional Prognostic Index (MPI), based on a Comprehensive Geriatric Assessment (CGA), was assessed for predictive performance in a different geographical patient population.

Wells and revised Geneva scores were calculated in 1,724 patients referred to Flinders Emergency Department (ED) and FMC with suspected PE between January 2013 and May 2014. PE was confirmed using CTPA, V/Q scan, or compression ultrasound. Calibration and discrimination of the risk scores were evaluated. Subgroup analysis was conducted on patients assessed <24 vs. ≥24-hr from hospital presentation as well as patient hospital location (ED, medical, and surgical wards). The MPI score was calculated within the first three days in 737 patients admitted to FMC General Medicine or Acute Care of the Elderly (ACE) wards between September 2015 and February 2017. Discrimination of the MPI was evaluated for primary outcome, 6-month all-cause mortality, and secondary outcomes. Confirmatory and exploratory factor analysis (CFA and EFA) was conducted on the primary outcome for testing the dimensionality of the MPI. Additional analyses were conducted on three optimised versions of the MPI using the ARS score or RUDAS score or in combination.

PE results: Observed and predicted PE prevalence within each risk category (low, intermediate, and high) was similar for all three categories in the Wells and revised Geneva scores. The area under the ROC curve was 0.61 for the Wells score and 0.62 for the revised Geneva score. These results are substantially lower than in the derivation studies for the Wells and revised Geneva scores. Area under the ROC curve for patients assessed after 24 hours (Wells, AUC 0.56; revised Geneva, AUC 0.59) was substantially lower than patient assessed within 24 hours (Wells, AUC 0.62; revised Geneva, AUC 0.64).

MPI results: The MPI as either continuous or categorical variable was associated with 6-month mortality (MPI continuous: OR 2.34; MPI categorical, Mild: reference group; moderate: OR 2.97; severe: OR 5.06). The area under the ROC curve for 6-month mortality was 0.63. These results are substantially lower than in the derivation study. Optimised versions of the MPI did not differ to the original MPI. CFA showed poor model fit in a one-dimensional MPI model. EFA identified a two-factor model: one factor related to physical function and the other comorbidities. The goodness of fit tests indicated good model fit for the two-factor solution.

This study highlights several concerns regarding the routine use of original CPRs in different geographical patient populations or in an all-inclusive patient population which the derivation studies did not assess. It also highlights the importance of validating CPRs in large prospective multicentre studies with populations representative of those for which the tools will be used.

ABBREVIATIONS

ABS	Anticholinergic burden scale
AC	Anticholinergic
ACE	Acute care of the elder
ADL	Activities of daily
ADR	Adverse drug reaction
ADS	Anticholinergic drug scale
AIC	Alkaike's information criteria
ANTELOPE	Advances in New Technologies re the localisation of Pulmonary Embolism
AMT	Abbreviated mental test
AMU	Acute medical unit
ANT	Anterior
ARS	Anticholinergic risk scale
AUC	Area under the curve
BBS	Berg balance scale
BMI	Body mass index
BOD	Burden of disease
BPM	Beats per minute
C	Concordance statistic
CAD	Coronary artery disease
CAP	Community acquired pneumonia
CC	Calf circumference
CES-D	Centre for Epidemiology studies Depression scale
CFA	Confirmatory factor analysis
CGA	Comprehensive Geriatric Assessment
CHF	Congestive heart failure
CI	Confidence interval
CIRS	Cumulative medicine rating scale
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration formula
COG IMP	Cognitive impairment
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CPR	Clinical prediction rule
CRP	C-reactive protein
CT	Computed tomography
CTPA	Computed tomography pulmonary angiography
DALY	Disability adjusted life year

DBI	Drug burden index
DCA	Decision curve analysis
DOB	Date of birth
DVT	Deep vein thrombosis
EANM	European Association of Nuclear Medicine
ED	Emergency department
EBM	Evidence-based medicine
EFA	Exploratory factor analysis
ELISA	Enzyme linked immunosorbent assay
ESS	Exton Smith scale
eGFR	Estimated glomerular filtration rate
FABS	Fullerton advanced balance scale
FAI	Frenchay activities index
FDA	Food and dry administration
FDP	Fibrin degradation products
FI-CGA	Faulty index based on CGA
FMC	Flinders Medical Centre
FR	Functional reach
FU	Follow up
GAI	Geriatric anxiety inventory
GAS	Geriatric anxiety scale
GDS	Geriatric depression scale
GEMU	Geriatric evaluation and Management Unit
GI	Gastrointestinal
GPCOG	General Practitioner assessment of cognition
HF	Heart failure
HR	Heart rate
HRs	Hazard ratio
HRSD	Hamilton rating scale for depression
HRT	Hormone replacement therapy
IADL	Instrumental activities of daily living
IDI	Integrated discrimination index
IGF-1	Insulin-like growth factor - 1
In	Inpatient
In-Out	In and out patients
IRR	Incidence-rate ratio
Int.	Intermediate
I-RR	Inter -rate reliability
IRTD	Institutional Registry of Thromboembolism Disease
IUD	Intrauterine device
LA	Left atrium

LAO	Left anterior oblique
LASSO	Least absolute shrinkage and selection operator
LAT	Lateral
LCI	Lower confidence internal
LOS	Length of stay
LPO	Left posterior oblique
LT	Left
LV	Left ventricle
MAC	Mid arm circumference
MFS	Multidimensional frailty score
MIOPED	Manchester Investigation of Pulmonary Embolism
MMSE	Mini - mental state examination
MNA	Mini nutritional assessment
MNA-SF	Mini nutritional assessment – short form
MNST	Malnutrition universal screening tool
MOCA	Montreal cognitive assessment
Mod.	Moderate
MPI	Multidimensional prognostic index
MST	Malnutrition screening tool
NA	Not available
NB	Net benefit
NRI	Net reclassification index
NRS	Nutritional risk screening
NSAID's	Non-steroidal anti-inflammatory drugs
NuDESC	Nursing delirium screening scale
OACIS	Open Architecture Clinical Information Systems
OR	Odds ratio
Out.	Outpatient
PaO2	Partial pressure of oxygen
PaCO2	Partial pressure of carbon dioxide
PE	Pulmonary embolism
PE-UN	PE unlikely
PERC	Pulmonary embolism rule-out criteria
PHQ2	Patient health questionnaire 2
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
POMA	Performance – orientated mobility assessment
POST	Posterior
PRN	Pro re nata ("as needed")
Prob.	Probability
Q	Perfusion
RA	Right atrium

RAO	Right anterior oblique
REFS	Reported Edmonton frail scale
ROC	Receiver operating characteristic
RPO	Right posterior oblique
RT	Right
RUDAS	Rowland University dementia assessment scale
RV	Right ventricular
SA	South Australia
SAA	Serum Anticholinergic activity
SCr	Serum Creatinine
SD	Standard deviation
SGA	Subjective global assessment
SHR	Sub-hazard ratio
SPECT	Single-photon emission computed tomography
SPMSQ	Short portable mental state questionnaire
SSRI	Selective serotonin reuptake inhibitor
SysBP	Systolic Blood pressure
TAVI	Transcatheter aortic valve implantation
Tc	Radioactive Technetium
THREAD	Thromboembolism Assessment and Diagnosis
TP	True positive
UCI	Upper confidence internal
USA	United States of America
US	Ultrasound
V	Ventilation
V/Q	Ventilation/perfusion scintigraphy
VTE	Venous thromboembolism
χ^2	Chi squared test
Yrs.	Years

DECLARATION BY THE PHD CANDIDATE

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Kimberley Ruxton

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1 GENERAL INTRODUCTION

1.1 Prognosis and Prediction in Medicine

Prognosis (from the Greek pro: before, and gignōskein: know) is an opinion, based on medical experience, of the likely course of a medical condition. It is important to be able to predict future outcomes before its possible occurrence where patients are at higher risk of having or developing a disease (Abu Hanna and Lucas 2001, Steyerberg 2008). Prognosis is heavily reliant on diagnostic and therapeutic actions (Hilden and Habbema 1987, Vogenberg 2009).

1.1.1 Prediction Models and Decision-Making

Taking care of patients involves many predictions. Historically, such predictions are at the discretion of clinicians, and are based on their clinical experience and professional opinion. In the current era, medicine has moved from a more subjective approach to evidence-based medicine (EBM) that applies scientific method to medical practice (Steyerberg 2008). Evidence-based medicine is defined here as:

> *"the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients (Sackett et al. 1996).*

A convenient way to apply EBM into clinical practice is via clinical prediction rules (CPRs), with the ultimate goal of improving health outcomes through increasing accuracy in clinical decision making with regard to diagnosis and prognosis (Ebell 2001). CPRs are also referred to as clinical decision rules, clinical prediction models, clinical prediction tools, clinical scoring systems, and clinical prognostic models (Steyerberg et al. 2013). CPRs are tools that aim to improve patient health outcomes by quantifying contributing symptoms, clinical signs, and available diagnostic tests

to then stratify a patient's individual risk using smaller risk groups (i.e. low, intermediate, or high) for the diagnostic or prognostic outcome of interest. Hundreds of CPRs have been developed for a wide range of conditions, such as for infectious, cardiovascular, neurological, depressive, and anxiety disease states with a limited number of these CPRs being validated. Validation of such CPR's is a crucial step before it can be introduced into clinical practice to maintain predictive accuracy in different geographical populations. One of the most well-known and validated CPR's is the Ottawa ankle rule used to help clinicians determine if someone with an ankle injury is likely to have sustained a fracture and will therefore need an X-ray (Bachmann et al. 2003).

1.2 Clinical Prediction Rules

There is a widely accepted methodology when introducing a new prediction model, which includes model development, model evaluation, and model impact (McGinn et al. 2000, Laupacis et al. 1997, Steyerberg and Vergouwe 2014, Wallace et al. 2011, Lee et al. 2016, Royston et al. 2009, Steyerberg 2008, Altman et al. 2009, Steyerberg et al. 2010).

1.2.1 Model development

To develop an accurate and useful CPR it is important to identify the research questions which will affect the database selection and generation of the model (Steyerberg 2008, McGinn et al. 2000, Steyerberg and Vergouwe 2014, Lee et al. 2016). Table 1.1 identifies important research questions and examples.

Table 1.1 Research questions for model development

Questions	Examples
What is the target outcome to be predicted?	All-cause mortality Cardiovascular disease Type 2 diabetes mellitus
Who is the target population of the model?	General population Older adults ≥65 years Stroke patients
Who is the target user of the model?	Clinician Patient Other healthcare professions

Abbreviations: ≥ greater than or equal to.

Selecting what dataset will be used is an important step to consider with the aim to find the best-suited dataset (Lee et al. 2016, Royston et al. 2009). There are three levels of health care. Primary care refers to patient care provided in a general practice, community or allied health centre (Altman et al. 2009, Moons et al. 2009, Riley et al. 2016). Secondary care refers to services provided by medical specialists and other health professionals who are not in first contact with patients or includes acute care (i.e. Emergency Department) where the patient requires urgent short-term treatment of a serious injury or period of illness. Referral from the previous levels is known as tertiary care (inpatients). Secondary or administrative data sources are commonly used for CPR development as primary datasets with the outcome of interest and all key variables/predictors are not normally available (Steyerberg 2008, Steyerberg and Vergouwe 2014, Lee et al. 2016, Royston et al. 2009). Ideal datasets for modelling should be large in size, contemporary, and closely reflecting the target population.

Many datasets contain numerous variables, of which not all variables are relevant for the prediction model. Therefore, identifying the appropriate predictors in the model should be investigated. Known predictors from previous research should be considered (Lee et al. 2016, Royston et al. 2009). Another important step is the coding of categorical and continuous predictors (Steyerberg 2008, Steyerberg and

Vergouwe 2014). For continuous predictors, it is preferable to maintain the continuous form as dichotomising the predictor (i.e. single cut-off points) in the development stage can result in loss of valuable information (Steyerberg 2008, Steyerberg and Vergouwe 2014, Lee et al. 2016, Royston et al. 2009). This is not the case for categorical predictors where collapsing of categories may be required as the numbers in some categories may be too small (Royston et al. 2009).

A way of selecting predictors for the model can be done by regression analyses (Steyerberg 2008, Steyerberg and Vergouwe 2014, Lee et al. 2016, Royston et al. 2009). Using a full model approach allows all candidate predictors to be included in the model. Overfitting in prediction models is defined as fitting a statistical model with too many degrees of freedom or, in simplistic terms, adding too many predictors makes the model ineffective (Steyerberg 2008). A full model using all predictors is not always easy to define so other methods can be used. A stepwise regression method using backwards elimination is a common method used where all candidate predictors are included at the start with elimination of the least significant candidate predictors from a full model (Steyerberg 2008, Steyerberg and Vergouwe 2014, Lee et al. 2016, Royston et al. 2009). A stepwise regression method does have its limitations. The model can become too adapted to the data through overfitting (Steyerberg 2008, Steyerberg and Vergouwe 2014, Royston et al. 2009). This produces selection bias and optimism where the former can overestimate the true value of the regression coefficient and the latter causes the performance of the model to be overestimated (Steyerberg 2008, Steyerberg and Vergouwe 2014, Royston et al. 2009).

Some modern methods such as statistical shrinkage (Van Houwelingen and Le

Cessie 1990), penalised maximum likelihood estimation (Moons et al. 2004), and the least absolute shrinkage and selection operator (LASSO) (Tibshirani 1996, Steyerberg et al. 2000) can be used to limit overfitting of a model (Steyerberg 2008, Steyerberg and Vergouwe 2014). Table 1.2 provides a summary of each method. This provides a more reliable regression coefficient that can improve predictions in new population data.

Table 1.2 Characteristics of modern estimation methods

Name	Label	Characteristics
Shrinkage	Shrinkage after estimation	Application of a shrinkage factor to the regression coefficient. The shrinkage factor is determined with a heuristic formula, or by bootstrapping
Penalised maximum likelihood estimation	Shrinkage during estimation	Regression coefficients are estimated with penalized maximum likelihood. The optimal penalty factor can be determined by AIC.
Least absolute shrinkage and selection operator (LASSO)	Shrinkage for selection	Regression coefficients are estimated with penalized maximum likelihood with a restriction on the sum of the coefficients. The optimal penalty factor can be determined by a cross-validation procedure, or AIC

AIC: Akaike's Information Criterion. Adapted from: (Steyerberg 2008).

1.2.2 Model evaluation

The developed model should undergo some form of evaluation (Steyerberg 2008, McGinn et al. 2000, Steyerberg and Vergouwe 2014, Lee et al. 2016, Altman et al. 2009, Steyerberg et al. 2010). This is done by either comparing actual and predicted outcomes for groups of people, known as calibration, and the ability of the model to distinguish between people who have an outcome or not, known as discrimination (Steyerberg 2008, Steyerberg and Vergouwe 2014, Altman et al. 2009, Steyerberg et al. 2010). For continuous outcomes, this is the distance between observed (Y) and predicted ($\hat{Y}$) outcomes (Steyerberg 2008, Steyerberg et al. 2010). As for binary outcomes $\hat{Y}$ is equal to the predicted probability (p) or, in survival outcomes, it is the time predicted to an event (Steyerberg 2008, Steyerberg et al. 2010). Overall, smaller

distances between observed and predicted outcomes produce better-fit models (Steyerberg 2008, Steyerberg et al. 2010). Common methods for evaluating performance of a model can be found in Table 1.3. It has been recommended that assessment of prediction models should undergo three key aspects: calibration, discrimination, and clinical usefulness (Steyerberg and Vergouwe 2014).

Table 1.3 Characteristics of some model performance measures

Aspect	Measure	Visualisation	Characteristics
Calibration	Calibration-in-the-large	Calibration or validation graph	Compares mean observed with mean predicted. Intercept in plot
	Calibration slope		Related to shrinkage of regression co-efficient. Regression slope in plot
	Hosmer-Lemeshow test		Compares observed to predicted by decile of predicted probability
Clinical usefulness	Net benefit (NB)	Cross-table	Net number of true positives using model v's no model at a single threshold (NB) or over a range of thresholds (DCA)
	Decision curve analysis (DCA)	Decision curve	
Discrimination	*c* statistic	ROC curve	Rank order statistic for prediction against true outcomes
	Discrimination slope	Box plot	Difference in mean of predictions between outcomes
Overall performance	R^2	Validation graph	Expresses the amount of variability in outcomes explained by model.
	Brier		
Reclassification	Reclassification table	Cross-table or scatter plot	Compare classification from 2 models for changes.*
	Reclassification statistic		Compare observed outcomes to predicted risks within cross-classified categories.
	Net reclassification index (NRI)		Compare classification from 2 models for changes by outcome for a net calculation of changes in the right direction.
	Integrated discrimination index (IDI)	Box plots*	Integrates NRI over all possible cut-offs. Equivalent to difference in discrimination slopes.

Note: *denotes one model with and one without a marker. *c*:concordance; ROC: Rank order statistic; R^2: explained variation. Adapted from: (Steyerberg et al. 2010).

1.2.2.1 Calibration

Calibration refers to the accuracy of predicted outcomes versus observed outcomes in populations classed in different risk strata (Vogenberg 2009, Steyerberg 2008, Steyerberg and Vergouwe 2014, Steyerberg et al. 2010). It can be graphically assessed where predictions are on the *x*-axis (between 0 – 100%) and actual observed

outcomes on the *y*-axis (1=dead, 0=alive) (Steyerberg 2008, Steyerberg and Vergouwe 2014, Steyerberg et al. 2010). Predictions that lay on the 45° line are considered ideal whereas predictions above or below the ideal line show overestimation or underestimation, respectively.

Results can also be plotted using similar probabilities by comparing the means of both predicted and observed outcomes (Steyerberg 2008, Steyerberg and Vergouwe 2014, Steyerberg et al. 2010). Goodness-of-fit tests such as the Hosmer-Lemeshow goodness-of-fit test can be graphically plotted by using observed outcomes by decile of predictions (Figure 1.1). The larger the spread between these deciles indicates a better functioning model (Steyerberg 2008, Steyerberg et al. 2010). This test is commonly used for binary outcomes. However, this test has its limitations where larger sample sizes can lead to overestimating the statistical significance and direction of miss-calibration of a model cannot be identified (Vogenberg 2009).

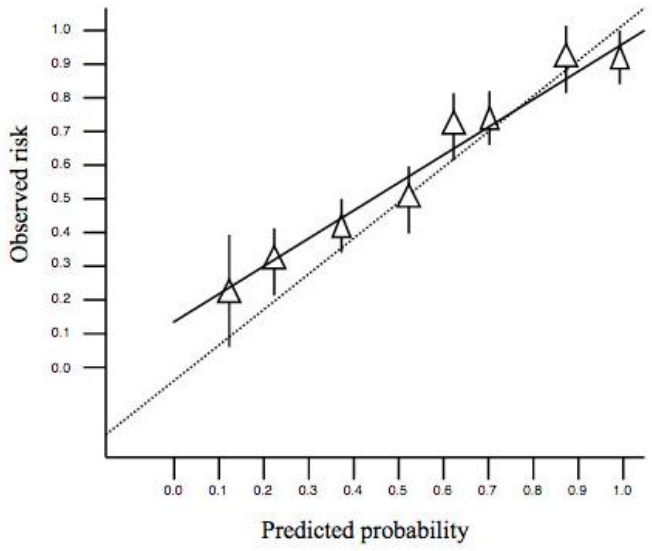


Figure 1.1 Calibration plot example. Triangles indicate the observed risk per decile of predicted risk. The vertical lines represent the corresponding 95% CI. Solid line shows the relationship between observed and predicted risk and the dotted line represents ideal calibration.

1.2.2.2 Discrimination

Calibration alone is insufficient to assess a model's prediction capability (Steyerberg 2008, Steyerberg and Vergouwe 2014, Steyerberg et al. 2010, Vogenberg 2009). It is also important for a model to be able to differentiate between people who have an outcome or not. Discrimination can be measured in a number of ways such as the concordance (*c*) statistic (a combination of sensitivity and specificity) or by plotting the sensitivity (true positive rate) against 1 – specificity (false positive rate) for consecutive cut-offs of an outcomes probability (Vogenberg 2009, Steyerberg 2008). This is known as a receiver operating characteristic (ROC) curve (refer to Figure 1.2).

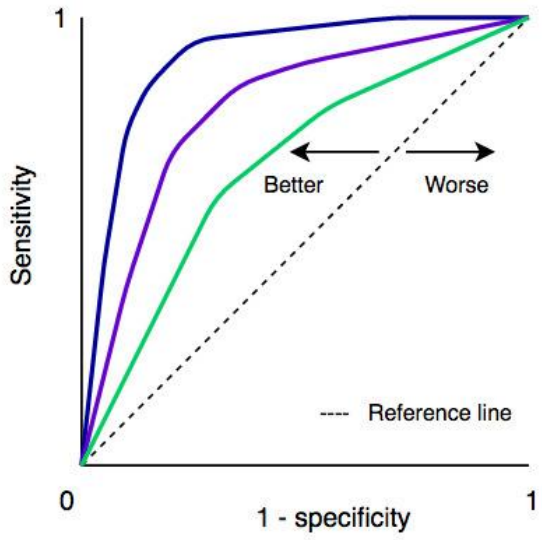


Figure 1.2 ROC curve. A plot of the true positive rate against the false positive rate. The closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the model i.e. blue line. The closer the curve comes to the reference line of the ROC space, the less accurate the model is i.e. green line.

The area under the curve (AUC) is interpreted as the probability that the model will rank a randomly chosen patient with the outcome higher than a patient randomly chosen without the outcome (Steyerberg 2008). The AUC is provided by the *c* statistic for binary outcomes. The latter is the most common method used for discriminating model performance (Steyerberg et al. 2010). As a general approach,

the area under the ROC or *c* statistic as less than 0.60 indicates poor discrimination; 0.60 to 0.75 moderate discrimination; and greater than 0.75 indicating suitable discrimination (Vogenberg 2009, Steyerberg 2008).

1.2.2.3 Clinical usefulness

To determine the clinical usefulness of a model appropriate predictive probability cut-off points need to be identified (Steyerberg 2008, Steyerberg and Vergouwe 2014). Therefore, predictions above the cut-off will be defined as positive and below will be negative (Steyerberg 2008). This defines clinical usefulness. The optimal cut-off is based more on a decision context as it is generally more important not to miss a patient with an outcome (false negative – higher sensitivity)) than to miss a patient without the outcome (false positive – higher specificity) (Steyerberg 2008). Clinical usefulness is described further in relation to model impact in section 1.2.3 Model impact.

1.2.2.4 Types of validation

There are two main types of validation strategies: internal and external validation (Steyerberg 2008, Steyerberg and Vergouwe 2014, Altman et al. 2009, Steyerberg et al. 2010). Internal validation is defined as assessing the model in the same setting as to where the development data originated from (Steyerberg 2008). External validation of a model is an important step where the model is to be tested in new data that's different from within the development model population (Steyerberg 2008). This is essential to support the general applicability of a prediction model.

For internal validation, there are four common methods used for validation of a model, shown in Figure 1.3 (Steyerberg 2008, Steyerberg and Vergouwe 2014, Altman et al. 2009, Steyerberg et al. 2010). Apparent validation refers to assessing the model performance in the direct sample that the model was derived from (refer to

Figure 1.3 part A). By using all the data this can provide somewhat stable estimates of model performance. At the same time, however, this leads to biased assessment with optimistic estimates of overall performance (Steyerberg 2008).

Split-sample validation refers to a randomisation of the data into two groups; the sample for model development and another group for assessing model performance (refer to Figure 1.3 part B). Data is typically split 50:50 or 2/3:1/3 (Steyerberg 2008). There are a number of limitations to this method in particular variance and bias. As only part of the data is used this can potentially make the validation less stable as well as the validation sample unreliable due to being relatively small (Steyerberg 2008). As this method was developed well before other statistical techniques, such as bootstrapping, this method is now less frequently used (Steyerberg and Harrell 2016).

Cross-validation is an improvement of split-sample validation (refer to Figure 1.3 part C). It assesses model performance in a smaller random sample, with model development in the other parts (Steyerberg 2008). This is suited to larger sample sizes. Again, as only a part of the data is used this makes the validation less stable.

The final model for internal validation is the Bootstrap validation (refer to Figure 1.3 part D). The model is developed in the bootstrap sample, and validated in the original sample. A bootstrap sample uses the original population data but resamples the data until the sample size of the bootstrap equals the original data sample size (Steyerberg 2008). This process is repeated multiple times (around 100-200) to stabilise the estimates. A limitation of bootstrapping is that only automated modelling strategies can be used (Steyerberg 2008).

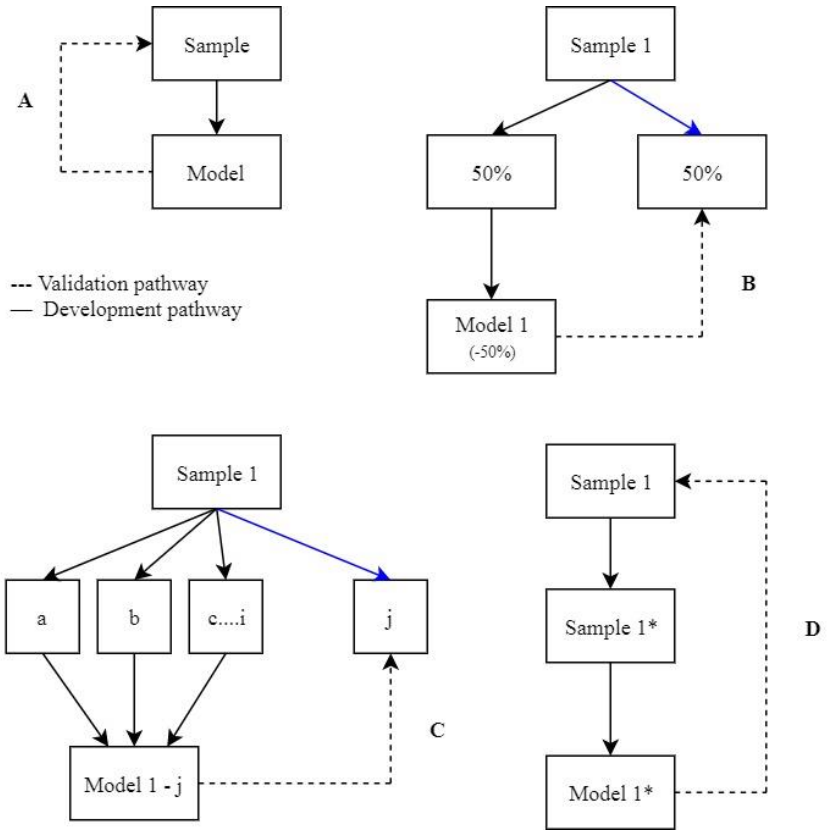


Figure 1.3 Internal validation methods. A) Apparent validation. B) Split sample validation. C) Cross-validation. D) Bootstrap validation. Adapted from (Steyerberg 2008).

External validation studies can address time-related (temporal validation), location (geographical/spatial validation), and general application (full-independent validation) aspects (Steyerberg 2008, McGinn et al. 2000, Steyerberg and Vergouwe 2014, Altman et al. 2009). Temporal validation is a common method used in the validation of a model. This approach uses data collected in an earlier population for the development of the model and then follows with a new set of population data where the model is assessed for performance (Steyerberg 2008, Altman et al. 2009). This allows the validation data to be collected in a prospective manner.

Geographical or spatial validation refers to assessing the model in a population separate to the developed sample, e.g. other hospital (Steyerberg 2008). It is similar to cross-validation where one site out of multiple sites is left out and used for validation. This differs from cross-validation by terms of not splitting the data at

random. A limitation of geographical validation is the samples may get too small causing results to become unreliable (Steyerberg 2008).

Lastly, fully independent validation externally validates a model by independent investigators and location making it a stronger test of model performance (Steyerberg 2008). An important point is that externally validating a model from outside the development setting can lead to external investigators using different definitions of predictors, outcomes, and selection of study population (Steyerberg 2008). In general, this external validation method tends to produce less favourable results than the other external validation methods.

1.2.3 Model impact

An important question that needs to be addressed is applying a model in the clinical process to improve decision-making (Vogenberg 2009, Steyerberg 2008, Steyerberg and Vergouwe 2014, Wallace et al. 2011, Lee et al. 2016, Traeger et al. 2017). A way to measure this is by decision curve analysis (Steyerberg 2008, Traeger et al. 2017). This approach estimates the net benefit (NB) of basing clinical decisions on a patient's prognostic score and compares to other alternative models or strategies (Traeger et al. 2017, Vickers and Elkin 2006). The decision curve considers a range of thresholds for benefit and harm and can be shown in the NB formula:

$$NB = \frac{TP - wFP}{N}$$

where TP is the true positive classifications, FP the number of false positive classifications, N is the total number of patients, and *w* is a weight equal to the odds of the threshold (p_t / (1 - p_t)), or the ratio of harm to benefit (Steyerberg 2008). If the NB is zero this means that no patients were treated while a higher NB identifies a

good model (Steyerberg 2008). An addition to this NB formula is subtracting test harm (per patient in units of TP results) (Steyerberg 2008). This takes into account any prediction model that collects data from medical tests that were invasive, dangerous or involved expenditure of time, or costly (Steyerberg 2008). Decision curves can also be used to assess the value of prognostic models.

Another important step of applicability for a model in the clinical setting is how the model is presented (Steyerberg 2008, Steyerberg and Vergouwe 2014). Common types of model formats are nomograms or score charts. The format should be relevant to the intended audience. In recent years, paper-based models have been updated into web-based calculators or as applications for mobile devices.

1.3 Challenges of using CPRs

The main objective of a clinical prediction rule is to identify any potential outcomes and to enhance clinical decision making (Vogenberg 2009, Traeger et al. 2017, Vickers and Elkin 2006, Wyatt and Altman 1995). Even though many prediction tools are published yearly, there is still limited use of such tools in clinical settings (Wyatt and Altman 1995). This may be due to a lack of clinical credibility, evidence of accuracy, clinical effectiveness, or generalizability (Vogenberg 2009, Traeger et al. 2017, Vickers and Elkin 2006, Wyatt and Altman 1995).

1.3.1 Credibility

The apprehensiveness of clinicians and the use of CPRs can be due to being unconvinced on the quality of the model and its predictions (Altman et al. 2009, Vogenberg 2009, Wyatt and Altman 1995). This could be due to the fact that, for example, not all the patient information was used in the development of the model. Other important factors for a model to be accepted are how easy it is to follow with

the promptly obtainable clinical data. Another factor is that the model needs to be easy to calculate or have other resources available for use that can calculate complicated models such as online calculators or mobile applications (Vogenberg 2009, Wyatt and Altman 1995).

1.3.2 Accuracy

In some cases, a model can be well used but doesn't have the accuracy that would be expected in a clinical setting (Moons et al. 2009). This could be due to poor methods used in the development of a model, overfitting was not well controlled for, or there were missing valuable predictors in the model (Altman et al. 2009). Ideally, a model should aim for a low false negative rate (fewer rates of the model predicting a negative outcome when outcome is positive) and a low false positive rate (fewer rates of the model predicting a positive outcome when outcome is negative) (Vogenberg 2009, Wyatt and Altman 1995). This should be done on a large test set to estimate the accuracy of the model (Wyatt and Altman 1995).

1.3.3 Generalizability

Generalizability refers to the extent to which a model can be applied to a setting outside of the developmental origin (Wyatt and Altman 1995). This is a major factor that deters the use of such CPRs in clinical settings due to a difference in case mix or heterogeneity (Steyerberg 2008, Altman et al. 2009, Wyatt and Altman 1995, Moons et al. 2009, Riley et al. 2016). A different case mix may arise due to changes in setting or a population that is more selective than in the development situation (Steyerberg 2008, Altman et al. 2009, Wyatt and Altman 1995, Moons et al. 2009, Riley et al. 2016).

When a model is being developed, the study populations usually have exclusion

criteria, such as age cut-offs, pregnancy, or patients on certain medications (Altman et al. 2009, Wyatt and Altman 1995, Moons et al. 2009). As part of the external validation process it is important to see if the model can be applied to a general patient population (Steyerberg 2008, Altman et al. 2009, Moons et al. 2009, Riley et al. 2016). Many validation studies tend to follow similar exclusion criteria as to that of the development study population (Moons et al. 2009). In turn, CPRs may be seen as appropriate to use in a clinical setting if other external studies have produced similar results to the developed study. Instead it should not be assumed that CPRs can simply be generalised from one population to another. Limiting the number of exclusions of the study population would give a more realistic overall predictive performance of a CPR in naturalistic setting (Moons et al. 2009).

Another form of case mix is the setting to which the model was developed and then validated in a different setting (Steyerberg 2008, Altman et al. 2009, Moons et al. 2009, Riley et al. 2016). Such settings can occur in different levels of health care (i.e. primary, secondary, and tertiary care) as previously described in model development section. Many CPRs are developed in secondary care (Moons et al. 2009). As secondary care is a sub-population of primary care these patients usually have increased severity of disease and worse outcomes (Moons et al. 2009). Therefore, applying a model that has been developed in a secondary care setting to a primary care setting usually leads to reduced model performance (Moons et al. 2009).

1.3.4 Effectiveness

How effective a model is will deem if it is worth using in a clinical setting (Wyatt and Altman 1995). Evidence of this should be collected through well-documented clinical trials that exhibit the accuracy of the model (Vogenberg 2009, Wyatt and Altman 1995). Another angle to consider is how useful is the model if there has been

changes in practice over time (Moons et al. 2009). Therefore, the model may need to be updated or modified to keep up to date with current scientific knowledge (Moons et al. 2009, Kappen et al. 2012). Otherwise this may lead to the model becoming redundant (Moons et al. 2009, Kappen et al. 2012).

1.4 Structure of Thesis

This thesis consists of three parts. Part A covers CPRs used in the decision process of patients with suspected pulmonary embolism (PE) and their predictive accuracy in a patient population with a wide range of co-morbidities and concomitant treatments. Part B focuses on the validation of a recently developed tool that provides quantitative information based on the comprehensive geriatric assessment (CGA), multidimensional prognostic index (MPI), in the Australian setting in a prospective study. Part C discusses both CPRs for different outcomes and their use in a hospital setting.

1.4.1 Part A: Clinical Prediction Rules in Pulmonary Embolism

Pulmonary embolism is a blood clot that dislodges from the deep veins, usually from the leg or pelvis, and travels through the circulation obstructing blood flow in the pulmonary arteries within the lungs (Tapson 2008). PE can be potentially fatal and falls under the broader term venous thromboembolism (VTE) (McRae 2010). Chapter 2 covers a brief introduction to PE followed the rationale and relevance of the study with emerging concerns of reduced predictive accuracy of such tools used in different hospital locations. A review of the literature is presented in Chapter 3, which includes current CPRs used in the diagnostic process of patients of suspected PE. The methods involved in this retrospective study conducted at Flinders Medical Centre (FMC) are covered in Chapter 4. Results and sub-analyses are presented in

Chapter 5 with the following chapter discussing and interpreting these findings.

1.4.2 Part B: Clinical Prediction Rules in Geriatric Medicine

The progressive ageing of the population, primarily due to reduced fertility and increased longevity, imposes significant public health and financial challenges in Australia and worldwide (Begg 2014). A key challenge in managing older inpatients is their increased inter-individual variability in organ function, homeostatic reserve and response to treatment (Mangoni and Jackson 2004). Due to this variability, there is a need for developing and validating new CPRs with Chapter 8 reviewing the literature on CGA used within the medical community. Chapter 9 covers the methods of the implementation of a multidimensional prognostic index (MPI) in a prospective study at FMC (Pilotto et al. 2008). Results and sub-analyses are presented in Chapter 10 with the following chapter discussing and interpreting these findings.

1.4.3 Part C: Concluding Remarks on Clinical Prediction Rules

The likelihood of deriving, validating, and then implementing CPRs to a high quality is limited. These limitations may be due to the fact that the methods to derive such CPRs are of lower quality and to the lack of validation studies that provide important information regarding the generalisability of CPRs before implementing into clinical practice. This section of the thesis summarises how well different studied CPRs performed at FMC.

Part A

CLINICAL PREDICTION RULES IN

PULMONARY EMBOLISM

2 PART A - LITERATURE REVIEW

VTE is a common disease that includes both DVT and PE (Tapson 2008). DVT and PE show similar pathophysiological changes, risk factors, epidemiology, and therapeutic recommendations (Kucher et al. 2005). PE is the third most common cause of death from cardiovascular disease (Goldhaber and Bounameaux 2012). New diagnostic and prognostic tools such as D-dimer and computer tomography testing have improved the care of patients with suspected VTE. The development of clinical prediction rules (CPRs) has also helped identify patients with high, intermediate, and low probability of PE as well as patients requiring anticoagulation treatment whilst awaiting confirmatory test results. Clinical prediction rules have their limitations, primarily because they have been derived in young and middle-age patient cohorts in the Emergency Department, and therefore lack evidence to their use outside this setting. This review summarises the available evidence regarding the development, validation, and limitations of CPRs and how well they reduce the risk of recurrent VTE.

2.1 Definition and Prevalence of PE

DVT and PE constitute VTE (refer to Figure 2.1). DVT is defined as the formation of a blood clot (thrombus) in the deep veins, usually in the leg or pelvic veins, which reduces or blocks blood flow. A blood clot that dislodges from the deep veins, travels through the venous circulation, and blocks the flow of blood in the pulmonary arteries in the lungs is defined as a PE (Tapson 2008).

While PE is a common disease the true prevalence of PE is unknown. Estimates of the incidence of VTE vary between countries. White et al (White 2003) claimed that the first-time incidence of VTE in the United States of America (USA) was about

100 people per 100,000 each year. In Australia, the estimated incidence rate of VTE was slightly lower, 70 people per 100,000 each year (Economics 2008).

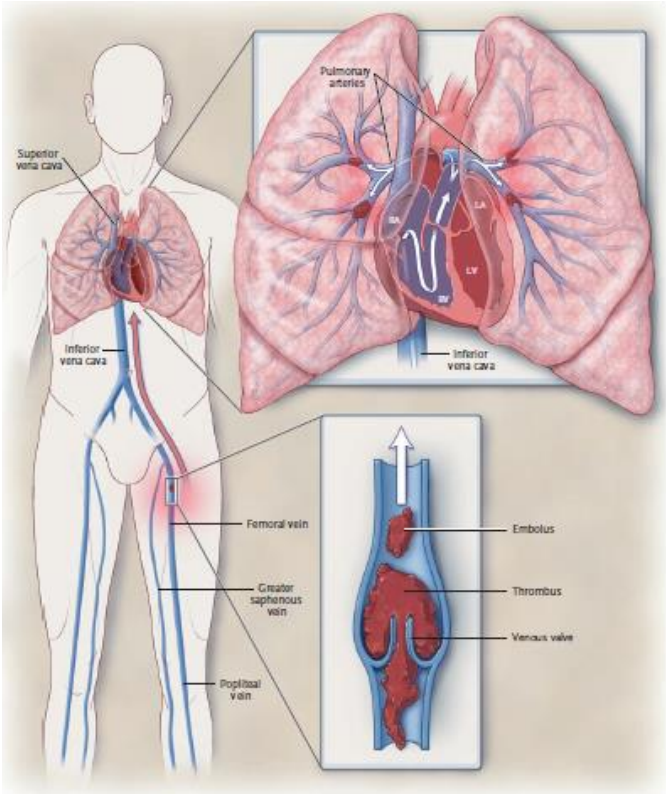


Figure 2.1 Pathophysiology of Pulmonary embolism. PE mostly arises from the deep veins of the leg. The thrombus originates from the venous valves traveling through the right side of the heart to the pulmonary circulation.
Abbreviations: LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle. Reproduced with permission from (Tapson 2008), Copyright Massachusetts Medical Society.

The first well-documented case of VTE, reported in 1271, describes the case of a young man, Raoul, who developed unilateral oedema in the right ankle that extended to his thigh (Galanaud et al. 2013, Mannucci 2002). In 1676, British surgeon Richard Wiseman first described VTE in childbirth where a woman who suffered a difficult labour developed swelling and pain of the right leg from the knee to the hip (Mannucci 2002). Wiseman hypothesised that thrombus formation was due to the changes in systemic circulation of the blood (Mannucci 2002). This pioneered the concept of hypercoagulability. A fundamental understanding of VTE was provided by Rudolf Virchow (1821-1902). Virchow first began research on VTE in which he

described a blood clot as a network of fibres where blood cells have become embedded (Kumar et al. 2010). The terms thrombosis and embolism were created by Virchow, supporting the concept that a clot in the pulmonary arteries or veins does not originate here but from the peripheral vascular system (Kumar et al. 2010). Virchow also described a principle, known as "Virchow's triad" to explain the pathogenesis of thrombosis which proposes that VTE occurs as a result of: stasis (alterations in blood flow), vascular endothelial injury, and inherited or acquired hypercoagulability (alterations in the constituents of the blood) (Fields and Goyal 2008, Turpie and Esmon 2011). Most known risk factors and features of VTE can be attributed to one or more of the mechanisms described by Virchow's triad.

2.1.1 Types of PE

Types of PE depend on the size of the clot and the location of where the clots are in the pulmonary circulation. A saddle PE is when the clot spans the main pulmonary trunk and its bifurcation (Satya et al. 2011). PE that occurs in the lobar pulmonary circulatory system are defined as lobar PE (Wittram et al. 2004). For segmental and subsegmental PE, they occur in the segmental and subsegmental pulmonary circulatory system (Le Gal et al. 2006a, Wittram et al. 2004).

2.2 PE risk factors

There are a number of known risk factors for VTE, depicted in Table 2.1. Often there is more than one factor at play in a given patient, with 75% to 96% of patients having at least one risk factor (Bauer and Lip 2014, Wilbur and Shian 2012). Some risk factors have been identified to hold a greater risk of VTE than others, with odds ratios for the different factors described in Table 2.2 (Anderson and Spencer 2003).

Table 2.1 Risk factors for VTE

Inherited thrombophilia	
Factor V Leiden mutation	Protein C deficiency
Prothrombin gene mutation	Antithrombin (AT) deficiency
Protein S deficiency	Rare disorders: Dysfibrinogenemia
Acquired disorders	
Malignancy	Hormone replacement therapy
Presence of central venous catheter	Tamoxifen, thalidomide, lenalidomide
Surgery (e.g. orthopaedics)	Immobilisation
Trauma	Nephrotic syndrome
Pregnancy	Antiphospholipid antibody syndrome
Oral contraceptives	Inflammatory bowel disease
Myeloproliferative disorders: Polycythemia vera and Essential thrombocythemia	Paroxysmal nocturnal haemoglobinuria
Medical comorbidities	
Congestive heart failure	
Stroke	
Chronic obstructive pulmonary disease	
Other	
Immobility	Smoking
Stroke	Obesity
Aged >45 years	

Abbreviations: >: greater than; VTE: Venous thromboembolism.

Table 2.2 Odds ratios for different risk factors for VTE

Strong risk factors (odds ratio > 10)
Fracture (hip or leg)
Hip or knee replacement
Major general surgery
Major trauma
Spinal cord injury
Intermediate risk factors (odds ratio 2 to 9)
Arthroscopic knee surgery
Central venous lines
Chemotherapy
Chronic heart or respiratory failure
Hormone therapy
Malignancy
Oral contraceptive therapy
Paralytic stroke
Pregnancy/postpartum
Previous VTE
Thrombophilia
Weak risk factors (odds ratio < 2)
Bed rest longer than three days
Immobility due to sitting (e.g., car or air travel longer than eight hours)
Increasing age
Laparoscopic surgery
Obesity (body mass index greater than 40 kg per m^2)
Pregnancy/antepartum
Varicose veins

Abbreviations: VTE: Venous thromboembolism. Adapted from: (Anderson and Spencer 2003).

2.3 PE clinical presentation

Clinical presentation of PE includes dyspnoea, chest pain, tachypnoea and cough, but can also occur asymptomatically (Wilbur and Shian 2012). Other, less common, clinical presentations include haemoptysis, syncope, and palpitations (Wilbur and Shian 2012) Other common signs of PE include tachycardia, abnormalities on lung examination (rales, wheezing, rhonchi), cardiac examination abnormalities (accentuated pulmonary component of the second heart sound, RV lift, jugular venous distension), and signs of DVT (Stein et al. 2007). Others less common signs include fever, cyanosis, hypotension, and diaphoresis (Stein et al. 2007, Wilbur and Shian 2012). PE symptoms are often nonspecific and other medical problems such as an infection, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and pneumonia can present with similar clinical features (Torbicki et al. 2008, Wilbur and Shian 2012).

2.4 Diagnostic testing

Since the 1960's a number of different diagnostic imaging tests have been developed which includes pulmonary angiography, V/Q scan and CTPA (Torbicki et al. 2008). Biochemical markers, in particular the D-dimer, have been used in the diagnostic work-up of patients with PE.

2.4.1 V/Q scan

The V/Q scan was introduced in the 1970's and played an essential role for a number of decades for the diagnosis of PE (Torbicki et al. 2008). Two components are involved in a V/Q scan: ventilation (V) and perfusion (Q). The scan is non-invasive and involves an injection of radioactive technetium (Tc)-99m labelled macro-aggregated albumin particles to assess lung perfusion. The perfusion scan displays

blood flow in the lungs. If an embolus is present these particles block pulmonary capillaries. The ventilation scan displays airflow and the movement of air in the lungs and is performed by patients inhaling a radioactive isotope. Both components are analysed to identify any ventilation-perfusion mismatch which can be present in patients with PE (refer to Figure 2.2). Mismatch is when good air flow is shown on the ventilation scan, however, the perfusion scan indicates poor blood flow. This results in a difference in the appearance of the perfusion scan to the ventilation scan.

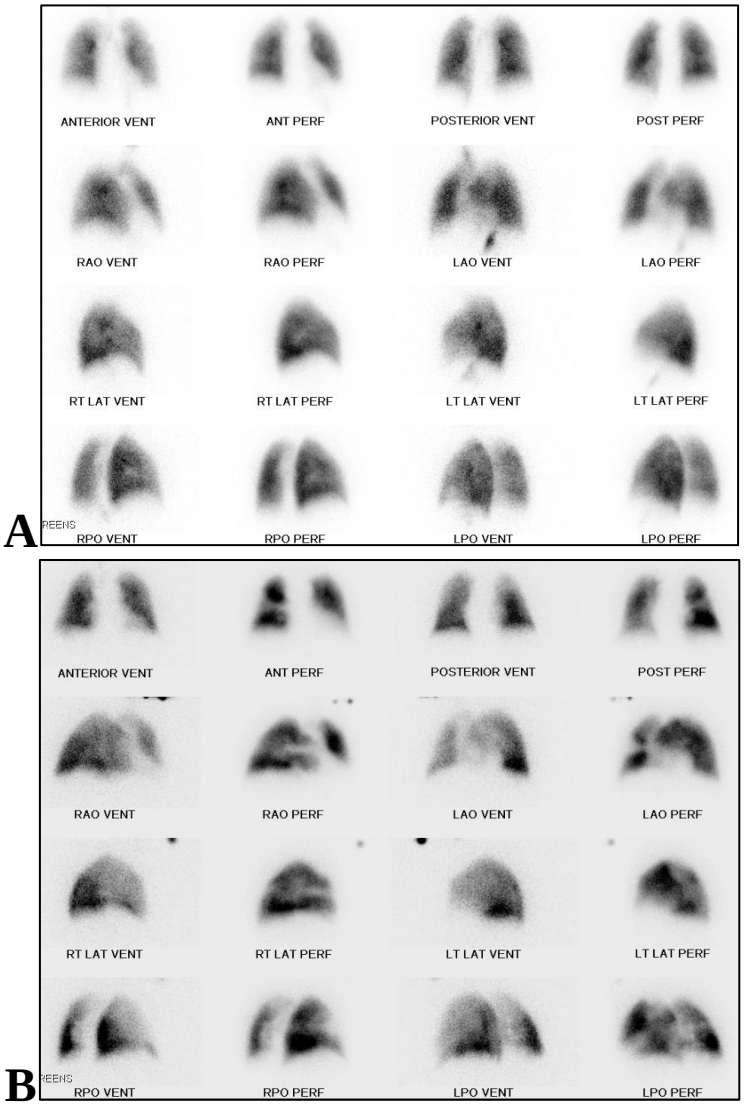


Figure 2.2 Ventilation/perfusion (V/Q) scintigraphy. A) Normal scan with no V/Q mismatch, B) multiple V/Q mismatches indicating high probability for pulmonary embolism.
Abbreviations: ANT: anterior; LAO: left anterior oblique; LAT: lateral; LPO: left posterior oblique; LT: left; PERF: perfusion; POST: posterior; RAO: right anterior oblique; RPO: right posterior oblique; RT: right; VENT: ventilation.

The prospective investigation of pulmonary embolism diagnosis (PIOPED) study was conducted to determine the sensitivity and specificity of the V/Q scan in PE diagnosis (PIOPED-Investigators. 1990). This study showed that the V/Q scan had 98% sensitivity (not miss patients with PE) but only 10% specificity (miss patients without PE). The PIOPED study classified scan results into normal, very low, low, intermediate, or high suggestion of PE shown in Table 2.3.

Table 2.3 PIOPED lung interpretation categories

PE probability	Perfusion defects
Normal	0 perfusion defects visible
Very Low	≥3 Small segmental perfusion defects
Low	Non-segmental perfusion defects enlarged aorta, hila, and mediastinum, and elevated diaphragm) 1 moderate mismatched segmental perfusion defect Any perfusion defect with large chest x-ray abnormality Large or moderate segmenta1 perfusion defects involving ≤ 4 segments in 1 lung and ≤ 3 segments in 1 lung region >3 Small segmental perfusion defects (<25% of a segment)
Intermediate	Not falling into normal, very low-, low-, or high-probability categories Borderline high or low Difficult to categorize as low or high
High	≥2 Large (>75% of a segment) segmental perfusion defects ≥2 Moderate segmental (≥25% and ≤75% of a segment) and 1 large segmental perfusion defects ≥4 Moderate segmental perfusion

Abbreviations: >: greater than; ≥: greater than or equal to; < less than; ≤: less than or equal to. Adapted from: (PIOPED-Investigators. 1990).

A major problem with the PIOPED criteria is the large percentage of scans falling in the category of intermediate (indeterminate) probability of PE. Therefore, a more recent criterion has been developed known as the European Association of Nuclear Medicine (EANM) Single-photon emission computed tomography (SPECT) criteria (refer to Table 2.4) (Bajc et al. 2009a, Bajc et al. 2009b). Studies have shown that SPECT has a greater sensitivity (100%) and specificity (87–98%), and a lower number of inconclusive results in the detection of PE compared to planar scans (Skarlovnik et al. 2014, Quirce et al. 2014, Gutte et al. 2010).

Table 2.4 EANM SPECT lung interpretation categories

PE probability	Perfusion defects
Negative	No perfusion defects visible Matched or reversed mismatch ventilation/perfusion defects of any size, shape or number in the absence of mismatch Mismatch that does not have a lobar, segmental or subsegmental pattern
Positive	Ventilation/perfusion mismatch of at least one segment or two subsegments that conforms to the pulmonary vascular anatomy defects
Non-diagnostic	Multiple ventilation/perfusion abnormalities not typical of specific diseases

Adapted from: (Bajc et al. 2009a).

2.4.2 Pulmonary angiography

Pulmonary angiography has been used since the 1960's and is the 'gold standard' test for diagnosis of PE, with a sensitivity of ~98% and a specificity between 95–98% (Aghajanzadeh et al. 2010). Unlike the V/Q scan, pulmonary angiography is an invasive test that involves the use of contrast media that is injected intravenously into the pulmonary arteries via a femoral vein catheter. Pulmonary angiography allows visualisation of the pulmonary circulation and provides not only haemodynamic data but also the option of treating PE with anticoagulation and vena cava filters (refer to Figure 2.3). There are limitations to pulmonary angiography such as being an expensive procedure, not available in small hospitals, requiring experienced investigators, and potentially resulting in fatal and non-fatal complications. The use of pulmonary angiography has lessened since the introduction of the CTPA, primarily due to the test limitations.

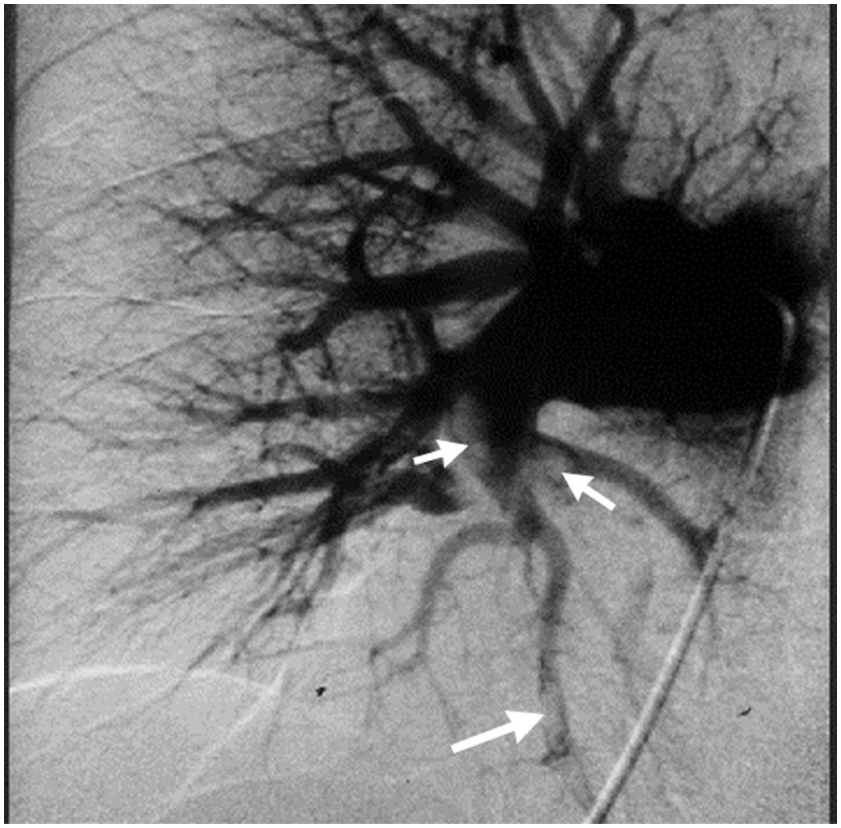


Figure 2.3 Conventional pulmonary angiogram of the right lung with intraluminal filling defects in the lobar artery and segmental and subsegmental arteries of the lower lobe. Reproduced with permission from (Kearon 2003), Copyright Canadian Medical Association.

2.4.3 CTPA

The use of CTPA is the most commonly used test for the diagnosis of PE mainly due to the disadvantages of pulmonary angiography and V/Q scan. CTPA has been shown to effectively exclude or confirm PE in suspected patients (Musset et al. 2002) (refer to Figure 2.4). First-generation single-detector CTPA had varying sensitivity (53–100%) and specificity (81–100%) (Aghajanzadeh et al. 2010). This led to the development of multi-detector CTPA with sensitivity and specificity for PE both above 90% (Aghajanzadeh et al. 2010). The multi-detector CTPA has improved scan speed, resolution, and sufficient imaging of pulmonary arteries up to segmental and subsegmental levels (Schoepf et al. 2004). CTPA is less expensive and uses less radioactive contrast media than in pulmonary angiography. Limitations of CTPA are the use of intravenous contrast which can induce allergic reactions or

nephropathy and the higher radiation exposure compared to the V/Q scan (Aghajanzadeh et al. 2010).

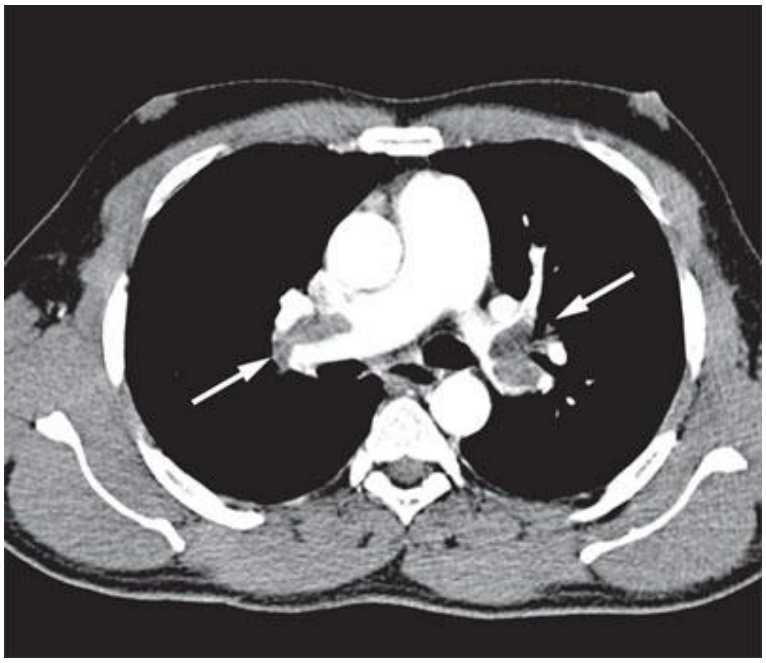


Figure 2.4 A transverse view computer tomography pulmonary angiogram positive for pulmonary embolism. PE filling defect in the right and left main pulmonary arteries (arrow). Adapted by permission from: Springer Nature, Nature Reviews Cardiology Copyright (Douma et al. 2010a).

2.4.4 D-dimer assay

D-dimer is the degradation product of cross-linked fibrin by plasmin seen in Figure 2.5 (Wakai et al. 2003).

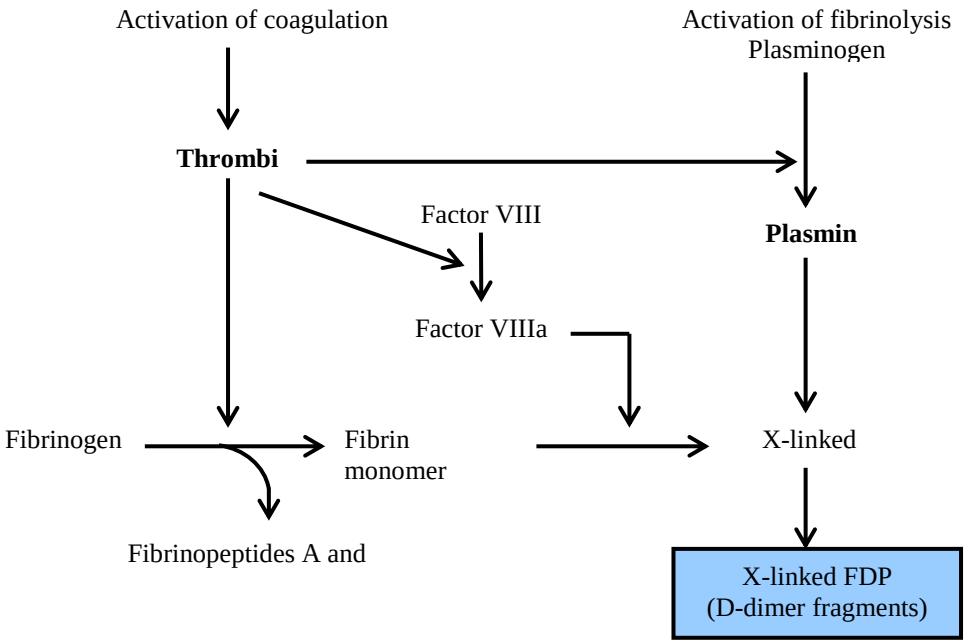


Figure 2.5 D-dimer as a reactive marker of the haemostatic balance. Activation of the fibrinolysis pathways results in the enzyme thrombin to initiate the cleavage of plasminogen to form plasmin. The activation of the coagulation system causes fibrinogen to be converted to fibrin via thrombin which cleaves terminal fibrinopeptides A and B from fibrinogen. At the same time factor XIII is activated to factor XIIIa by thrombin which allows fibrin to be further stabilised by covalent crosslinks. Plasmin allows the lysis of the cross-linked fibrin clot and therefore results in the formation of soluble cross-linked fibrin degradation products (FDP) of various sizes containing D-dimer fragments. Adapted from (Wakai et al. 2003).

The use of D-dimer tests form part of the pre-diagnostic work-up in suspected PE patients. There are a number of different D-dimer assays available that detect the presence of FDP that contain cross linked D fragments in blood or plasma (Youssf et al. 2014). The enzyme linked immunosorbent assay (ELISA) D-dimer test and second generation latex agglutination tests (immunoturbidimetric tests) have high sensitivity (95%) but lower specificity (50%) therefore more additional imaging may be required but can safely rule out PE in combination with CPRs (Righini et al. 2014). A D-dimer assay uses monoclonal antibodies binding to a specific D-dimer

fragment domain that is then measured. The D-dimer level is measured in µg/L or mg/L with a conventional cut-off of less than 500µg/L (0.5mg/L) as safely excluding VTE (Righini et al. 2014). The concentration of D-dimer increases with age; therefore, a study derived an age-adjusted D-dimer cut-off level defined as a patient's age multiplied by 10µg/L in patients aged ≥50 years (Douma et al. 2010b). A significant increase in the proportion of older patients in whom PE could be safely excluded was observed (25-30%) when combining CPR with age adjusted D-dimer cut-off values.

2.5 Pre-test probability scores

As the signs and symptoms of PE are non-specific a need for the development of CPRs for PE was required. Over the past 20 years there has been a number of pre-test probability CPRs developed. The use of D-dimer markers has been used in the diagnostic work-up of suspected PE patients since the 1990's (Bounameaux et al. 1991). Assessment of PE clinical probability, especially when it is combined with D-dimer tests, can reduce the need for additional investigational tests by 30% (Perrier et al. 2004).

The most commonly used pre-test probability scores are the Wells (Gibson et al. 2008, Wells et al. 2000, Wells et al. 1998) and Geneva scores (Klok et al. 2008b, Le Gal et al. 2006b, Wicki et al. 2001) with the Pisa scores not used as frequently (Miniati et al. 2008, Miniati et al. 2003a, Miniati et al. 2003b). The Wells, Geneva, and Pisa scores have a number of versions shown in Table 2.5, Table 2.6, and Table 2.7.

Table 2.5 Wells score

Original and Modified Wells	Points	Simplified Wells	Points
Clinical signs of DVT	3.0	Clinical signs of DVT	1.0
Recent surgery or immobilisation	1.5	Recent surgery or immobilisation	1.0
Heart rate > 100 bpm	1.5	Heart rate > 100 bpm	1.0
Previous history of PE or DVT	1.5	Previous history of PE or DVT	1.0
Haemoptysis	1.0	Haemoptysis	1.0
Malignancy	1.0	Malignancy	1.0
Alternative diagnosis less likely than PE	3.0	Alternative diagnosis less likely than PE	1.0
Original Wells (3-level)		**Simplified Wells (2-level)**	
Low	<2	PE unlikely	≤1
Intermediate	2-6	PE likely	>1
High	>6		
Modified Wells (2-level)			
PE unlikely	≤4		
PE likely	>4		

Abbreviations: DVT: deep vein thrombosis; >: greater than; <: less than; ≤ less than or equal to; PE: pulmonary embolism; bpm: beats per minute. Adapted from: (Gibson et al. 2008, Wells et al. 2000, Wells et al. 1998).

Table 2.6 Geneva score

Original Geneva	Points	Revised Geneva	Points	Simplified Geneva	Points
Recent surgery	3.0	Age > 65 years old	1.0	Age > 65 years old	1.0
Previous DVT or PE	2.0	Previous DVT or PE	3.0	Previous DVT or PE	1.0
Heart rate > 100 bpm	1.0	Surgery or fracture within 1 month	2.0	Surgery or fracture within 1 month	1.0
Age		Active malignancy	2.0	Active malignancy	1.0
60-79 years old	1.0	Heart rate (bpm)		Heart rate (bpm)	
≥80 years old	2.0	75-94	3.0	75-94	1.0
Chest radiograph		≥95	5.0	≥95	1.0
Atelectasis	1.0	Pain on leg venous palpation and unilateral oedema	4.0	Pain on leg venous palpation and unilateral oedema	1.0
Elevated hemidiaphragm		Unilateral leg pain	3.0	Unilateral leg pain	1.0
PaO_2		Haemoptysis	2.0	Haemoptysis	1.0
< 49 mm Hg (6.5 kPa)	4.0				
49-59 mm Hg (6.5 – 7.99 kPa)	3.0				
60-71 mm Hg (8-9.49 kPa)	2.0	**3-level**		**3-level**	
72-82 mm Hg (9.5-10.99 kPa)	1.0	Low	≤3	Low	≤1
$PaCO_2$		Intermediate	4-10	Intermediate	2-4
< 36 mm Hg (4.8 kPa)	2.0	High	≥11	High	≥5
36-38.9 mm Hg (4.8-5.2 kPa)	1.0				
3-level				**2-level**	
Low	≤4			PE unlikely	<3
Intermediate	5-8			PE likely	≥3
High	≥9				

Abbreviations: DVT: deep vein thrombosis; >: greater than; ≥ greater than or equal to; <: less than; ≤ less than or equal to; PE: pulmonary embolism; bpm: beats per minute; kPa: kilopascal; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide Adapted from: (Klok et al. 2008b, Le Gal et al. 2006b, Wicki et al. 2001).

Table 2.7 Pisa score

Pisa score	Regression coefficient	Revised Pisa score	Coefficient
Male sex	0.81	Male sex	0.60
Age		Age	
63-72 years old	0.59	57-67 years old	0.80
≥73 years old	0.92	68-74 years old	0.87
Pre-existing disease		≥75 years old	1.14
Cardiovascular	-0.56	Immobilisation	0.42
Pulmonary	-0.97	DVT (ever)	0.64
Thrombophlebitis (ever)	0.69	Pre-existing disease	
Symptoms		Cardiovascular	-0.51
Dyspnoea (sudden onset)	1.29	Pulmonary	-0.89
Chest pain	0.64	Symptoms	
Haemoptysis	0.89	Dyspnoea (sudden onset)	2.00
Temperature > 38°C	-1.17	Orthopnoea	-1.51
Electrocardiographic signs of acute right ventricular overload	1.53	Chest pain	1.01
Findings on chest radiology		Fainting or syncope	0.66
Oligemia	3.86	Haemoptysis	0.93
Amputation of hilar artery	3.92	Leg swelling (unilateral)	0.80
Consolidation (infarction)	3.55	Temperature > 38°C	-1.47
Consolidation (no infarction)	-1.23	Wheezes	-1.20
Pulmonary oedema	-2.83	Crackles	-0.61
Constant	-3.26	Acute cor pulmonae on electrocardiography*	1.96
		Constant	-3.43
Pisa (4-level)#	**Range, %**	**Pisa (4-level) †**	**Range, %**
Low	0-10	Low	0-10
Intermediate	11-50	Intermediate	11-50
Moderately high	51-80	Moderately high	51-80
High	81-100	High	81-100
# To estimate, add all of the regression coefficients that apply to a particular patient to the constant (-3.26). The probability of PE then equals $1 \div (1 + e^{-sum})$		† To calculate, add all of the coefficients that apply to a given patient to the constant. The probability of PE then equals $1 \div (1 + e^{-sum})$.	

Abbreviations: DVT: deep vein thrombosis; >: greater than; ≥ greater than or equal to; PE: pulmonary embolism. * One or more of S1Q3T3, S1S2S3, or negative T waves in right precordial leads, transient right bundle branch block, or pseudoinfarction. Adapted from: (Miniati et al. 2008, Miniati et al. 2003a, Miniati et al. 2003b).

Two other types of CPRs have been developed (Kline et al. 2002, Kline et al. 2006a). The Charlotte rule determines whether a patient can have PE ruled out with either a negative D-dimer plus alveolar dead space measurement or a quantitative D-dimer assay of less than 500 µg/mL (Kline et al. 2002). This decision rule separates patients into 2 groups: 'safe' patients eligible for D-dimer testing with pre-test probability of PE of 13.3% and 'unsafe' patients ineligible for D-dimer testing with pre-test PE probability of 42.1% (refer to Figure 2.6).

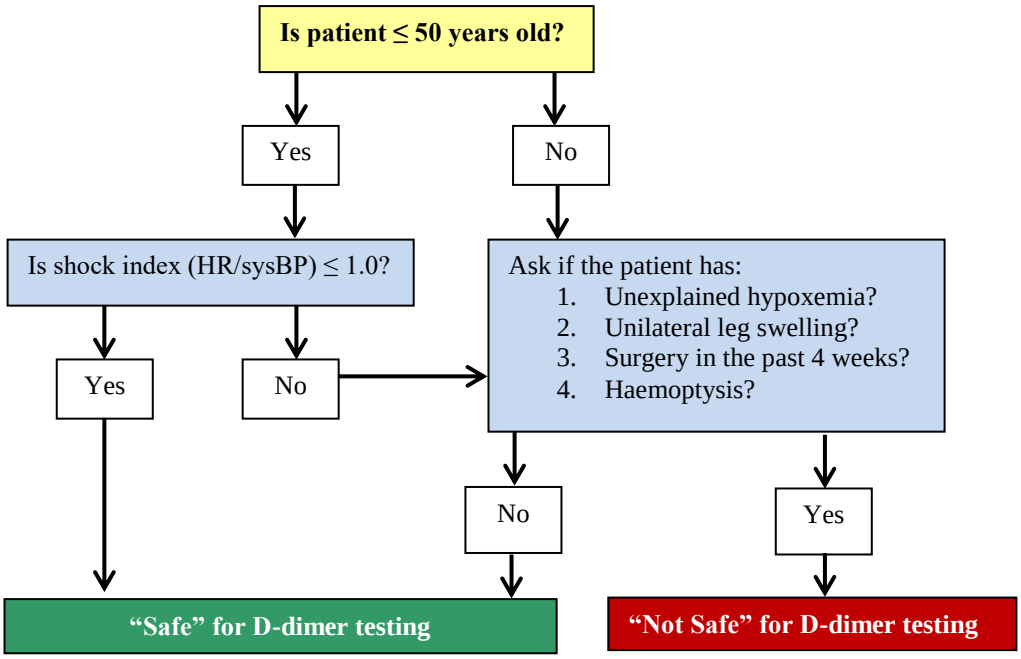


Figure 2.6 Charlotte rule: for "Safe" D-dimer Testing in ED patients with Suspected PE.
Abbreviations: HR: heart rate; PE: pulmonary embolism; sysBP: systolic blood pressure. Adapted from: (Kline et al. 2002).

The other clinical decision rule, known as the pulmonary embolism rule-out criteria (PERC) rule, identifies patients with a low pre-test probability for PE where a D-dimer test would not be necessary in their medical evaluations (Kline et al. 2008). For a negative result, the clinician must answer "no" to the 8 questions in the PERC rule shown in Table 2.8. Both the Charlotte and PERC rule will not be further discussed in the review due to the lack of use in the clinical setting.

Table 2.8 Pulmonary embolism rule-out criteria (PERC) rule

Pulmonary Embolism Rule-out Criteria Rule
For a negative result, the clinician must answer "no" to the following 8 questions:
Is the patient aged > 49 yrs?
Is the pulse > 99 beats/min?
Is the pulse oximetry reading < 95% while the patient breathes room air?
Is there a history of haemoptysis?
Is the patient receiving exogenous oestrogen?
Does the patient have a previous diagnosis of VTE?
Has the patient had recent surgery or trauma that required endotracheal intubation or hospitalization in the previous 4 weeks?
Does the patient have unilateral leg swelling (on the basis of visual observation of asymmetry of the calves)?

Abbreviations: > greater than; < less than; Min: minute; VTE: venous thromboembolism Yrs: years. Adapted from: (Kline et al. 2008).

2.5.1 Derivation of pre-test probability scores

The original Wells score was derived from a large prospective patient cohort from 5 Canadian centres that included inpatients and outpatients (Wells et al. 2000). Of the forty variables that were identified as being significant in the univariate regression analysis only 7 variables were considered significant in the stepwise logistic regression. For each variable, a regression co-efficient was obtained and points were assigned based on doubling of the co-efficient. Cut-off points were based on the original study (Wells et al. 1998) shown in Table 2.9. A dichotomised version (modified Wells) was also developed, with groups labelled as either PE unlikely or PE likely (Wells et al. 2000). A common problem that has been identified from numerous studies is the item "an alternative diagnosis is less likely than PE" in the Wells scores (Wells et al. 2000). This item is one of the highest weighted criteria at 3 points and is based on or influenced by the medical profession's opinions at the time of predicting a patient's probability of PE. This problem led to the simplification of the Wells score of PE unlikely and PE likely, with each item in the score being assigned a maximum of 1 point as seen in Table 2.5 (Gibson et al. 2008).

Compared to the Wells scores the derivations for the Geneva scores differ slightly. The original score was derived from a large prospective patient cohort from a Geneva hospital that included patients presenting to the ED (Wicki et al. 2001). A number of variables were collected using a standardised case report form. Candidate variables identified as being significant in the univariate regression analysis were considered for the multivariate logistic regression analysis. Eight variables were identified as being significantly associated with PE and points were assigned based on each variables regression co-efficient. Cut-off point for low risk group was based on other previous studies (PIOPED-Investigators. 1990, Perrier et al. 1999) with PE

prevalence shown in Table 2.9. An issue with the original Geneva score is that it requires arterial blood gas values while breathing room air and interpretation of chest x-ray imaging (Wicki et al. 2001). The former variable is not commonly available and in an external validation of this clinical prediction score arterial blood gas values were missing in 15% of patient's assessments (Chagnon et al. 2002). This led to the revision of the Geneva score by Le Gal et al. (2006b). The revised Geneva score (Le Gal et al. 2006b) was derived similar to the original Geneva score with a collection of variables from a standardised patient form (Wicki et al. 2001). Ten variables were significant in the univariate regression analysis and were subjected to a multivariate regression analysis of which 8 variables were significant. The regression co-efficient for each variable was collected and cut-off values assigned that is shown in Table 2.9. Simplification of the revised Geneva score was developed by Klok et al (2008b) with each variable from the revised version assigned only 1 point with new cut-off values for low, intermediate, and high probability groups. A dichotomised score was also used with cut-off values for PE unlikely and PE likely groups presented in Table 2.9.

Table 2.9 Cut-off scores and PE prevalence for pre-test probability rules

Rule	Authors	PE prev (%)	Categories 4-level			
			Low % (cut-off %)	**Intermediate % (cut-off %)**	**Mod. high % (cut-off %)**	**High % (cut-off %)**
Original Pisa	Miniati et al (2003)	40	4 (≤10)	22 (>10 - ≤50)	74 (>50 - ≤90)	98 (>90)
Simplified Pisa	Miniati et al (2008)	40	4 (≤10)	26 (>10 - ≤50)	65 (>50 - ≤90)	91 (>90)
			3-level			
			Low % (cut-off pts)	**Intermediate % (cut-off pts)**	**High % (cut-off pts)**	
Original Wells	Wells et al (2000)	17.6	3 (<2)	28 (2-6)	78 (>6)	
Original Geneva	Wicki et al (2001)	27	10 (<5)	38 (5-8)	81 (>8)	
Revised Geneva	Le Gal et al (2006)	23	9 (<4)	27.5 (4-10)	71.7 (>10)	
Simplified revised Geneva	Klok et al (2008)	23	7.7 (<2)	29.4 (2-4)	64.3 (>4)	
			2-level			
			PE unlikely % (cut-off pts)	**PE likely % (cut-off pts)**		
Modified Wells	Wells et al (2000)	17.6	7.8 (<4)	40.7 (≥4)		
Simplified Wells	Gibson et al (2008)	20	11 (≤1)	35.8 (>1)		
Simplified revised Geneva	Klok et al (2008)	23	11.5 (<3)	41.6 (≥3)		

Abbreviations: >: greater than; ≥ greater than or equal to; <: less than; ≤ less than or equal to; %: Mod.: moderately; percentage; pts: points; PE: pulmonary embolism; Prev: prevalence.

The original Pisa score was derived from a large prospective patient cohort from a single-centre Italian institute that included inpatients and outpatients (Miniati et al. 2003a). The derivation process of the Pisa score is similar to the Wells scores using a univariate regression analysis to identify variables as being significant and included these variables in the multivariate logistic regression analysis. Ten characteristics were identified as being significant and a regression co-efficient for each was obtained. Cut-off percentages were assigned to 4 categories depicted in Table 2.9. A problem with this model is that it rests heavily on the interpretation of chest radiograph which relies on substantial medical expertise. This led to a simplified Pisa

model developed by Miniati and associates (Miniati et al. 2008). The simplified Pisa score is based on signs and symptoms of PE as well as electrocardiogram interpretation (Miniati et al. 2008). The same study cohort from the original Pisa score was used as well as the score derivation process (Miniati et al. 2003a). The co-efficient for each variable was obtained and cut-off percentages were assigned to 4 categories depicted in Table 2.9.

A number of studies have investigated the use of PE clinical probability rules in suspected PE patients. Table 2.12 summarises the studies which can be found at the end of this chapter.

2.5.1.1 Wells scores validation

The original Wells study (Wells et al. 2000) used their CPR in a validation population of patients by retrospectively calculating the Wells score and categorised patients into low, intermediate, or high probability. Categorisation was also used in combination with D-dimer results. The prevalence of PE in low, intermediate, and high probability categories was 2%, 18.8%, and 50%, respectively. For the PE unlikely and PE likely categories, the prevalence was 5.1% and 39.1%, respectively. When the Wells score was used in combination with D-dimer test results only 2.7% and 1.7% of patients with a negative D-dimer and either a low or PE unlikely probability score had a PE, respectively (Wells et al. 2000). The simplified Wells score (Gibson et al. 2008) was internally validated in both in- and out-patients with similar prevalence of PE in both PE unlikely and PE likely groups compared to the modified Wells score in the validation set (Wells et al. 2000).

All of the Wells scores (Wells et al. 2000, Gibson et al. 2008) have been validated in a number of studies (refer to Table 2.12) with similar PE proportions to the original

study (Hogg et al. 2006, Hogg et al. 2011, Bosson et al. 2005, Douma et al. 2009, Kabrhel et al. 2005, Kearon et al. 2006, Kline et al. 2006a, Penaloza et al. 2011, Wells et al. 2001, Wolf et al. 2004, Douma et al. 2011). Four studies included both in- and out-patients (Hogg et al. 2011, Bosson et al. 2005, Kearon et al. 2006, Douma et al. 2011). Other studies were limited to patients presenting to the ED and outpatients (Hogg et al. 2006, Douma et al. 2009, Kabrhel et al. 2005, Kline et al. 2006a, Penaloza et al. 2011, Wells et al. 2001, Wolf et al. 2004). For low, intermediate, and high probability groups the prevalence of PE in each group ranged from 1.3–6.3%, 13.7–32.5%, and 33.3–100%, respectively. Studies with PE prevalence for PE unlikely and PE likely ranged from 5.6–13.2% and 22.8–56%, respectively. A study by Penaloza et al (2007) explored the performance of the Wells score for PE in a group of training physicians. This study showed that the use of the Wells score (original and modified versions) to determine the clinical probability of PE in training physicians was safe and did not require the supervision of senior staff (Penaloza et al. 2007).

Other studies (refer to Table 2.12) have explored the variations of the Wells scores but have not achieved similar results to the original study (Arnason et al. 2007, Calisir et al. 2009, Chagnon et al. 2002, Douma et al. 2011, Geersing et al. 2012, Goekoop et al. 2007, Kline et al. 2002, Miniati et al. 2005, Ollenberger and Worsley 2006, Runyon et al. 2005, Sanson et al. 2000, van Belle et al. 2006, Yap et al. 2007, Steeghs et al. 2005, Hogg et al. 2006). Some studies (Runyon et al. 2005, Kline et al. 2006a, Hogg et al. 2006) showed higher proportion of patients in the low probability category (73–86.6%) than that seen in the original study (Wells et al. 2000). Similarly, other studies (Calisir et al. 2009, Miniati et al. 2005, Ye et al. 2012) have shown much higher proportion of patients in the high probability group (15.3–

22.2%) compared to the original study (Wells et al. 2000). The prevalence of PE in the low probability group was shown to be much higher than the 2% cut-off from the original study (Wells et al. 2000) ranging between 12–28% (Gruettner et al. 2015, Guo et al. 2015, Guo et al. 2009, Penaloza et al. 2013). As for high probability category, PE prevalence in three studies (Kabrhel et al. 2005, Kline et al. 2006a, Runyon et al. 2005) ranged between 25–33% which is much lower than 78.4% in the original study (Wells et al. 2000). Some differences were observed in the prevalence of PE in the PE unlikely group with higher PE prevalence (10.4–13.2%) in the former group (Douma et al. 2009, Douma et al. 2011, Goekoop et al. 2007, Steeghs et al. 2005, van Belle et al. 2006) and lower PE prevalence (14–22.8%) in the latter group (Arnason et al. 2007, Kabrhel et al. 2005).

A large prospective cohort study (known as the Christopher study) conducted in 12 centres in the Netherlands examined patients with clinically suspected PE (van Belle et al. 2006). A simplified algorithm using the modified Wells score and D-dimer results was developed, as shown in Figure 2.7. Patients with D-dimer ≤500ng/mL were deemed as normal and no further testing was performed. Compared to the modified Wells study (Wells et al. 2000) the number of patients that were assigned to PE unlikely was higher at 66.7% and lower at 33.3% for PE likely (van Belle et al. 2006). Slight differences in PE prevalence were seen in the PE unlikely group at 12.1% and PE likely group at 37.1% compared to the original derivation study. This study concluded that the management of PE using a simple pre-test probability score, D-dimer testing, and CTPA is effective in the evaluation of patients with suspected PE (van Belle et al. 2006).

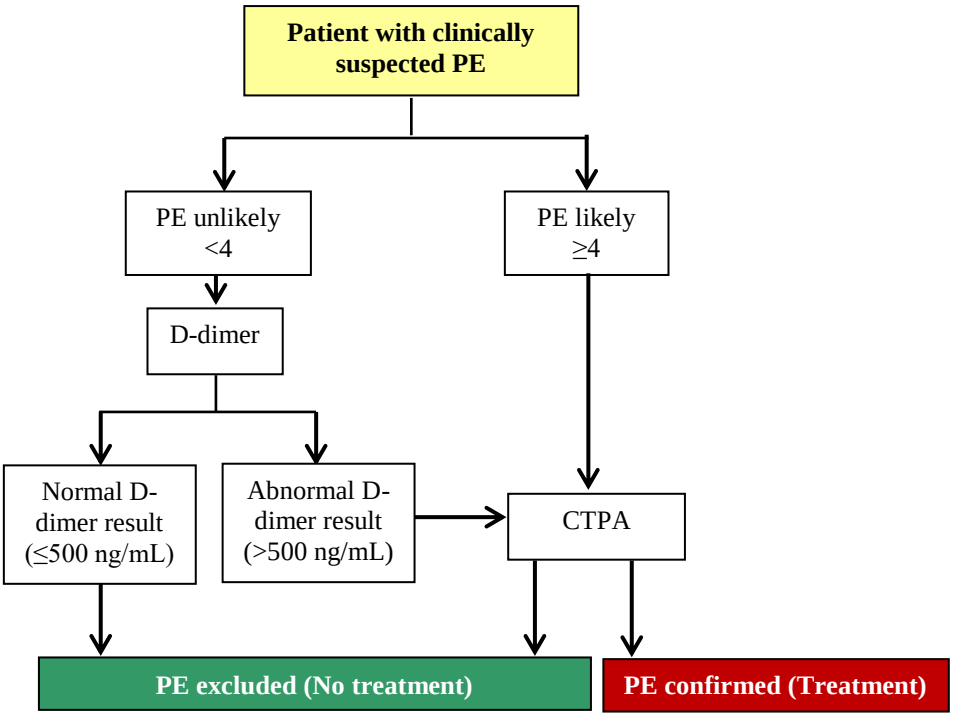


Figure 2.7 A diagnostic algorithm for suspected acute pulmonary embolism.
Abbreviations: CTPA: computed tomography pulmonary angiography; PE: pulmonary embolism. Modified Wells score used as pre-test probability rule. Adapted from: (van Belle et al. 2006).

2.5.1.2 Geneva scores validation

The authors who developed the revised Geneva score, internally and externally validated the rule in two separate prospective cohorts from 3 Geneva hospitals (Le Gal et al. 2006b). The score however was calculated retrospectively (refer to Table 2.12). The derivation set showed prevalence of PE in low, intermediate, and high probability scores of 9%, 28% and 72%, respectively. In the same study (Le Gal et al. 2006b) similar PE prevalence was seen in the validation set, 8%, 29% and 74% for low, intermediate and high, respectively. For the simplified revised Geneva scores the rule was applied to previously published studies for validation (Perrier et al. 2005, van Belle et al. 2006). The PE prevalence for the trichotomised and dichotomised probability categories were, respectively: 7.7%, 29.4%, 64.3% for low, intermediate, and high probability; and 11.5% and 41.6% for PE unlikely and PE likely. This retrospective analysis performed similarly to previous original (Wicki et al. 2001) and revised (Le Gal et al. 2006b) Geneva scores without losing accuracy.

The original Geneva score (Wicki et al. 2001) has been validated in a number of studies (Table 2.12) with similar PE prevalence to the original study (Aujesky et al. 2003, Chagnon et al. 2002, Perrier et al. 2004, Perrier et al. 2005). Validation of the original Geneva score was limited to patients presenting to the ED and outpatients (Aujesky et al. 2003, Chagnon et al. 2002, Perrier et al. 2004, Perrier et al. 2005). For low, intermediate, and high probability groups the prevalence of PE in each group ranged from 7–13%, 30–41.4%, and 59.1–95.1%, respectively. For the revised Geneva score, studies showed higher PE prevalence (13–24.6%) for the low probability category, lower PE prevalence (18–22.8%) in the intermediate probability category, and lower PE prevalence (50–54%) for the high probability category (Di Marca et al. 2015, Guo et al. 2015, Luo et al. 2014, Penaloza et al. 2013) than PE prevalence reported in the original study (Le Gal et al. 2006b). Results for the simplified revised Geneva score were comparable to the original study (Klok et al. 2008b) with prevalence of PE for low, intermediate, and high probability of 4%, 25%, and 56%, respectively (Penaloza et al. 2011). For PE unlikely, (10%) and PE likely (37%) the prevalence of PE was similar as well. One study has investigated the use of the simplified revised Geneva score in both in- and out-patients prospectively (Douma et al. 2011). The simplified revised Geneva score showed similar performance to original versions for exclusion of acute PE when combined with a normal D-dimer result. This study suggested that the simplified scores may be used in clinical practice (Douma et al. 2011).

Two studies have explored the use of the original Geneva score in both in- and out-patient cohorts (Miniati et al. 2005, Ollenberger and Worsley 2006). Both studies indicated that the use of the original Geneva score did not perform well in inpatients and recommended to avoid using this CPR in this patient group (Miniati et al. 2005,

Ollenberger and Worsley 2006).

2.5.1.3 Pisa scores validation

The original Pisa study (Miniati et al. 2003a) did not further validate the rule; however, the simplified Pisa rule was externally validated in a different study population (Miniati et al. 2008). Similar PE prevalence was observed in the validation set with low, intermediate, moderately high, and high probability groups showing 2%, 28%, 67%, and 94%, respectively. Study summaries are shown in Table 2.12.

The original Pisa score was used in a comparison with the original Wells and Geneva scores (Miniati et al. 2005). The Pisa score had to be altered to a trichotomised version with low, intermediate, and high probability showing 4%, 33%, and 56% PE prevalence. The Pisa model proved more accurate than all the variations of the Wells and Geneva clinical prediction scores. Only one study (El Wahsh and Agha 2012) has externally validated the simplified Pisa score in a small inpatient cohort. The PE prevalence for each probability categories were, respectively: 0% for low, 36.8% for intermediate, 80% for moderately high and 90% for high probability.

2.5.2 Comparison of clinical prediction performance

Some studies have compared the performance of the CPRs for PE (Chagnon et al. 2002, Kabrhel et al. 2005, Miniati et al. 2005, Ollenberger and Worsley 2006, Gibson et al. 2008, Calisir et al. 2009, Penaloza et al. 2013, Hogg et al. 2006, Hogg et al. 2011, Klok et al. 2008a, Luo et al. 2014, Guo et al. 2015, Di Marca et al. 2015, Shen et al. 2016, Douma et al. 2011, El Wahsh and Agha 2012, Lucassen et al. 2011, Penaloza et al. 2011). A study by El Wahsh et al (2012) evaluated the role of estimating clinical probability of PE with pre-test probability scores in regards to

their sensitivity and specificity. This was performed in a small cohort who presented to the chest department (El Wahsh and Agha 2012). The simplified Wells had the highest sensitivity (92%) compared to the original Wells (67%), original Geneva (25%), revised Geneva (54%), simplified revised Geneva (79%), and the Pisa score (71%) (El Wahsh and Agha 2012). Specificity was highest in the Pisa score (82%) and lowest in the original Wells score (12%). The accuracy of the simplified Pisa score showed the highest accuracy (76%) and the lowest accuracy was seen in the original Geneva, revised Geneva, and original Wells score with all receiving 44%. A meta-analysis by Lucassen et al (2011) pooled studies for original and modified Wells, and original and revised Geneva scores. Both original Wells and Geneva had high sensitivity at 84% (Lucassen et al. 2011). The modified Wells showed the highest specificity at 80%. When the specificity and sensitivity of the modified Wells, simplified Wells, revised Geneva, and simplified revised Geneva were analysed in a large inpatient and outpatient cohort the sensitivity ranged from 49-65% and specificity was similar across all 3 scores (70-80%) (Douma et al. 2011). When the same scores were combined with normal D-dimer results the sensitivity of all 3 studies was high at 99.5%, however the specificity was low, between 29-31%. Penaloza et al (2011), compared to the performances of the Wells score and the simplified revised Geneva score in terms of trichotomised and dichotomised probability categories. Both scores meaningfully categorised patients suspected of PE into clinical probability groups. The Wells score in both probability models performed better in patients with suspected PE than the simplified revised Geneva score (Penaloza et al. 2011). This was also seen in another study of high-risk older inpatients (Di Marca et al. 2015). A recent meta-analysis identified the Wells score to be more effective at discriminating PE in suspected patients compared to the

Revised Geneva score (Shen et al. 2016).

The diagnostic accuracy of the Wells and Revised Geneva score have been well documented in the literature(Chagnon et al. 2002, Miniati et al. 2005, Ollenberger and Worsley 2006, Gibson et al. 2008, Calisir et al. 2009, Penaloza et al. 2013, Turedi et al. 2008, Klok et al. 2008a, Klok et al. 2008b, Guo et al. 2009, Penaloza et al. 2011, Tsimogianni et al. 2011, Hogg et al. 2011, Correia et al. 2012, Ye et al. 2012, Luo et al. 2014, Posadas-Martinez et al. 2014, Guo et al. 2015, Di Marca et al. 2015, Gruettner et al. 2015). Table 2.10 summarises the overall weighted AUC for the different versions of the Wells and Geneva scores. The Wells score AUC has ranged from 0.68 to 0.87. Similar data are found for the Revised Geneva score ranging from 0.63 to 0.83. Only one study has reported a much lower overall weighted AUC for both scores (Correia et al. 2012). This study was however in patients admitted to hospital for decompensated heart failure and a very small sample size of 51 patients. Overall weighted AUC for the modified Wells and the Simplified-revised Geneva scores have been similar to the other scores (refer to Table 2.10).

Table 2.10 Receiver operating characteristic (ROC) scores for CPRs.

	Original Wells	Modified Wells	Revised Geneva	Simplified-revised Geneva
	3-level	2-level	3-level	3-level
Chagnon et al. 2002	0.78 (0.72-0.84)			
Miniati et al. 2005	0.75 (0.69-0.81)			
Ollenberger et al. 2006	0.68 (CI's NA)			
Turedi et al. 2008	0.77 (0.68-0.85)		0.66 (0.56-0.76)	
Gibson et al. 2008	0.74 (0.72-0.76)	0.74 (0.72-0.76)		
Klok et al. 2008a	0.79 (0.72-0.87)		0.73 (0.65-0.81)	
Klok et al. 2008b			0.70 (0.66-0.74)	0.68 (0.64-0.72)
Calisir et al. 2009	0.82 (CI's NA)		0.73 (CI's NA)	
Guo et al. 2009	0.82 (0.76-0.87)		0.66 (0.60-0.72)	
Penaloza et al. 2011	0.85 (0.81-0.89)			0.76 (0.71-0.80)
Tsimogianni et al. 2011	0.86 (0.79-0.92)		0.83 (0.77-0.90)	
Hogg et al. 2011	THREAD: 0.76 (0.71-0.81) MIOPED: 0.68 (0.64-0.73)			
Correia et al. 2012	0.53 (0.27-0.80)		0.43 (0.13-0.73)	
Ye et al. 2012	0.87 (0.81-0.93)			0.73 (0.64-0.83)
Penaloza et al. 2013	0.71 (0.68-0.75)		0.66 (0.63-0.70)	
Luo et al. 2014	0.72 (0.57-0.83)		0.70 (0.57-0.82)	
Posadas-Martinez et al. 2014		0.79 (0.75-0.82)		
Guo et al. 2015	Elderly: 0.68 (0.61-0.75) Non-elderly: 0.73 (0.65-0.80)		Elderly: 0.66 (0.58-0.77) Non-elderly: 0.63 (0.55-0.71)	
Di Marca et al. 2015	0.79 (0.67-0.91)		0.71 (0.58-0.84)	
Gruettner et al. 2015	0.68 (0.58-0.77)			

Abbreviations: CI: confidence interval; NA: Not available.

2.5.3 CPR limitations

There are some limitations of CPRs. Both the original and modified Wells score initially derived the rules by excluding patients summarised in Table 2.11 (Wells et al. 2000). Inpatients and outpatients were incorporated, however many studies have only used ED or outpatients as a cohort for validation (Douma et al. 2009, Geersing et al. 2012, Kabrhel et al. 2006, Kline et al. 2006a, Kline and Hogg 2006b, Penaloza et al. 2007, Penaloza et al. 2011, Runyon et al. 2005, Steeghs et al. 2005, Wells et al. 2001, Wolf et al. 2004, Gruettner et al. 2015). The original, revised, and simplified revised Geneva scores had some limitations relating to patient exclusion (refer to Table 2.11) (Wicki et al. 2001, Le Gal et al. 2006b). Only outpatients were used in the derivation of both scores which has been shown to not perform well in inpatient cohorts (Ollenberger and Worsley 2006). Exclusion criteria of the simplified revised Geneva score differed slightly as seen in Table 2.11 (Gibson et al. 2008). The internal validation set was performed on two previously published study cohorts (Perrier et al. 2005, van Belle et al. 2006). There have been limited studies to validate the use of the simplified revised Geneva score in both inpatient and outpatient cohorts (Douma et al. 2011). Derivation of the Pisa rules (Miniati et al. 2008, Miniati et al. 2003a) did not exclude particular patients as seen in the Wells and Geneva score variations. This was done to collect variables that included signs and symptoms associated with PE. However, both Pisa scores lack validation studies outside those of the study authors, with only the one study (El Wahsh and Agha 2012) externally validating the simplified Pisa score. This study however included a very small patient cohort and only selected patients who presented to the chest department.

A common exclusion criterion applied over numerous studies was pregnancy. The

use of the original and modified Wells scores, all Geneva scores, and both Pisa scores in pregnant patients is not validated in other studies. Only one study has validated the modified Wells score as safely excluding PE before resorting to CTPA in pregnant patients (O'Connor et al. 2011) but no other studies have confirmed such findings. Therefore, using such CPRs in pregnant women is not suitable with clinicians relying on their clinical judgment.

Differences in CPRs between the derivation study and validation studies could have been due to the large variations in total PE prevalence. The comparison between all Geneva score versions, original and simplified Wells score, and the simplified Pisa score in a small patient cohort indicated that the Pisa score performed better than the other scores (El Wahsh and Agha 2012). In this patient cohort, the prevalence of PE was 43.3% which is similar to the derivation study of 40% prevalence in the simplified Pisa score (Miniati et al. 2008). For the other scores the prevalence of PE in each derivation study varied from 17.6% in the original Wells to 27% in the original Geneva study. Potential reasons for these differences in the performance of the CPRs are different types of confirmatory tests used and improvements in the sensitivity to detect PE. For instance, in the derivation study for the Wells score, PE was confirmed using two confirmatory tests: V/Q scan and leg ultrasound (Wells et al. 2000). The derivation study for the revised Geneva score used CTPA in addition to V/Q scan (Wicki et al. 2001, Le Gal et al. 2006b). Since these derivation studies were conducted, CTPA sensitivity has improved from 4-16 slices to 256-320 slices. Therefore, this improvement has resulted in much smaller subsegemental PE’s to be detected.

Table 2.11 Exclusion criteria used in CPR studies.

CPR	Patients excluded from studies
Original & Modified Wells score	• upper extremity suspected DVT as likely source of PE • no symptoms of PE within 3 days of presentation • anticoagulation therapy for > 24hrs • expected survival time of <3 months • contradictions to contrast media • pregnancy • geographic inaccessibility to follow-up • aged <18 years
Original & Revised Geneva score	• suspected PE during hospital stay • symptoms of DVT • VTE within previous 3 months • ongoing anticoagulation therapy at study entry • expected survival time of <3 months • pregnancy • contraindications or impossibility to perform pulmonary angiography • not able to follow-up • lung scan read in comparison to a previous examination
Simplified Revised Geneva score	• patients with ongoing anticoagulation therapy >24 hours • expected survival time of <3 months • pregnancy • contraindications or impossibility to perform CT (allergy, too ill) • renal insufficiency • diagnosis made before admission • unavailability for follow-up • hospitalisation in another institution for >24 hours before admission • transfer to another facility • absence of peripheral venous access • haemodynamically instability

Abbreviations: CPR: Clinical prediction rule; CT: computed tomography; DVT: Deep vein thrombosis; >: greater than; <: less than; PE: Pulmonary embolism; VTE: Venous thromboembolism.

2.5.4 D-dimer limitations

The use of D-dimer tests has its limitations for excluding PE in low probability groups. D-dimer clinical usefulness differs between inpatient and outpatient populations. The use in inpatients results in a dramatic decrease in sensitivity compared to outpatients (Rathbun et al. 2004). The specificity is poor in inpatients as this group frequently have other medical conditions such as myocardial infarction, renal failure, pregnancy, cancer that can cause elevated levels of D-dimer (Stein et al. 2004b). Thus, an elevated D-dimer is not specific for PE and confirmatory imaging is frequently required.

2.6 Long-term outcome of PE

2.6.1 Recurrent VTE

A number of studies have explored the recurrence of VTE using CPRs, diagnostic algorithms, and D-dimer testing (Baglin et al. 2010, Murin et al. 2002, Perrier et al. 2005, Schulman et al. 2006, Stein et al. 2004a, van Belle et al. 2006). Murin and associates (2002) showed that the recurrence of a VTE within 6 months from the index date of a DVT or PE was 5.5% and 2%, respectively. Low and intermediate probability groups in one study showed a recurrence rate of 1.7% for VTE over a 3-month follow-up (Perrier et al. 2005). In the Christopher study, patients in whom CTPA demonstrated PE, 3% had a recurrent VTE in the 3-month follow-up despite anticoagulation treatment (van Belle et al. 2006). A number of studies have shown recurrent VTE at 3 months ranged from 0.6–5.0% for patients treated with anticoagulant such as enoxaparin, low molecular weight heparin, and dalteparin (Buller et al. 2007, Buller et al. 2003, Nijkeuter et al. 2007, Simonneau et al. 1997, van Strijen et al. 2003, Wells et al. 2001, Wells et al. 2005). Other studies have shown patients with an initial PE are three to four times more likely to get a recurrent episode as a PE than a DVT (Baglin et al. 2010, Schulman et al. 2006).

2.6.2 Mortality

PE is a potentially fatal disorder with highly varying mortality rates. In the US, mortality rate of PE is about 3.8 per 100,000 (Horlander et al. 2003) and slightly higher in England at 4.2 per 100,000 per year (Aylin et al. 2008). In Australia, mortality rates for PE are much lower with a rate of 1.73 per 100,000 per year (Shiraev et al. 2013). When algorithms are appropriately used PE can be adequately treated and mortality rate is significantly reduced to 2–8% when compared to untreated PE with estimated 30% mortality rate (Nijkeuter et al. 2007, Torbicki et al.

2000). In one study, patients who were diagnosed with PE had a 5.9% risk of mortality compared to 4.9% in patients without PE at 3 months (Perrier et al. 2001). Other studies have shown the risk of mortality ranged from 0.0–8.2% over a 3-month follow-up period (Buller et al. 2007, Buller et al. 2003, Nijkeuter et al. 2007, Perrier et al. 2004, Simonneau et al. 1997, van Strijen et al. 2003, Wells et al. 2001, Wells et al. 2005).

2.7 Conclusion

Due to the ambiguous signs and symptoms of PE the need for CPRs are essential for improving PE diagnosis in patients. Using such scores, algorithms and/or D-dimer tests has improved the management of PE. When algorithms are appropriately used PE can be adequately treated and mortality rates are significantly reduced. These tools, however, have their limitations as certain patient categories do not have studies validating the use of the rules for safely excluding or confirming PE. Such groups are pregnant women, older patients aged > 80 years old, and different inpatient ward locations. Additionally, diagnostic accuracy of the CPRs varies quite considerably across studies. Therefore, further studies should explore these issues to determine if they can be appropriately used in a more extensive clinical setting rather than certain patient groups.

2.8 The research problem

There are several important issues with the current clinical management guidelines, based on the available CPRs, in hospitalised patients with suspected VTE:

- The expected VTE risk has been primarily derived in young and middle-age patient cohorts. Virtually no information is available in older patients, particularly those aged >80 and frail with multiple co-morbidities.

- VTE risk has been largely estimated from patients presenting to the ED. The CPRs and algorithms for patients from locations other than the emergency setting (e.g. aged care, intensive care units, medical inpatients, post-operative setting) have not been prospectively validated in a robust manner.
- Since the introduction of a PE clinical prediction calculator and algorithm at FMC in 2012, the adherence of staff with following the local treatment guidelines on suspected PE have not been assessed.

2.9 Rationale

2.9.1 Significance of the study

Exploring the use of PE clinical prediction calculators and algorithms in a hospital setting gives insight into whether these tools are appropriate for use in different patient populations and hospital locations. In 2012, the Department of Respiratory Medicine at Flinders Medical Centre (FMC) started routine collection of electronic data on PE risk factors for individual medical patients being assessed for VTE risk using the Wells score and the revised Geneva score. At an average rate of 100 patients per month, the database currently holds information for approximately 1,700 patients. This is an invaluable data source as additional patients' clinical information can be linked with biochemical parameters, medication prescribing information and results of imaging tests, including the preferred CTPA test. This research will provide information about how reliable these CPRs are in identifying patients with PE and possibly finding other variables that could contribute to improved PE detection.

2.9.2 The objectives of the study

- To retrospectively assess the performance of the currently available PE CPRs at FMC.

- To retrospectively assess the performance of the currently available PE CPRs at FMC on patient hospital locations (e.g. medical, surgical).
- To assess additional variables such as clinical signs, symptoms, and prescribed medications (e.g. hormone replacement therapy) that can independently predict PE.
- To check the adherence of staff with following the local FMC treatment guidelines of patients with suspected PE.

Table 2.12 Summary of study characteristics and results for different CPR scores and PE outcomes.

Studies	Study feature	CPR collected	Population	No.	Age, yrs	Sex (%F)	Setting	FU days	No. (%) of participants in each pre-test risk level			No. (%) of participants with established PE; overall and within each risk level			
									In each level No. (%)			Study No. (%)	In each level No. (%)		
Wells 3-level Original									**Low**	**Int.**	**High**		**Low**	**Int.**	**High**
Wells et al. 2000	P; D	R	Canada 5 hospitals '93-'96 (Wells et al. 1998)	972	N/A	N/A	In-Out	90	392 (40.3)	511 (52.6)	69 (7.1)	165 (17)	14 (3.6)	105 (20.5)	46 (66.7)
Wells et al. 2000	P; V	R	Wells et al. 1998 cohort	247	N/A	N/A	In-Out	90	99 (40.1)	128 (51.8)	20 (8.1)	36 (16)	2 (2)	24 (18.8)	10 (50)
Sanson et al. 2000	P; V	R	ANTELOPE study cohort '97-'98	414	51	58	In-Out	0	147 (35.5)	259 (62.6)	8 (1.93)	122 (29)	41 (28)	78 (30)	3 (38)
Wells et al. 2001	P; V	P	Canada 4 hospitals '98-'99	930	50.5	62.7	Out	90	527 (56.7)	339 (36.5)	64 (6.9)	81 (9)	6 (1.3)	52 (16.2)	23 (37.5)
Chagnon et al. 2002	P; V	R	Switzerland 3 hospitals '00-'01	277	63	56	Out	90	162 (58.5)	104 (37.5)	11 (4)	71 (26)	19 (11.7)	42 (40.4)	10 (90.9)
Wolf et al. 2004	P; V	P	Kasier Permanente '01-'02	134	58*	54	Out	90	59 (44)	61 (45.5)	14 (10.4)	16 (12)	1 (1.69)	9 (14.75)	6 (42.9)
Bosson et al. 2005	P; V	P	France 1 hospital	1528	67	54.1	In-Out	0	666 (43.6)	697 (45.6)	165 (10.8)	305 (20)	37 (5.5)	186 (26.7)	82 (49.6)
Kabrhel et al. 2005	P; V	P	USA Brigham & Women's hospital '01-'02	607	47.9	74	Out	90	325 (53.5)	234 (38.6)	48 (7.90)	61 (10)	13 (4)	32 (13.7)	16 (33.3)
Miniati et al. 2005	P; V	P	Italy 1 hospital '00-'01	215	70	64	In-Out	365	64 (29.7)	118 (54.9)	33 (15.3)	93 (43)	8 (12.5)	64 (54.2)	21 (63.6)
Runyon et al. 2005	R; V	R	USA Carolinas hospital '01-'05	2477	45	70	Out	45	1801 (73)	N/A	N/A	N/A (6)	54 (3)	N/A (12)	N/A (33)
Hogg et al. 2006	P;V	P	MIOPED study, UK '02-'03	408	38.3	51.1	Out	90	N/A (86.6)	N/A (10.1)	N/A (3.3)	N/A (5.4)	N/A	N/A	N/A
Kline et al. 2006a	P; V	P	USA Carolinas hospital '01-'04	2302	44.7	69	Out	90	1704 (74)	559 (24.3)	39 (1.7)	108 (5)	50 (2.9)	48 (8.6)	10 (25.6)

Studies	Study feature	CPR collected	Population	No.	Age, yrs	Sex (%F)	Setting	FU days	No. (%) of participants in each pre-test risk level			No. (%) of participants with established PE; overall and within each risk level			
									In each level No. (%)			Study No. (%)	In each level No. (%)		
Kline et al. 2006b	P; V	P	USA Carolinas hospital '03-'04	178	48	N/A	Out	90	110 (62)	55 (31)	13 (7)	24 (14)	3 (2.7)	13 (23.6)	8 (61.5)
Kearon et al. 2006	P; V	P	Canada 7 hospitals '98-'02	1126	57	65	In-Out	180	670 (60)	385 (34)	71 (6.3)	194 (15)	33 (5)	99 (25.7)	62 (55.4)
Ollenberger et al. 2006	R; V	R	PIOPED study cohort	1359	55	55	In-Out	365	615 (45.3)	632 (46.5)	112 (8.2)	399 (29)	107 (17.4)	230 (36.3)	62 (55.4)
Penaloza et al. 2007	P; V	P	Western Europe '03-'05	185	56	58.9	Out	90	101 (54.6)	77 (41.6)	7 (3.8)	34 (18)	2 (2)	25 (32.5)	7 (100)
Yap et al. 2007	R; V	R	Australia 1 hospital ‘04-'05	625	60	49.6	In-Out	0	415 (66.4)	195 (31.2)	15 (2.4)	54 (9)	18 (4)	26 (13)	10 (67)
Gibson et al. 2008	R; V	R	Christopher study cohort	3298	53	N/A	In-Out	90	N/A	N/A	N/A	N/A (21)	N/A (7.1)	N/A (25.5)	N/A (57.6)
Calisir et al. 2009	P; V	P	Turkey '07-'07	148	62*	47	In-Out	0	51 (34.5)	68 (46)	29 (19.5)	48 (32.4)	4 (7.8)	18 (26.4)	26 (89.6)
Guo et al. 2009	P;V	P	China hospital ’04-‘06	570	55	43.7	In-Out	0	341 (59.8)	168 (29.5)	24 (4.2)	169 (29.6)	51 (15.0)	98 (58.3)	20 (83.3)
Hogg et al. 2011	R;V	P	THREAD study cohort ’08-‘09	354	57	59	In-Out	90	192 (54.2)	145 (41.0)	17 (4.8)	68 (19.2)	12 (6.3)	45 (31.0)	11 (64.7)
Penaloza et al. 2011	P; V	P	Penaloza et al. 2007 cohort	339	56	57	Out	90	157 (43.7)	167 (46.5)	15 (4.2)	65 (19)	4 (2)	47 (28)	14 (93)
Ye et al. 2012	P;V	P	China 1 hospital ’09-‘11	117	72.5	54.7	In-Out	0	42 (35.9)	49 (41.8)	26 (22.2)	47 (40.2)	3 (7.1)	21 (42.9)	23 (88.5)
Penaloza et al. 2013	R; V	R	France & Belgium 116 ED's	1038	64	62	Out	90	486 (47)	478 (46)	74 (7)	325 (31.3)	61 (12.6)	221 (42.6)	43 (58.1)
Luo et al. 2014	P;V	P	China 1 hospital ‘11	57	61.2	49.1	In	0	46 (80.7)	8 (14.0)	3 (5.3)	12 (21.1)	7 (15.2)	3 (37.5)	2 (66.7)
Guo et al. 2015	R;V	R	China 1 hospital ’06-‘11	196 ≥65 yrs	76.1	46.1	In-Out	0	N/A	N/A	N/A	N/A (28.6)	(20.6)	(42.4)	(88.9)

Studies	Study feature	CPR collected	Population	No.	Age, yrs	Sex (%F)	Setting	FU days	No. (%) of participants in each pre-test risk level			No. (%) of participants with established PE; overall and within each risk level			
									In each level No. (%)			Study No. (%)	In each level No. (%)		
				140 <65 yrs								N/A (N/A)	(17.1)	(35.7)	(72.2)
Di Marca et al. 2015	P;V	P	Italy 1 hospital '11-'13	102	77	N/A	In	0	65 (63.7)	29 (28.4)	8 (7.8)	22 (21.6)	6 (9)	9 (31)	7 (88)
Gruettner et al. 2015	R;V	R	Germany 1 hospital '10-'11	326	69	54.0	Out	0	280 (85.9)	37 (11.3)	9 (2.8)	N/A (13.5)	N/A	N/A	N/A
Wells 2-level Modified									**PE-un.**		**PE likely**		**PE-un.**		**PE likely**
Wells et al. 2000	P; D	R	Wells et al. 1998 cohort	964	N/A	N/A	In-Out	90	689 (71.5)		275 (28.5)	166 (18)	54 (7.8)		112 (40.7)
Wells et al. 2000	P; V	R	Wells et al. 1998 cohort	247	N/A	N/A	In-Out	90	17 (19.8)		69 (80.2)	36 (15)	9 (5.1)		27 (39.1)
Wolf et al. 2004	P; V	P	Kasier Permanente '01-'02	134	58*	54	Out	90	88 (65.7)		46 (34.3)	31 (12)	3 (3.4)		28 (60.9)
Kabrhel et al. 2005	P; V	P	USA Brigham & Women's hospital '01-'02	607	47.9	74	Out	90	449 (74)		158 (26)	61 (10)	25 (5.6)		36 (22.8)
Steeghs et al. 2005	P; V	P	Netherlands '02-'03	331	51	61.9	Out	90	279 (84.3)		52 (15.7)	46 (14)	30 (10.8)		16 (30.8)
van Belle et al. 2006 (Christopher study)	P; V	P	Netherlands 12 centres '02-'04	3306	53	57.4	In-Out	90	2206 (66.7)		1100 (33.3)	634 (20.4)	226 (12.1)		408 (37.1)
Arnason et al. 2007	R; V	R	Canada 1 hospital '02-'05	863	63*	61	Out	90	455 (73)		170 (27)	34 (4)	10 (2.2)		24 (14)
Goekoop et al. 2007	P; V	P	Netherlands 4 hospitals '02-'04	879	51	62.6	In-Out	180	450 (51.4)		426 (48.6)	168 (13)	47 (10.4)		121 (28.4)
Penaloza et al. 2007	P; V	P	Western Europe '03-'05	185	56	58.9	Out	90	144 (77.8)		41 (22.2)	34 (18)	10 (6.9)		24 (58.5)

Studies	Study feature	CPR collected	Population	No.	Age, yrs	Sex (%F)	Setting	FU days	No. (%) of participants in each pre-test risk level			No. (%) of participants with established PE; overall and within each risk level			
									In each level No. (%)			Study No. (%)	In each level No. (%)		
Douma et al. 2009	P; V	R	Switzerland, France 3 hospitals '00-'02	922	N/A	N/A	Out	90	722 (78.3)		200 (21.7)	207 (23)	95 (13.2)		112 (56)
Bahia et al. 2011	R; V	R	USA 1 hospital '06-'07	286	N/A	N/A	In	0	74 (26)		212 (74)	20 (7)	1 (5)		19 (95)
Douma et al. 2011	P; V	P	Netherlands 7 hospitals '08-'09	807	53	60.3	In-Out	90	584 (72.4)		223 (27.6)	185 (23)	90 (15.4)		95 (42.6)
Penaloza et al. 2011	P; V	P	Penaloza et al. 2007 study cohort	339	56	57	Out	90	235 (69.3)		104 (30.7)	65 (19)	19 (8)		46 (44)
Geersing et al. 2012	P; V	P	Netherlands '07-'10	598	48	71	Out	90	422 (70.6)		176 (29.4)	73 (12)	21 (5)		52 (29.5)
Posadaz-Martinez et al. 2014	Cross Intituti onal; V	R	IRTD study cohort '06-'11	613	N/A	42	In	90	394 (66)		219 (34)	224 (36)	78 (19.8)		146 (66.7)
Guo et al. 2015	R;V	R	China 1 hospital '06-'11	196 ≥65 yrs 140 <65 yrs	76.1	46.1	In-Out	0	N/A		N/A	N/A N/A (28.6)	N/A (19.6) N/A (17.6)		N/A (65.8) N/A (65.6)
Wells 2-level Simplified									**PE-un.**		**PE likely**		**PE-un.**		**PE likely**
Gibson et al. 2008	R;V	R	Christopher study cohort	3298	53	N/A	In-Out	90	N/A		N/A	N/A (21)	N/A (11)		N/A (35.8)
Douma et al. 2009	P;V	R	Switzerland, France 3 hospitals '00-'02	922	N/A	N/A	Out	90	644 (69.8)		278 (30.2)	207 (23)	77 (12)		130 (46.8)
Douma et al. 2011	P;V	P	Netherlands 7 hospitals '08-'09	807	53	60.3	In-Out	90	499 (62)		308 (38)	185 (23)	65 (13)		120 (40)
Geneva 3-level Original									**Low**	**Int.**	**High**		**Low**	**Int.**	**High**
Wicki et al. 2001	P; D	R	Geneva Switzerland '92-'97	986	62*	55	Out	90	486 (49.3)	437 (44.3)	63 (6.4)	265 (27)	48 (10)	166 (38)	51 (81)

Studies	Study feature	CPR collected	Population	No.	Age, yrs	Sex (%F)	Setting	FU days	No. (%) of participants in each pre-test risk level			No. (%) of participants with established PE; overall and within each risk level			
									In each level No. (%)			Study No. (%)	In each level No. (%)		
Chagnon et al. 2002	P; V	P	Switzerland 3 hospitals '00-'01	277	63	56	Out	90	152 (55)	113 (41)	12 (4)	59 (25.6)	20 (13)	43 (38)	8 (67)
Aujesky et al. 2003	P; V	P	Switzerland 1 hospital '00-'02	259	63*	58	Out	90	116 (44.8)	99 (38.2)	44 (17)	77 (30)	10 (8.6)	41 (41.4)	26 (59.1)
Perrier et al. 2004	P; V	P	Switzerland, France 3 hospitals '00-'02	965	61	58	Out	90	522 (54.1)	369 (38.2)	74 (7.7)	222 (23)	34 (7)	125 (34)	63 (85)
Perrier et al. 2005	P; V	P	Switzerland, France 3 hospitals '02-'02	756	60	60	Out	90	N/A	N/A	82 (10.8)	N/A (26)	N/A (7)	N/A (30)	78 (95.1)
Miniati et al. 2005	P; V	R	Italy 1 hospital '00-'01	215	70	64	In-Out	365	26 (12.1)	128 (59.5)	61 (28.4)	93 (43)	13 (50)	50 (39)	30 (49.2)
Ollenberger et al. 2006	R; V	R	PIOPED study cohort	998	55	55	In-Out	365	332 (33.3)	492 (49.3)	174 (17.4)	289 (29)	61 (18.4)	152 (30.9)	76 (43.7)
Gruettner et al. 2015	R;V	R	Germany 1 hospital '10-'11	326	69	54.0	Out	0	146 (44.8)	172 (52.7) 8 (2.5)		N/A (13.5)	N/A	N/A	N/A
Geneva 3-level Revised									**Low**	**Int.**	**High**		**Low**	**Int.**	**High**
Le Gal et al. 2006b	P; D	R	Switzerland, France 3 hospitals '00-'02	956	60.6	58.2	Out	90	354 (37)	549 (57.4)	53 (5.5)	189 (23)	32 (9)	151 (27.5)	38 (71.7)
Le Gal et al. 2006b	P; V	P	Switzerland, France 3 hospitals '02-'03	749	N/A	N/A	Out	90	229 (30.6)	463 (61.8)	57 (7.6)	192 (26)	18 (7.9)	132 (28.5)	42 (73.7)
Klok et al. 2008a	R; V	R	Christopher study cohort	300	N/A	N/A	Out	90	157 (52.3)	136 (45.3)	7 (2.3)	49 (16)	13 (8.3)	31 (22.8)	5 (71.4)
Righini et al. 2008	P; V	P	Switzerland, France 6 hospitals '05-'06	1693	59.3	55.3	Out	90	N/A	N/A	50 (3)	N/A (20.6)	N/A (9)	N/A (25)	42 (84)
Calisir et al. 2009	P; V	P	Turkey '07-'07	148	62*	47	In-Out	0	15 (10)	109 (74)	24 (16)	48 (32.4)	0 (0)	28 (25.6)	20 (83.3)

Studies	Study feature	CPR collected	Population	No.	Age, yrs	Sex (%F)	Setting	FU days	No. (%) of participants in each pre-test risk level			No. (%) of participants with established PE; overall and within each risk level			
									In each level No. (%)			Study No. (%)	In each level No. (%)		
Penaloza et al. 2013	R; V	R	France & Belgium 116 ED's	1038	64	62	Out	90	270 (26)	669 (65)	99 (10)	325 (31.3)	35 (13)	222 (33.2)	68 (68.7)
Luo et al. 2014	P;V	P	China 1 hospital ‘11	57	61.2	49.1	In	0	23 (40.4)	32 (56.1)	2 (0.4)	12 (21.1)	2 (8.7)	9 (28.1)	1 (50.0)
Di Marca et al. 2015	P;V	P	Italy 1 hospital '11-'13	102	77	N/A	In	0	18 (17.6)	71 (69.6)	13 (12.7)	22 (21.6)	2 (11)	13 (18)	7 (54)
Guo et al. 2015	R;V	R	China 1 hospital ’06-‘11	196 ≥65 yrs 140 <65 yrs	76.1	46.1	In-Out	0	N/A	N/A	N/A	N/A N/A (28.6)	N/A (18.5) N/A (24.6)	N/A (31.2) N/A (22.4)	N/A (75.0) N/A (76.9)
Geneva 3-level Simplified Revised									**Low**	**Int.**	**High**		**Low**	**Int.**	**High**
Klok et al. 2008b	R; V	R	Perrier et al. 2005 & Christopher study cohort	1049	60	60.1	Out	90	378 (36)	629 (60)	42 (4)	241 (25.6)	29 (7.7)	185 (29.4)	27 (64.3)
Guo et al. 2009	P;V	P	China hospital ’04-‘06	570	55	43.7	In-Out	0	225 (39.5)	277 (48.6)	31 (5.4)	169 (29.6)	45 (20.0)	105 (37.9)	19 (61.3)
Penaloza et al. 2011	P; V	P	Penaloza et al. 2007 study cohort	339	56	57	Out	90	114 (33.6)	216 (63.7)	9 (2.7)	65 (19)	5 (4)	55 (25)	5 (56)
Ye et al. 2012	P;V	P	China 1 hospital ’09-‘11	117	72.5	54.7	In-Out	0	30 (25.6)	37 (65.8)	10 (8.5)	47 (40.2)	3 (10.0)	37 (48.1)	7 (70.0)
Geneva 2-level Simplified Revised									**PE-un.**		**PE likely**		**PE-un.**		**PE likely**
Klok et al. 2008b	R; V	R	Perrier et al. 2005 & Christopher study cohort	1049	60	60.1	Out	90	681 (64.9)		368 (35.1)	231 (25.6)	78 (11.5)		153 (41.6)
Douma et al. 2011	P;V	P	Netherlands 7 hospitals '08-'09	807	53	60.3	In-Out	90	576 (71)		231 (21)	185 (23)	95 (17)		90 (39)
Penaloza et al. 2011	P; V	R	Penaloza et al. 2007 study cohort	339	56	57	Out	90	224 (66)		115 (33.9)	65 (19)	22 (10)		43 (37)

Studies	Study feature	CPR collected	Population	No.	Age, yrs	Sex (%F)	Setting	FU days	No. (%) of participants in each pre-test risk level				No. (%) of participants with established PE; overall and within each risk level				
									In each level No. (%)				Study No. (%)	In each level No. (%)			
Guo et al. 2015	R;V	R	China 1 hospital '06-'11	196 ≥65 yrs 140 <65 yrs	76.1	46.1	In-Out	0	N/A		N/A		N/A N/A (28.6)	N/A(18.5) N/A (24.6)		N/A (32.4) N/A (32.4)	
Pisa 4-level Original									**Low**	**Int.**	**Mod. High**	**High**		**Low**	**Int.**	**Mod. High**	**High**
Miniati et al. 2003	P; D	P	Italy '91-'99	1100	68*	55	In-Out	180	432 (39)	283 (26)	72 (7)	313 (28)	440 (40)	19 (4)	62 (22)	53 (74)	306 (98)
Pisa 4-level Revised									**Low**	**Int.**	**Mod. High**	**High**		**Low**	**Int.**	**Mod. High**	**High**
Miniati et al. 2008a	R; D	R	Miniati et al. 2003 study cohort	1100	68*	55	In-Out	365	309 (28)	371 (34)	195 (18)	225 (20)	440 (40)	11 (4)	98 (26)	126 (65)	205 (91)
Miniati et al. 2008b	P; V	R	Italy '03-'05	400	70	58	In-Out	180	136 (34)	104 (26)	64 (16)	96 (24)	165 (41.3)	3 (2)	29 (28)	43 (67)	90 (94)

Note: Age in means. * denotes age median. Abbreviations: ANTELOPE: Advances in New Technologies in the Localisation of Pulmonary Embolism**;** CPR: Clinical Prediction Rules; ED: Emergency Department; FU: Follow-up; In: Inpatients; Int.: Intermediate; In-Out: Inpatients and Outpatients; IRTD: Institutional Registry of Thromboembolic Disease; MIOPED: Manchester Investigation Of Pulmonary Embolism Diagnosis; Mod.: Moderately; PE: Pulmonary Embolism; PE-un.: PE unlikely; PIOPED: Prospective Investigation of Pulmonary Embolism Diagnosis; Out: Outpatients; N/A: Not available; No.: Number; THREAD: Thromboembolism Assessment and Diagnosis: USA: United States of America; Yrs: years.

3 PART A - METHODS

3.1 Research study design

This was a retrospective cohort study conducted at FMC, a large metropolitan teaching hospital with a catchment area of ~400,000 people located in Southern Adelaide, South Australia (SA). Patients presenting to the FMC ED, outpatient clinics or FMC inpatient groups, in whom the attending physician considered the diagnosis of PE, were included. The study included patients over a 17-month period, from the 1st January 2013 to the 31st May 2014. Patients were followed up for 3 months after the risk calculation index date.

3.1.1 Study flow

At FMC, the patient flow for suspected PE diagnosis uses two algorithms: one for medical patients and the other for patients who had surgery in the past 6 weeks. Both algorithms are described in Appendix A and B. Using the clinical prediction calculations for both the original and modified Wells score and the revised Geneva score this allowed conventional algorithms to be used for comparison to other studies identified in the literature.

3.2 Ethics

Approval for the study was obtained from the Southern Adelaide Clinical Human Research Ethics Committee of Flinders University on the 2nd April 2014. The approval letter is included in Appendix C.

3.3 Study Population

All patients with suspected PE were eligible to participate in the study, including those in the ED, inpatient and short-stay wards, and outpatient clinics.

3.4 Participant selection

All patients with suspected PE presenting with clinical signs and symptoms such as dyspnoea, chest pain, tachypnoea and haemoptysis, and receiving PE CPR calculation were included. Patients who did not receive a PE CPR calculation were identified using CTPA and V/Q scans reports during the study period, however they were not included in the main patient cohort (refer to Figure 4.7 and Figure 4.8). Poor gatekeeping in the FMC Radiology Department may have contributed to patients not receiving a CPR calculation prior to receiving a confirmatory test.

3.5 Data collection techniques

A database containing clinical information regarding patients admitted at FMC since 2012 was created to link the following sources: electronic data of patients with suspected VTE (Department of Respiratory Medicine, FMC), the State-wide Clinical Information System (OACIS), and individual patient medical records. The death registry was used to collect information on vital status and linked to the new database. The database was housed in a university server located in the Department of Clinical Pharmacology, FMC. Data collection was from 1st January 2013 to 18th August 2017. A list of patient demographic and clinical parameters is in Table 3.1.

Table 3.1 Demographic and clinical parameters collected for FMC patients suspected with pulmonary embolism.

Hospital Demographics		
Location in FMC		
	ED	
	Outpatients	
	Inpatients	
Hospital stay		
	Triage/departure, admission/discharge date/time	
	Length of stay (days)	
	Length of stay before PE suspected	
Patient Demographics		
General		
	Age, (DOB)	
	Gender	
	Current smoker	
	Pregnant	
Clinical		
	Blood studies	
		Serum creatinine
		D-dimer
	Medications	
		Total number of regular drugs
		Anticoagulants
		Antiplatelets
		NSAID's
		HRT
PE related		
	Clinical prediction calculator	
		Assessment date/time
		Score, category
	Confirmatory imaging	
		CTPA, V/Q scan, compression US
		PE outcome and type
Follow-up		
	Re-admission	
	All-cause mortality	

Abbreviations: DOB: date of birth; ED: emergency department; FMC: Flinders Medical Centre; HRT: hormone replacement therapy; NSAID's: non-steroidal anti-inflammatory drugs; PE: pulmonary embolism; US: ultrasound; V/Q: ventilation/perfusion.

3.5.1 D-Dimer result

At FMC, the pathology laboratories test for D-dimer levels using an immune-turbidimetric assay (STA® Liatest D-Di PLUS). A value less than 0.5mg/L is considered a negative predictor of both DVT and PE. Results of D-dimer assay were collected directly from the hospital's clinical information system.

3.5.2 Medications

For each patient, the total number of medications was collected using medication charts and clinical notes found in patient medical records. Medications used as pro re nata (PRN – "as needed") were not included in the total number of medications. Subtypes of medications were also collected: anticoagulants, antiplatelets, non-steroidal anti-inflammatory drugs (NSAID's), and hormone replacement therapy (HRT). Table 3.2 lists the types of medications by generic names used in Australia.

Table 3.2 Medications used within Australia using generic names for patients with suspected pulmonary embolism.

Anticoagulants		**Antiplatelets**	
Heparins	Dalteparin Danaparoid Enoxaparin Heparin	Glycoprotein IIb/IIIa Inhibitors	Abciximab Eptifibatide Tirofiban
Direct thrombin Inhibitors	Bivalirudin Dabigatran	Thienopyridines	Clopidogrel Prasugrel Ticlopidine
Factor Xa Inhibitors	Apixaban Fondaparinux Rivaroxaban	Other antiplatelet drugs	Aspirin* Dipyridamole Ticagrelor
Other	Warfarin		
NSAID's		**HRT**	
Non-selective (COX-1, -2 inhibitors)	Aspirin* Diclofenac Ibuprofen Indomethacin Ketorolac Mefenamic acid Naproxen Piroxicam Sulindac	Combined oral contraceptives	Cyproterone with Ethinyloestradiol Desogestrel with Ethinyloestradiol Dienogest with Ethinyloestradiol Drospirenone with Ethinyloestradiol Gestodene with Ethinyloestradiol Levonorgestrel with Ethinyloestradiol Nomegestrol with Oestradiol Norethisterone with Ethinyloestradiol Norethisterone with Mestranol
Selective (COX-2 inhibitors)	Celecoxib Etoricoxib Meloxicam Paracoxib	Progestogens	Etongestrel Levonorgestrel Levonogestrel IUD Medroxyprogesterone Norethisterone
Intrauterine devices	Copper IUD Levonorgestrel IUD	Other combined contraceptives	Etonogestrel with Ethinyloestradiol

Note:*Aspirin has both antiplatelet and NSAID properties. Abbreviations: COX: cyclooxygenase; IUD: Intrauterine device; HRT: hormone replacement therapy; NSAID's: non-steroidal anti-inflammatory drugs.

3.5.3 Estimated GFR

At FMC, the estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey et al. 2009). This formula uses four equations based on serum creatinine (SCr) levels, age and gender.

Females:

SCr ≤ 62µmol/L:

$$eGFR = 144 \times (SCr \times \frac{0.0113}{0.7})^{-0.329} \times (0.993)^{age\ in\ years}$$

SCr > 62µmol/L:

$$eGFR = 144 \times (SCr \times \frac{0.0113}{0.7})^{-1.209} \times (0.993)^{age\ in\ years}$$

Males:

SCr ≤ 80µmol/L:

$$eGFR = 141 \times (SCr \times \frac{0.0113}{0.9})^{-0.411} \times (0.993)^{age\ in\ years}$$

SCr > 80µmol/L:

$$eGFR = 141 \times (SCr \times \frac{0.0113}{0.9})^{-1.209} \times (0.993)^{age\ in\ years}$$

3.5.4 Diagnostic investigations of PE

3.5.4.1 Confirmatory imaging

Diagnosis of PE was based on confirmatory imaging using computer tomography pulmonary angiography (CTPA), ventilation/perfusion (V/Q) scan, and compression ultrasound (US). V/Q scan reports were examined if CTPA was either not done or

non-diagnostic. Two criteria were used for the diagnosis of PE using V/Q scan, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria and the European Association of Nuclear Medicine (EANM) Single-photon emission computed tomography (SPECT) criteria (PIOPED-Investigators. 1990, Bajc et al. 2009a, Bajc et al. 2009b). If patients did not receive a CTPA and/or V/Q scan, a lower or upper extremity compression ultrasound was considered. A lack of venous compression was diagnostic for DVT and was also considered positive for PE.

3.5.4.2 Follow-up

Patients with missing confirmatory imaging or when imaging was inconclusive for PE were followed up for three months. For this group of patients, secondary care information (medical records) was obtained and reviewed by a qualified clinician (A.A.M.) to identify any PE or DVT events during the 3-month period. Deaths that occurred in the hospital during the follow-up period were assessed by A.A.M. to rule out any possible PE or DVT using medical case notes. If no sufficient information was provided to make an alternative diagnosis then the patients PE status remained inconclusive.

3.6 Outcome measures

The primary outcome of the study was the incidence of symptomatic PE identified using CTPA, V/Q scan, lower or upper extremity compression ultrasound, or VTE at 3-month follow-up. A diagnosis of PE was counted as a positive outcome defined by any of the following:

- Positive CTPA reported by a staff radiologist or nuclear medicine physician. This includes thrombus (either occlusive or non-occlusive) reported anywhere within the pulmonary circulation.

- PIOPED criteria - high probability V/Q scan reported by a staff radiologist or nuclear medicine physician. This includes moderate and large segmental perfusion defects.
- EANM SPECT criteria – positive V/Q scan reported by a staff radiologist or nuclear medicine physician. This includes ventilation/perfusion mismatch of at least one segment or two subsegments that conforms to the pulmonary vascular anatomy defects.
- Positive compression US reported by a staff radiologist or nuclear medicine physician. Test showing a lack of vein compression was diagnostic for DVT but also deemed positive for PE.
- Hospital admissions to any South Australian public hospital or to the emergency department during the 3-month follow-up period with a confirmatory test that matched the above criteria were deemed positive for PE.

A diagnosis of PE was counted as a negative outcome defined by any of the following:

- Negative CTPA reported by a staff radiologist or nuclear medicine physician. This includes no thrombus defects reported anywhere within the respiratory circulation.
- PIOPED criteria – normal, very low or low probability V/Q scan reported by a staff radiologist or nuclear medicine physician. This includes no perfusion defects or small segmental perfusion defects of <25%.
- EANM SPECT criteria – negative V/Q scan reported by a staff radiologist or nuclear medicine physician. This includes either no perfusion defects visible,

matched or reversed mismatch ventilation/perfusion defects of any size, shape or number in the absence of mismatch, or mismatch that does not have a lobar, segmental or subsegmental pattern.

- Any hospital admissions to FMC or to the emergency department during the 3-month follow-up period with a confirmatory test that matched the above criteria were deemed negative for PE.
- No hospital admissions to any South Australian public hospital or to the emergency department during the 3-month follow-up period were deemed negative for PE.

An inconclusive diagnosis of PE was defined by any of the following:

- Inconclusive or indeterminate CTPA reported by a staff radiologist or nuclear medicine physician due to poor contrast opacification.
- PIOPED criteria - intermediate probability V/Q scan reported by a staff radiologist or nuclear medicine physician.
- Negative compression ultrasound reported by a staff radiologist or nuclear medicine physician. Test showing compressions of veins were deemed inconclusive for PE.
- Deaths occurring within the 3-month follow-up with lack of evidence to provide a cause of death were deemed inconclusive.

3.7 Data analysis

All data analyses were performed using the STATA statistical software Version 15 (StataCorp©, College Station, TX).

3.7.1 Descriptive statistics

The characteristics of the patient cohort were described with simple descriptive statistics including percentages, means, and standard deviations. This included the number of patients in different hospital locations, how many patients received confirmatory testing (CTPA, V/Q scan, compression US), and patients with a D-dimer test.

3.7.2 Inferential statistics

The probability of PE was stratified into low, intermediate and high risk based on the Wells score and revised Geneva score (refer to Table 2.5 and Table 2.6) (Le Gal et al. 2006b, Wells et al. 2000). Difference in mean PE prevalence was assessed using a two-sample t-test for the FMC study cohort against either Wells or revised Geneva derivation study cohorts. Calibration of the CPRs was evaluated by the observed PE risk in FMC study compared with each decile of predicted PE risk. Decile predicted risk was calculated by grouping equal number of patients into 10 groups.

Discrimination of the Wells and revised Geneva scores was evaluated by the area under the receiver operating characteristic (ROC) curve (i.e. C-statistic) based on the total scores for each patient. Sub-group analyses were undertaken to evaluate whether the discrimination of the scores differed based on timing since presentation and location (<24-hr vs. ≥24-hr and medical vs. surgical ward).

In a sensitivity analysis, additional exclusion criteria were applied to better match the current study to the derivation studies of the Wells and revised Geneva scores. These exclusion criteria included age <18 years; pregnancy; receiving anticoagulant treatment; and contraindications to contrast media or renal failure.

Univariate and multivariable logistic regression analyses were performed to re-

estimate the coefficients of variables used in the Wells and revised Geneva score using the present dataset. Patients with inconclusive results were removed from the primary analysis. An additional analysis was performed where all inconclusive data was deemed positive for PE, however, results did not differ from the primary analysis (not reported). Using Pearson's chi-squared (χ^2) test variables were identified as being significantly associated in the diagnosis of PE for timing since presentation and hospital location. These variable coefficients were also compared with those of the published Wells and revised Geneva score (Wells et al. 2000, Le Gal et al. 2006b) using a Wilcoxon signed-ranks test. A test of independent proportions was performed between current study and derivation study cohorts.

3.8 Pilot study

To determine what variables that could be collected retrospectively a sample of 15 patients who had a PE clinical prediction calculation performed were used to identify what type of variables were reliable to collect. This was conducted in late April 2014 which identified a small number of variables, such as body mass index (BMI) and D-dimer, which were not reliable and consequently were removed from the variable list.

4 PART A - RESULTS

4.1 Study Characteristics

From January 1, 2013 to May 31, 2014, 1,724 patients who received a PE clinical prediction calculation at FMC were included in the study. Patients' characteristics are described in Table 4.1. The mean age of the study cohort was 63 years and just over half were female (55.9%). Thirty patients were pregnant at the time of assessment. A total of 1,237 (71.8%) patients were assessed for PE either in ED or as an outpatient. Amongst inpatients, 311 (18.0%) were located in medical wards while 176 (10.2%) were located in surgical wards. D-dimer data were missing in 56.4% of patients.

CTPA, V/Q scans, and compression ultrasound were performed in 1,302, 128, and 15 patients, respectively, with 1,380 being diagnostic. Thirty patients died within the 3-month follow-up period. Breakdown of this is illustrated in Figure 4.7 for the Wells score and in Figure 4.8 for the revised Geneva score at end of this chapter.

In comparison to the derivation study of the revised Geneva score (Le Gal et al. 2006b) the patients in the current study were more likely to have active cancer, recent surgery or lower limb fracture, or both, with the past month, to be immobilised for more than 3 days, to have signs of DVT and to report chest pain (Table 4.1). A comparison of study patient characteristics with the derivation study cohort of the Wells score was not possible as patient characteristics in the original study were not reported (Wells et al. 2000).

Table 4.1 Study Characteristics of current study with Le Gal Study

Characteristic	Current Study (N=1,724)		Le Gal Study (N=965)		*p*-value
	Number (%) or Mean (SD)				
Demographic characteristics					
Age, mean (SD), years	63	(18.6)	61	(19.4)	
Female gender	964	(55.9)	562	(58.2)	*0.244*
Clinical characteristics					
Previous VTE	238	(13.8)	166	(17.2)	*0.018*
Active cancer (1 year)	341	(19.9)	89	(9.2)	*<0.001*
Recent surgery, lower limb fracture, or both (<4 weeks)	342	(19.8)	67	(6.9)	*<0.001*
Recent immobilisation (> 3 days)	544	(31.6)	165	(17.1)	*<0.001*
Signs of DVT	219	(12.7)	51	(5.3)	*<0.001*
Haemoptysis	96	(5.6)	43	(4.5)	*0.211*
Unilateral lower limb pain	260	(15.1)	138	(14.3)	*0.584*
Dyspnoea	1,185	(68.7)	637	(66.0)	*0.147*
Heart rate >100 bpm	592	(34.3)			
Chest pain	980	(56.8)	681	(70.6)	*<0.001*
Tachycardia	657	(38.1)	N/A		
Atrial fibrillation	156	(9.1)	N/A		
Hypotension	115	(6.7)	N/A		
Hypoxia	596	(34.6)	N/A		
Alternative diagnosis less likely than PE	999	(58.0)	N/A		
Pregnant	30	(1.7)	10	(1.0)	*0.148*
Hormone therapy	84	(4.9)	69	(7.2)	*0.014*
Anticoagulant	268	(15.7)	N/A		
Antiplatelet	539	(31.5)	N/A		
NSAIDs	483	(28.2)	N/A		

Note: Le Gal et al. (2006b) study using derivation cohort only. Hormone therapy defined as oral contraceptives and hormone replacement therapy. Abbreviations: bpm: beats per minute; DVT: deep vein thrombosis; N/A: Not available; NSAIDs: Non-steroidal anti-inflammatory drugs; SD: standard deviation; VTE: venous thromboembolism. Wells et al. study characteristics not available (Wells et al. 2000).

In terms of patient allocation into the Wells and revised Geneva scores categories, fewer patients were in the low probability category and more in the intermediate and high probability categories for the derivation studies (Table 4.2).

Table 4.2 Proportion of patients in the two clinical models categorized into low, intermediate and high clinical probability groups.

CPR categories Number (%)	Wells Score				Revised Geneva Score			
	Current Study (n=1,724)		Wells Study (n=1,219)		Current Study (n=1,724)		Le Gal Study (n=1,705)	
Low	477	(27.7)	491	(40.3)	282	(16.4)	583	(34.2)
Intermediate	1,055	(61.2)	639	(52.4)	1,261	(73.1)	1,012	(59.4)
High	192	(11.1)	89	(7.3)	181	(10.5)	110	(6.5)

Abbreviations: CPR: clinical prediction rule; n: number.

4.2 Performance of clinical prediction rules

4.2.1 Validation of Wells and revised Geneva

PE prevalence within each category differed from the derivation studies for both CPRs. In a comparison with the Wells score derivation study (Figure 4.1A) the PE prevalence was significantly higher for the low probability category (9.30% vs. 3.26%; p <0.001) and significantly lower for both the intermediate (15.51% vs. 20.19%; p = 0.014) and high (29.41% vs. 62.92%; p <0.001) probability categories. In comparison with the revised Geneva derivation study (Figure 4.1B) the PE prevalence was significantly lower for both the intermediate (18.24% vs. 27.96%; p <0.001) and the high (26.26% vs. 72.73%; p <0.001) probability categories. However, the PE prevalence in the low probability category was similar (8.49% vs. 8.58%; p = 0.969). With respect to calibration in the FMC study cohort, observed and predicted PE prevalence within each risk category (low, intermediate, and high) was similar for all three categories in both CPRs.

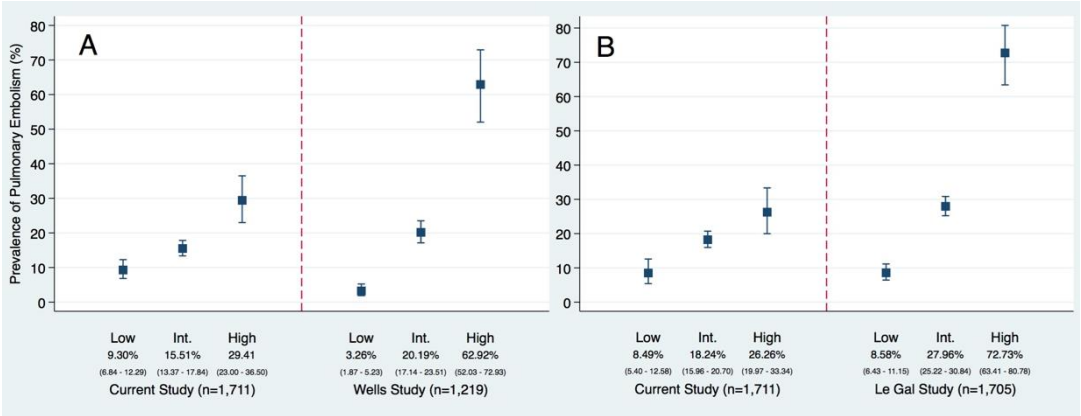


Figure 4.1 Current study prevalence of pulmonary embolism with 95% CI in the three risk categories of the A) the Wells score and B) revised Geneva score, with comparison to the respective derivation studies (Wells et al. 2000, Le Gal et al. 2006b).
Abbreviations: CI: confidence interval; Int: Intermediate.

When exclusion criteria were applied (n=1,146 patients), PE prevalence within each category was similar to results for the primary analysis for both CPRs. In a comparison with the Wells score derivation study (Figure 4.2A) the PE prevalence

was significantly higher for the low probability category (9.14% vs. 3.26%; p <0.001) and significantly lower for both the intermediate (16.16% vs. 20.19%; p = 0.057) and high (30.28% vs. 62.92%; p <0.001) probability categories. In comparison with the revised Geneva derivation study (Figure 4.2B) the PE prevalence was significantly lower for both the intermediate (15.76% vs. 27.96%; p <0.001) and the high (27.96% vs. 72.73%; p <0.001) probability categories. However, the PE prevalence in the low probability category was similar (8.56% vs. 8.58%; p = 0.970).

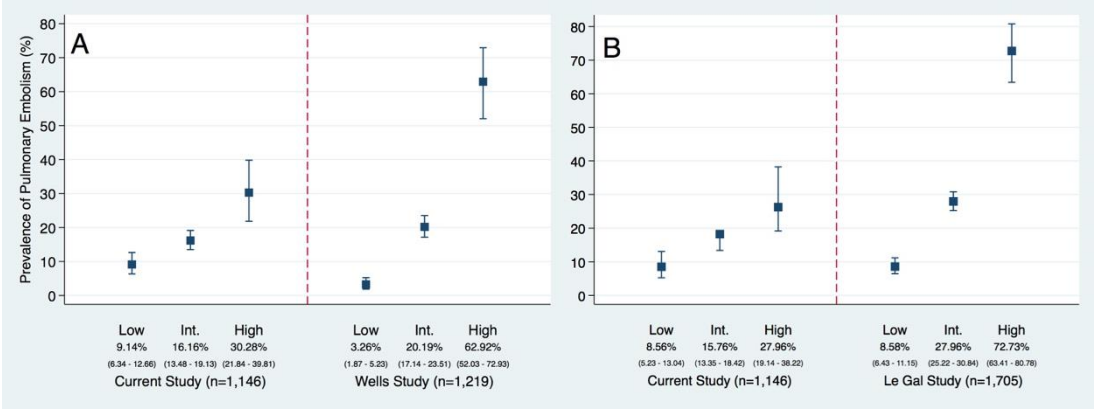


Figure 4.2 Current study with exclusion criteria applied prevalence of pulmonary embolism with 95% CI in the three risk categories of the A) the Wells score and B) revised Geneva score, with comparison to the respective derivation studies (Wells et al. 2000, Le Gal et al. 2006b).
Abbreviations: CI: confidence interval; Int: Intermediate.

In terms of discrimination, the area under the ROC curve was 0.61 (95% CI: 0.57 to 0.65) for the Wells score and 0.62 (95% CI: 0.59 to 0.66) for the revised Geneva score (Figure 4.3).

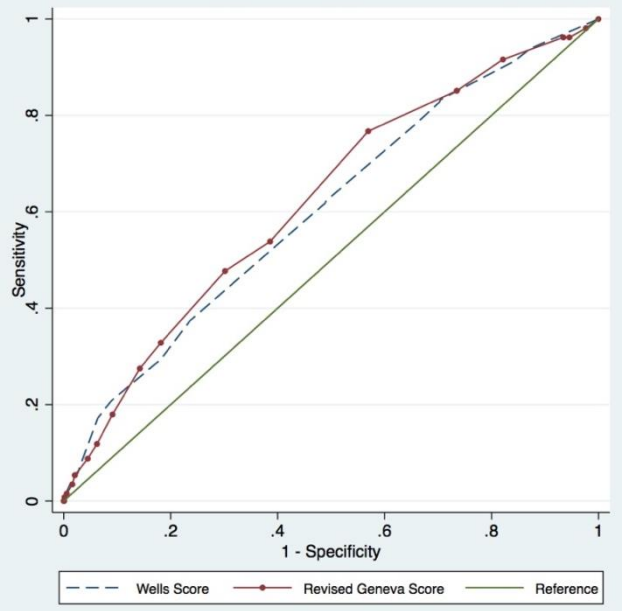


Figure 4.3 Comparison of the predictive accuracy of the Wells and revised Geneva clinical probability assessment of pulmonary embolism.

In a sensitivity analysis, using exclusion criteria similar to the derivation studies, the area under the ROC curve estimated for the Wells score and the revised Geneva score was 0.61 (95% CI: 0.57 to 0.66) and 0.64 (95% CI: 0.59 to 0.68), respectively.

4.2.2 CPR risk factors for PE

With respect to the association between the seven PE individual risk factors forming the Wells score, the effect sizes re-estimated using the current study cohort were significantly attenuated compared to the derivation study of the Wells risk score (p = 0.018; Table 4.3).

Table 4.3 Multivariable odd ratios for the variables of the Wells CPR for pulmonary embolism and those observed in the FMC study.

Variables	OR with 95% CI for current study	
	Current Study	Wells Study (Wells et al. 2000)
Clinical signs of DVT	1.9 (1.3 – 2.7)	5.8
Recent surgery or immobilization	1.4 (1.1 – 1.8)	3.0
Heart rate > 100 bpm	1.1 (0.8 – 1.4)	2.5
Previous history of PE or DVT	1.9 (1.4 – 2.7)	2.4
Haemoptysis	0.9 (0.5 – 1.6)	2.4
Malignancy	1.6 (1.1 – 2.1)	2.3
Alternative diagnosis less likely than PE	1.3 (1.0 – 1.8)	4.6

Abbreviations: bpm: beats per minute; CI: confidence interval; DVT: Deep vein thrombosis; PE: Pulmonary embolism; >: greater than; OR: Odds ratio.

Similarly, the effect size of the nine risk factors forming the revised Geneva score were also attenuated in comparison to the derivation study of the Geneva risk score, barring age >65 years (p = 0.015, Table 4.4).

Table 4.4 Multivariable odd ratios for the variables of the revised Geneva risk prediction tools for pulmonary embolism and those observed in the current study.

Variable	OR with 95% CI for current study	
	Current Study	Le Gal Study (Le Gal et al. 2006b)
Age > 65 years old	1.5 (1.1 – 1.9)	1.48
Previous DVT or PE	2.0 (1.4 – 2.8)	2.86
Surgery or fracture within 1 month	1.5 (1.1 – 2.0)	2.18
Active malignancy	1.6 (1.1 – 2.8)	1.57
Heart rate (bpm)		
75-94	1.7 (1.0 – 2.8)	3.32
≥95	1.6 (1.0 – 2.7)	1.95
Pain on leg venous palpation and unilateral oedema	2.1 (1.3 – 3.3)	3.82
Unilateral leg pain	0.9 (0.6 – 1.5)	2.64
Haemoptysis	0.9 (0.5 – 1.6)	2.10

Abbreviations: bpm: beats per minute; CI: confidence interval; DVT: Deep vein thrombosis; > greater than; ≥ greater than and equal to; PE: Pulmonary embolism.

4.2.3 Influence of time of assessment and hospital location

Patients assessed <24 hours after presentation (71.8%) were younger (mean age 61 vs. 67 years, p <0.001), more likely to have a history of VTE (15.8% vs. 8.6%, p <0.001), to report chest pain (64.9% vs. 36.3%, p <0.001), and to receive hormone therapy (6% vs. 2.3%, p = 0.002) and NSAIDs (31.6% vs. 26.8%, p = 0.001) than those assessed ≥24 hrs after presentation. Patients assessed ≥24-hr from presentation

were more likely to be on anticoagulants (39.5% vs. 15.7%, *p* <0.001) and antiplatelet drugs (35.7% vs. 31.5%, p=0.012), to have had recent surgery (37.2% vs. 11.9%, *p* <0.001), to be immobilised (67.6% vs. 17.4%, *p* <0.001), to have a lower limb fracture (8.0% vs. 0.8%, *p* <0.001), and to be tachycardic (47.6% vs. 34.4%, *p* <0.001), and hypoxic (50.9% vs. 28.1%, *p* <0.001; Table 4.5) Among the ≥24-hr patients (n=487), 64% were hospitalised in a medical ward and 36% in a surgical ward.

Table 4.5 Study Characteristics based on time of assessment

Characteristic	Total (n=1724)		<24 hours (n=1237)		≥24 hours (n=487)		*p* value
	Number (%) or Mean (SD)						
Demographic characteristics							
Age, mean (SD), y	63	(18.6)	61	(18.7)	67	(17.8)	*<0.001*
Female gender	964	(55.9)	693	(55.7)	271	(56.0)	*0.887*
Clinical characteristics							
Previous VTE	238	(13.8)	196	(15.8)	42	(8.6)	*<0.001*
Active cancer (1 year)	373	(21.6)	253	(20.5)	120	(24.6)	*0.057*
Recent surgery (<4 weeks)	328	(19.0)	147	(11.9)	181	(37.2)	*<0.001*
Recent immobilisation (> 3 days)	544	(31.6)	215	(17.4)	329	(67.6)	*<0.001*
Signs of DVT	219	(12.7)	164	(13.3)	55	(11.3)	*0.270*
Haemoptysis	96	(5.6)	76	(6.1)	20	(4.1)	*0.097*
Lower limb fracture (<4 weeks)	49	(2.8)	10	(0.8)	39	(8.0)	*<0.001*
Unilateral lower limb pain	260	(15.1)	196	(15.8)	64	(13.1)	*0.158*
Heart rate	592	(34.3)	396	(32.0)	196	(40.3)	*0.001*
Dyspnoea	1185	(68.7)	838	(67.7)	347	(71.3)	*0.157*
Chest pain	980	(56.8)	803	(64.9)	177	(36.3)	*<0.001*
Tachycardia	657	(38.1)	425	(34.4)	232	(47.6)	*<0.001*
Atrial fibrillation	156	(9.1)	103	(8.3)	53	(10.9)	*0.096*
Hypotension	115	(6.7)	73	(5.9)	42	(8.6)	*0.041*
Hypoxia	596	(34.6)	348	(28.1)	248	(50.9)	*<0.001*
Alternative diagnosis less likely than PE	999	(58.0)	735	(59.4)	264	(54.2)	*0.049*
Pregnant	30	(1.7)	23	(1.9)	7	(1.4)	*0.546*
Hormone therapy	84	(4.9)	73	(6.0)	11	(2.3)	*0.002*
Anticoagulant	268	(15.7)	93	(7.6)	175	(35.9)	*<0.001*
Antiplatelet	539	(31.5)	365	(29.8)	174	(35.7)	*0.012*
NSAIDs	483	(28.2)	329	(31.6)	154	(26.8)	*0.001*

Note: <24 or ≥24 hours: Time of assessment since presenting to FMC. Hormone therapy defined as oral contraceptives and hormone replacement therapy. Abbreviations: DVT: deep vein thrombosis; N/A: Not available; NSAID's: Non-steroidal anti-inflammatory drugs; SD: standard deviation; VTE: venous thromboembolism.

The area under the ROC curve for the Wells score was 0.62 (95% CI: 0.58 to 0.68) and 0.56 (95% CI: 0.49 to 0.63; $p = 0.109$) for patients assessed for PE <24 and ≥24-hr from presentation, respectively (Figure 4.4).

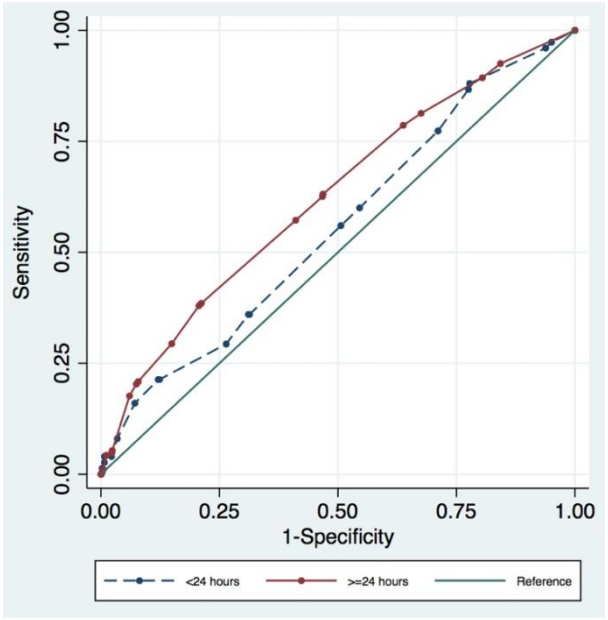


Figure 4.4 Comparison of the predictive accuracy of time since admission of the Wells score.

The area under the ROC curve for the revised Geneva score was 0.64 (95% CI: 0.59 to 0.68) for <24-hr and 0.59 (95% CI: 0.52 to 0.66; $p = 0.273$) for ≥24-hr (Figure 4.5).

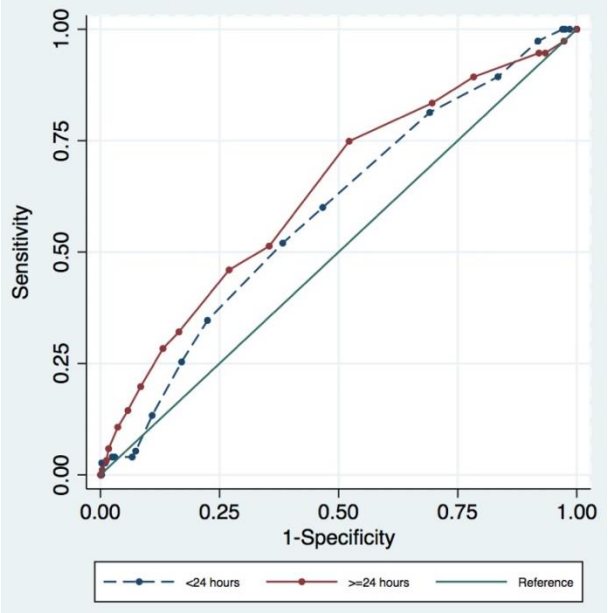


Figure 4.5 Comparison of the predictive accuracy of time since admission of the revised Geneva score.

In the ≥24-hr group, the area under the ROC curve for the Wells and revised Geneva scores was 0.54 (95% CI: 0.45 to 0.63) and 0.55 (95% CI: 0.46 to 0.65) in medical ward patients, and 0.57 (95% CI: 0.45 to 0.67) and 0.60 (95% CI: 0.50 to 0.69) in surgical ward patients, respectively (Figure 4.6). Refer to Table 4.6 found at the end of this chapter for summary of all ROC numbers for each analysis on both Wells and Revised Geneva scores.

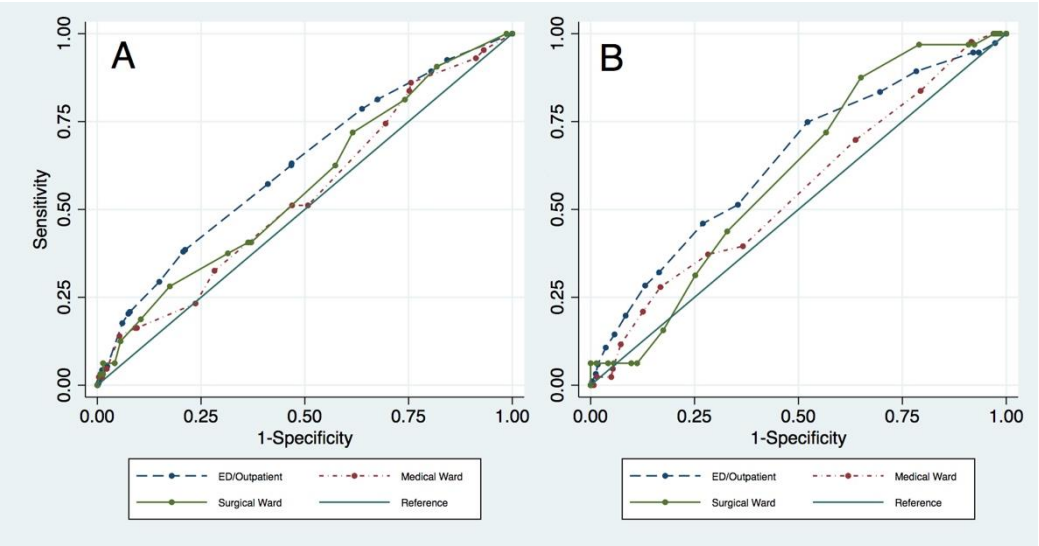


Figure 4.6 Comparison of the predictive accuracy of the A) Wells score and B) revised Geneva

in emergency/outpatients vs. medical vs. surgical ward patients.

4.2.4 CPR risk factors for PE and patient location

In univariate analysis, five items of the Wells score (clinical signs of DVT, recent surgery or immobilisation, previous DVT or PE, malignancy, and alternative diagnosis less likely than PE) were associated with PE. In multivariate analysis, the same five items were associated with PE. Three items (clinical signs of DVT, previous DVT or PE, and alternative diagnosis less likely than PE) were associated with PE for patients assessed within 24 hours in both univariate and multivariate analyses. Malignancy was the only item associated with PE for patients assessed after 24 hours in both univariate and multivariate analyses. Refer to Table 4.7 and Table 4.8 at the end of this chapter for univariate and multivariate logistic regression analyses for the Wells score and different patient populations.

The revised Geneva score had six items (age >65 years, previous DVT or PE, surgery and/or fracture within 1 month, active malignancy, unilateral lower-limb pain, and pain on leg venous palpation and unilateral oedema) associated with PE in univariate analysis. In multivariate analysis, seven items (age >65 years, previous DVT or PE, surgery and/or fracture within 1 month, active malignancy, heart rate between 75 to 94 bpm, heart rate ≥ 95 and pain on leg palpation and unilateral oedema) were associated with PE. For patients assessed within 24 hours for PE, five items were statistically significant (age >65 years, previous DVT or PE, surgery and/or fracture within 1 month, unilateral lower-limb pain, and pain on leg venous palpation and unilateral oedema) in univariate analysis. Similar results were observed in multivariate analysis; however unilateral lower-limb pain was not associated with PE whereas heart rate between 75 to 94 bpm was associated with PE. Active malignancy was the only item statistically significant in univariate analyses

for patients assessed ≥24 hours, however, in multivariate analysis three items (age >65 years, active malignancy, and pain on leg venous palpation and unilateral oedema) were associated with PE. Active malignancy was also associated for PE in surgical ward patients. Refer to Table 4.7 and Table 4.8 at the end of this chapter for univariate and multivariate logistic regression analyses for the revised Geneva score and different patient populations.

Ten other variables were assessed for independent association with PE using univariate logistic regression analyses. One item, chest pain, was associated with PE (p = 0.006) in the total patient population. In patients assessed within 24 hours, dyspnoea (p = 0.035), chest pain (p = 0.035), hypotension (p = 0.022), and hypoxia (p = 0.004) were predictive for PE. No associations for the 10 variables were predictive for PE in patients assessed ≥24 hours or medical ward patients. Chest pain (p = 0.016) was independently associated with PE in surgical ward patients. Refer to Table 4.7 for univariate logistic regression analyses for additional variables collected.

4.3 Staff adherence to use of PE clinical prediction rules

Over the study period 130 (8.4%) patients did not undergo a PE clinical probability assessment prior to confirmatory imaging. A comparison based on confirmatory imaging between this patient group and the present study cohort showed similar PE prevalence (17.8% vs. 15.3%, respectively).

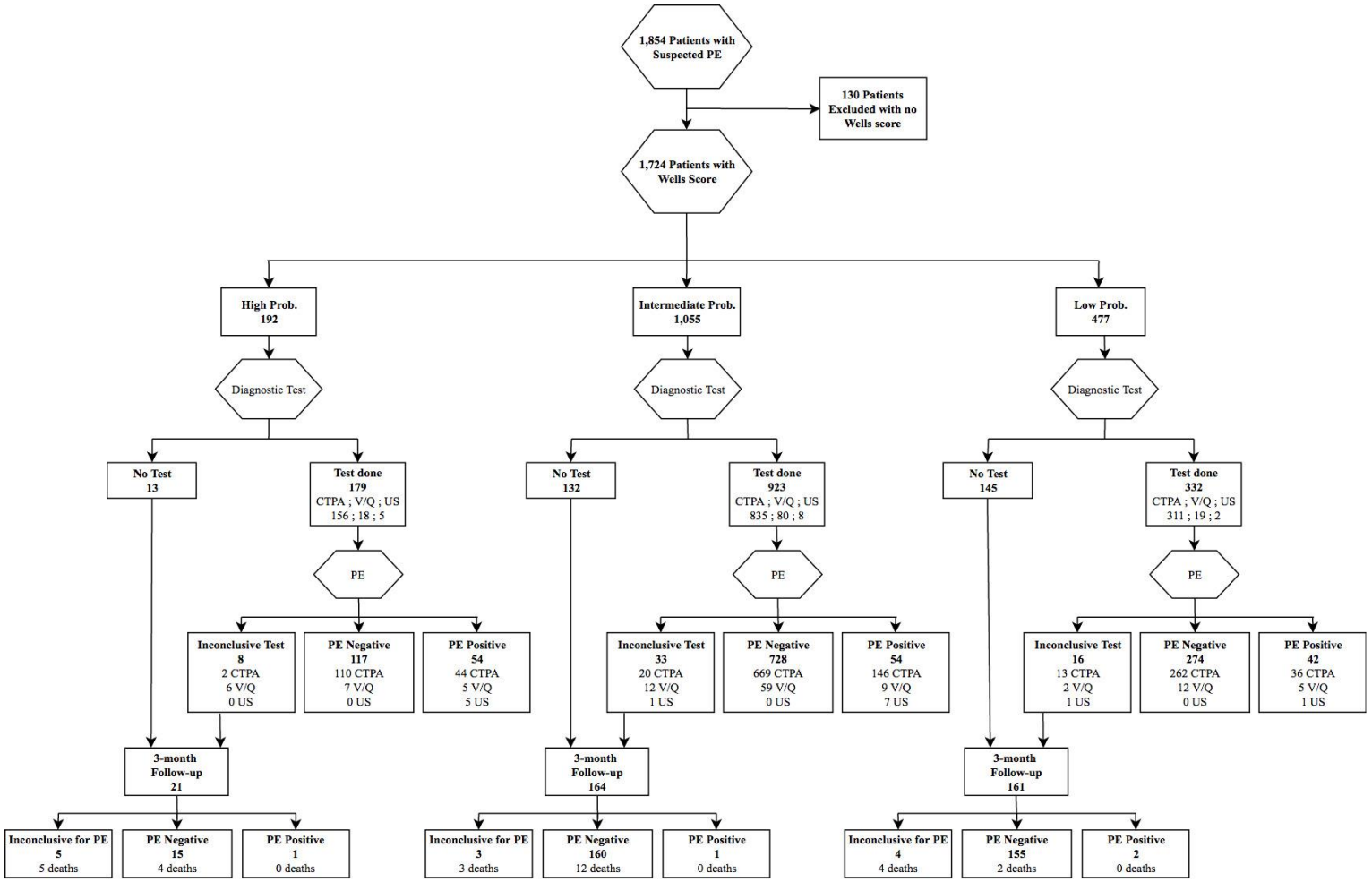


Figure 4.7 Diagnostic flow diagram of the Wells score.
Abbreviations: CTPA: computer tomography pulmonary angiography; PE: pulmonary embolism; Prob. Probability; US: ultrasound (compression); V/Q: ventilation/perfusion.

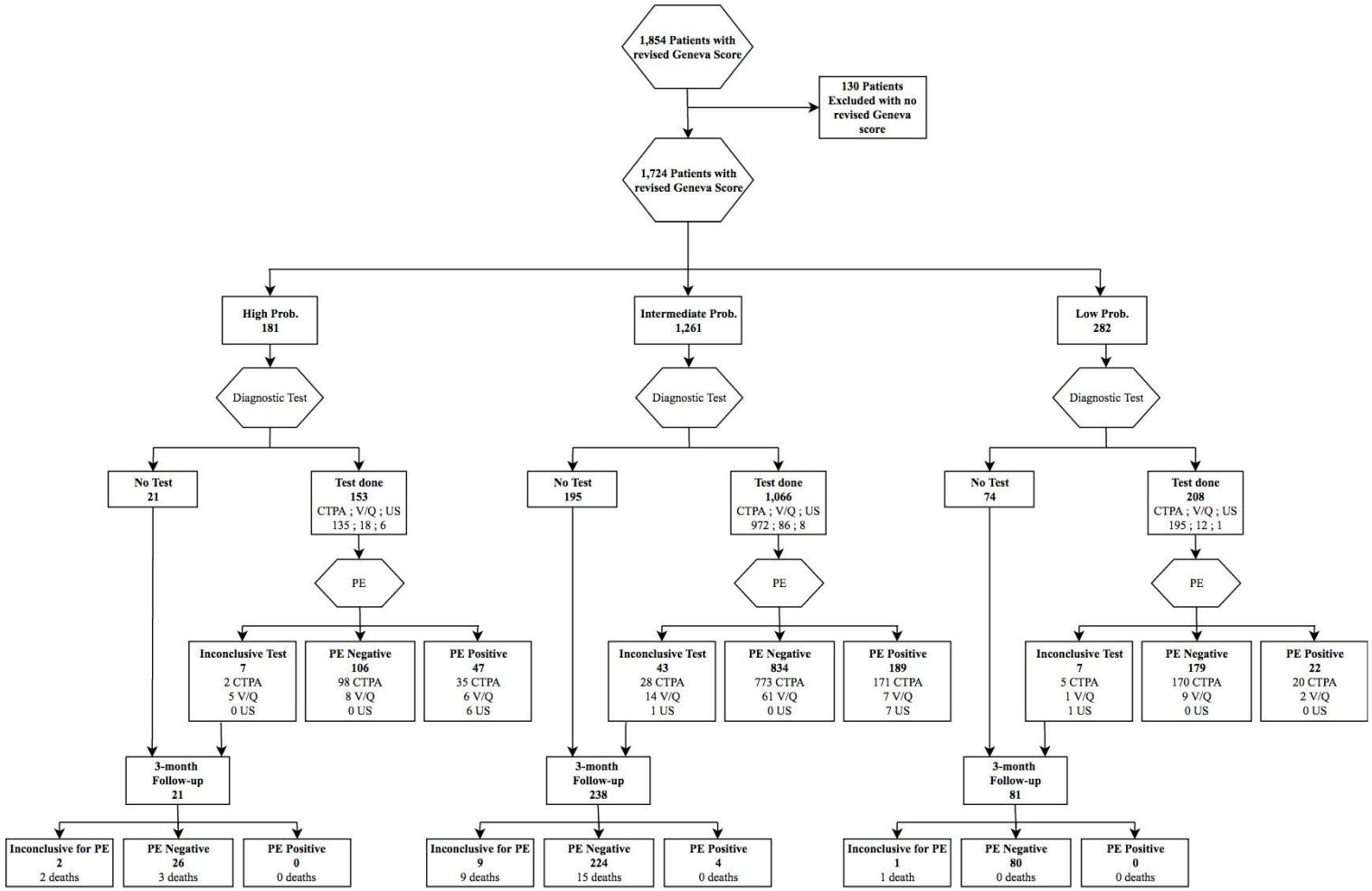


Figure 4.8 Diagnostic flow diagram of the revised Geneva score.
Abbreviations: CTPA: computer tomography pulmonary angiography; PE: pulmonary embolism; Prob. Probability; US: ultrasound (compression); V/Q: ventilation/perfusion

Table 4.6 ROC summary data for primary study analyses and applied with exclusion criteria.

CPR analysis type	Primary analysis n=1,711			Exclusion criteria applied n=1,146		
	AUC	LCI	UCI	AUC	LCI	UCI
Wells Score						
Whole	0.6048	0.56767	0.64186	0.6135	0.56822	0.65877
<24 hrs	0.6236	0.57973	0.66749	0.620	0.56737	0.67266
≥24 hrs	0.5557	0.48531	0.62613	0.5728	0.47993	0.66572
Medical ward	0.5395	0.44702	0.63197	0.4861	0.37661	0.59550
Surgical ward	0.5645	0.45442	0.67451	0.6842	0.53554	0.83288
Revised Geneva						
Whole	0.6232	0.5869	0.65956	0.6348	0.58985	0.67973
<24 hrs	0.6347	0.59119	0.67817	0.6319	0.57982	0.68405
≥24 hrs	0.5898	0.52226	0.65733	0.6266	0.53291	0.72031
Medical ward	0.5533	0.46093	0.64576	0.5548	0.42846	0.68112
Surgical ward	0.5989	0.50352	0.69425	0.6812	0.54535	0.81700

Note: <24 or ≥24 hours: Time of assessment since presenting to FMC. Abbreviations: AUC: area under the curve; CPR: clinical prediction rule; LCI: lower confidence interval; UCI: upper confidence interval. An AUC closer to 0.70 is respectable for CPR discrimination. This can be seen in surgical ward patients in both CPRs.

Table 4.7 Univariate logistic regression OR of items from the Wells, revised Geneva scores and other variables collected.

Univariate OR **Wells items**	**Wells study**	**FMC study** **Whole**	***p* value**	**<24 hrs**	***p* value**	**≥24 hrs**	***p* value**	**Medical**	***p* value**	**Surgical**	***p* value**
Clinical signs of DVT	5.1	1.99	*<0.0001*	2.21	*<0.0001*	1.45	*0.310*	1.41	*0.477*	1.47	*0.487*
Recent surgery or immobilisation	2.4	1.38	*0.018*	1.40	*0.590*	1.78	*0.076*	1.82	*0.106*	1.01	*0.993*
Heart rate >100 bpm	2.0	1.08	*0.591*	1.00	*0.980*	1.26	*0.367*	1.19	*0.611*	1.31	*0.495*
Previous DVT/PE	2.8	1.97	*<0.0001*	2.20	*<0.0001*	1.30	*0.524*	1.18	*0.776*	1.43	*0.558*
Haemoptysis	2.0	0.86	*0.620*	0.84	*0.611*	0.95	*0.937*	1.55	*0.588*	0.48	*0.494*
Malignancy	1.7	1.47	*0.015*	1.33	*0.142*	1.83	*0.032*	1.64	*0.186*	2.06	*0.090*
Alternative diagnosis less likely than PE	6.2	1.58	*0.003*	1.84	*<0.0001*	1.01	*0.956*	0.87	*0.677*	1.25	*0.570*
Revised Geneva items	**Le Gal study**	**FMC study** **Whole**	***p* value**	**<24 hrs**	***p* value**	**≥24 hrs**	***p* value**	**Medical**	***p* value**	**Surgical**	***p* value**
Age > 65 years	-	1.54	*0.001*	1.51	*0.010*	1.67	*0.059*	1.59	*0.199*	1.89	*0.128*
Previous DVT/PE	-	1.97	*<0.0001*	2.20	*<0.0001*	1.30	*0.524*	1.18	*0.776*	1.43	*0.558*
Surgery or fracture(1 month)	-	1.45	*0.018*	1.67	*0.018*	1.28	*0.330*	1.51	*0.316*	0.73	*0.494*
Active malignancy	-	1.52	*0.006*	1.30	*0.167*	2.15	*0.004*	1.78	*0.109*	2.70	*0.015*
Unilateral lower limb pain	-	1.45	*0.032*	1.77	*0.004*	0.74	*0.461*	0.76	*0.630*	0.67	*0.495*
Haemoptysis	-	0.86	*0.620*	0.84	*0.611*	0.95	*0.937*	1.55	*0.588*	0.48	*0.494*
HR 75-94	-	1.14	*0.346*	1.19	*0.275*	1.01	*0.967*	1.29	*0.448*	0.70	*0.429*
HR ≥95	-	1.06	*0.641*	1.02	*0.887*	1.17	*0.541*	0.90	*0.752*	1.74	*0.194*
Pain on lower limb/unilateral oedema	-	1.98	*<0.0001*	2.21	*<0.0001*	1.45	*0.310*	1.41	*0.477*	1.47	*0.487*
Other variables											
Dyspnoea	-	1.19	*0.230*	1.46	*0.035*	0.73	*0.237*	0.98	*0.959*	0.59	*0.179*
Chest pain	-	0.69	*0.006*	0.71	*0.035*	0.59	*0.062*	0.90	*0.751*	0.29	*0.016*
Tachycardia	-	1.13	*0.383*	1.03	*0.361*	1.38	*0.204*	0.98	*0.954*	2.17	*0.063*
Atrial fibrillation	-	0.80	*0.383*	1.03	*0.919*	0.42	*0.105*	0.65	*0.500*	0.19	*0.108*
Hypotension	-	1.56	*0.065*	1.92	*0.022*	0.98	*0.966*	1.24	*0.707*	0.67	*0.606*
Hypoxia	-	1.30	*0.054*	1.63	*0.004*	0.81	*0.410*	0.90	*0.744*	0.71	*0.375*
Hormone therapy*	-	1.03	*0.924*	1.23	*0.517*	1.00	-	1.00	-	1.00	-
Anticoagulant	-	0.80	*0.247*	0.74	*0.374*	0.77	*0.330*	0.61	*0.197*	0.92	*0.833*
Antiplatelet	-	1.04	*0.769*	1.09	*0.625*	0.94	*0.819*	0.87	*0.682*	1.17	*0.711*
NSAIDs	-	1.03	*0.812*	1.15	*0.427*	0.80	*0.434*	0.73	*0.382*	0.97	*0.951*

Note: <24 or ≥24 hours: Time of assessment since presenting to FMC. Abbreviations: bpm: beats per minute; DVT: deep vein thrombosis; > greater than; ≥ greater than and equal to; HR: heart rate; < less than; ≤ less than and equal to; NSAIDs: Nonsteroidal anti-inflammatory drugs; OR: Odds ratio; PE: Pulmonary embolism.

Table 4.8 Multivariate logistic regression OR of items from the Wells, revised Geneva scores and other variables collected.

Multivariate OR **Wells items**	**Wells study**	**FMC study** **Whole**	***p* value**	**<24 hrs**	***p* value**	**≥24 hrs**	***p* value**	**Medical**	***p* value**	**Surgical**	***p* value**
Clinical signs of DVT	5.8	1.92	*<0.0001*	2.03	*0.001*	1.59	*0.215*	1.48	*0.429*	1.94	*0.273*
Recent surgery or immobilisation	2.5	1.38	*0.020*	1.30	*0.147*	1.74	*0.092*	1.83	*0.106*	0.82	*0.810*
Heart rate >100 bpm	3.0	1.08	*0.598*	1.03	*0.873*	1.21	*0.461*	1.16	*0.660*	1.24	*0.593*
Previous DVT/PE	2.4	1.94	*<0.0001*	2.11	*<0.0001*	1.25	*0.595*	1.17	*0.794*	1.12	*0.861*
Haemoptysis	2.4	0.89	*0.708*	0.85	*0.641*	0.95	*0.938*	1.53	*0.612*	0.54	*0.570*
Malignancy	2.3	1.56	*0.006*	1.43	*0.740*	1.88	*0.027*	1.70	*0.164*	2.25	*0.075*
Alternative diagnosis less likely than PE	4.6	1.34	*0.041*	1.58	*0.010*	0.98	*0.926*	0.89	*0.743*	1.17	*0.703*
Revised Geneva items	**Le Gal study**	**FMC study** **Whole**	***p* value**	**<24 hrs**	***p* value**	**≥24 hrs**	***p* value**	**Medical**	***p* value**	**Surgical**	***p* value**
Age > 65 years	1.48	1.48	*0.005*	1.50	*0.014*	1.76	*0.044*	1.56	*0.236*	2.40	*0.054*
Previous DVT/PE	2.86	1.99	*<0.0001*	2.18	*0.308*	1.25	*0.648*	1.17	*0.790*	1.03	*0.959*
Surgery or fracture(1 month)	2.18	1.48	*0.016*	1.76	*0.272*	1.33	*0.272*	1.54	*0.304*	0.66	*0.418*
Active malignancy	1.57	1.56	*0.005*	1.37	*0.003*	2.29	*0.003*	1.90	*0.080*	3.01	*0.012*
Unilateral lower limb pain	2.64	0.94	*0.799*	1.21	*0.087*	0.42	*0.087*	0.50	*0.315*	0.29	*0.125*
Haemoptysis	2.10	0.87	*0.650*	0.87	*0.817*	0.06	*0.817*	1.27	*0.771*	0.45	*0.492*
HR 75-94	3.32	1.71	*0.031*	1.72	*0.306*	2.21	*0.306*	2.73	*0.353*	1.47	*0.736*
HR ≥95	1.95	1.65	*0.042*	1.66	*0.269*	2.31	*0.269*	2.27	*0.445*	2.33	*0.437*
Pain on lower limb/unilateral oedema	3.82	2.08	*0.002*	1.89	*0.047*	2.49	*0.047*	1.94	*0.263*	4.26	*0.066*

Note: <24 or ≥24 hours: Time of assessment since presenting to FMC. Abbreviations: bpm: beats per minute; DVT: deep vein thrombosis; > greater than; ≥ greater than and equal to; HR: heart rate; hrs: hours; < less than; ≤ less than and equal to; OR: Odds ratio; PE: Pulmonary embolism.

5 PART A - DISCUSSION

This study demonstrated that although the Wells and revised Geneva scores were well calibrated in a representative hospital population, discrimination of the scores were both substantially inferior to what would be expected based on the respective derivation studies (Le Gal et al. 2006b, Wells et al. 2000). The CPRs demonstrated particularly poor discrimination in patients assessed in medical wards.

With respect to calibration, there was a higher prevalence of PE (9.30%) in the low probability category for the Wells score in this study compared to what would be predicted (3.26%) based on the derivation study (Wells et al. 2000). A number of studies have also shown, similarly to our FMC study, a PE prevalence between 7.1% to 28% in the low probability group (Calisir et al. 2009, Chagnon et al. 2002, Gibson et al. 2008, Miniati et al. 2005, Penaloza et al. 2013, Di Marca et al. 2015, Ye et al. 2012, Guo et al. 2015, Guo et al. 2009, Luo et al. 2014, Ollenberger and Worsley 2006, Sanson et al. 2000). There was also a much lower prevalence of PE (29.41%) in the high probability category for this study when compared to the derivation study (62.92%) (Wells et al. 2000). This has been shown in a number of studies where PE prevalence for the high probability group has ranged between 26.5% to 42.9% (Kabrhel et al. 2005, Kline et al. 2006a, Runyon et al. 2005, Sanson et al. 2000, Wolf et al. 2004) including a study by Wells et al. (2001). Other larger observational studies have followed similar PE prevalence of patients into each of the three categories as the derivation study for the Wells score (Bosson et al. 2005, Kearon et al. 2006, Kline and Hogg 2006b, Yap et al. 2007).

As for the revised Geneva score, there was a significantly lower prevalence of PE (18.24%) in the intermediate probability category compared to the derivation study

(27.96%) (Le Gal et al. 2006b). Another study in patients aged ≥65 years has shown similar PE prevalence (18.0%) for the intermediate probability group to our study (Di Marca et al. 2015). There was also a much lower prevalence of PE (26.26%) in the high probability category for the FMC study cohort when compared to the derivation study (72.73%) (Le Gal et al. 2006b). Although the validation studies are limited for the revised Geneva score, this has been shown in a few studies where PE prevalence for the high probability group was between 50% to 55% (Di Marca et al. 2015, Guo et al. 2015). Other larger observational studies have followed similar PE prevalence of patients into each of the three categories as the derivation study (Klok et al. 2008a, Righini et al. 2008).

The discrimination of the Wells score in the derivation study was not conducted (Wells et al. 2000). In other large (>1,000 patients) studies, the overall performance of the Wells score ranged between 0.68 and 0.76 (Gibson et al. 2008, Ollenberger and Worsley 2006, Penaloza et al. 2013), much higher than our study (AUC 0.61, 95% CI 0.57 to 0.64). However, a retrospective study conducted at a Western Australian hospital had figures similar to our study of 0.62 (95% CI: 0.52 – 0.72) (Wong et al. 2011). This was a small study of 98 patients assessed in the ED (Wong et al. 2011).

At Flinders Medical Centre, PE risk tools are used as clinical practice in conjunction with a diagnostic algorithm that includes a D-dimer test. With the risk tools forming a large part of the diagnostic algorithm for PE, this FMC study shows these tools are being used in patients that would have been excluded in derivation studies (Le Gal et al. 2006b, Wells et al. 2000). Applying similar exclusion criteria to the derivation study (Wells et al. 2000) resulted in one third of the FMC patient cohort to be

excluded. However, even when this sensitivity analysis was performed, the AUC 0.61 (95% CI 0.57 to 0.66) did not differ from the primary analysis AUC 0.61 (95% CI 0.57 to 0.64). One study has reported low predictive performance of the Wells score with AUC of 0.53 (95% CI 0.27 to 0.80), however, this study was conducted in a small patient population (n=51) who were admitted in hospital with decompensated heart failure. These findings in the FMC study are still much lower than previously reported AUC (0.68 to 0.87) for the Wells score (Calisir et al. 2009, Chagnon et al. 2002, Di Marca et al. 2015, Gibson et al. 2008, Gruettner et al. 2015, Guo et al. 2015, Guo et al. 2009, Hogg et al. 2011, Klok et al. 2008a, Klok et al. 2008b, Miniati et al. 2008, Penaloza et al. 2011, Penaloza et al. 2013, Posadas-Martinez et al. 2014, Tsimogianni et al. 2011, Turedi et al. 2008, Ye et al. 2012).

The area under the ROC curve of the revised Geneva score in this FMC study performed much lower (AUC 0.62, 95% CI 0.59 to 0.66) than the derivation and validation cohorts study cohorts, 0.74 (95% CI 0.70 to 0.78) and 0.73 (95% CI 0.69 to 0.77), respectively (Le Gal et al. 2006b). Four studies investigating the performance of the revised Geneva score for predicting PE reported AUC figures of 0.65 to 0.73 (Calisir et al. 2009, Di Marca et al. 2015, Klok et al. 2008a, Wong et al. 2011) to the derivation study (Le Gal et al. 2006b). However, patient cohorts in these studies were small in sample, ranging from 98 outpatients (Wong et al. 2011) to a mix of 300 inpatient and outpatients (Klok et al. 2008a). Again, for the FMC study, when applying similar exclusion criteria to the derivation study, these findings (AUC 0.64, 95% CI 0.59 to 0.68) are still lower than previously reported in Le Gal et al. (2006). This reflects that variances in CPR performance could be due to differences in patient populations rather than the specific inclusion/exclusion criteria applied within studies.

Discrimination of the Wells scores in the FMC study cohort, when assessed after 24 hours (AUC 0.56, 95% CI 0.49 to 0.63), were much lower when compared to patients assessed within 24 hours (AUC 0.62, 95% CI 0.58 to 0.67). As for the revised Geneva score, discrimination was also lower for patients assessed after 24 hours (<24 hours: AUC 0.64, 95% CI 0.59 to 0.68; ≥24 hours: AUC 0.59, 95% CI 0.52 to 0.66), but not to the same extent as the Wells score (AUC difference: Wells score 0.068; revised Geneva score 0.045). These findings are not surprising as the Wells and revised Geneva scores were originally developed and attuned in ED/outpatients. After further assessing the Wells and revised Geneva scores for inpatients (assessed after 24 hours) in different hospital locations the discrimination in medical ward patients (Wells: AUC 0.54, 95% CI 0.45 to 0.63; revised Geneva: AUC 0.55, 95% CI 0.46 to 0.66) was much lower to that of patients assessed within 24 hours (ED/outpatients) and slightly lower to those of surgical ward patients (Wells: AUC 0.57, 95% CI 0.45 to 0.67; revised Geneva: AUC 0.60, 95% CI 0.50 to 0.69). Only one study has previously reported on the performance of the Wells score in different hospital locations (Ollenberger and Worsley 2006). This study showed similar performance to the FMC study with poor discrimination (AUC 0.58 ± 0.04) in the Wells score for surgical ward patients (Ollenberger and Worsley 2006). However, when comparing discrimination of medical ward patients, the FMC study showed much lower performance to Ollenberger and Worsley (2006) study cohort (AUC 0.66 ± 0.03). As for the revised Geneva score, no studies have previously reported on the performance of such CPR for different hospital locations. Inpatients in the FMC study represented almost one-third of the patient population with medical ward patients representing a substantial number in this group. Poor discrimination in hospitalised patients, particularly those from long-stay medical

wards, may be due to differences in patient characteristics when compared to ED/outpatients, with the former group likely to be older and to have significant comorbidities and high inter-individual variability in organ function. These factors may affect *per se* the interpretation of some of the PE CPRs-related items such as tachycardia, immobilisation, and cancer. A lack of studies validating current PE CPRs in different hospital locations identifies an area of research that urgently needs attention.

Of the seven items that form the Wells score, five were predictive of PE in both univariate and multivariate analyses of this study cohort. In addition, the OR values were much lower (*p* value = 0.018) when comparing these items to the derivation study (Wells et al. 2000). Further analyses of the seven Wells items showed that when patients were assessed within 24 hours, only three items were significant for PE prediction. As for patients assessed ≥24 hours only one item, malignancy was significant for PE prediction. In addition, no items of the Wells score were significant for PE in medical or surgical ward patients.

When assessing the nine items that form the revised Geneva score, six were predictive of PE in univariate analyses in this study cohort. For the multivariate analysis, seven items were predictive of PE in this study cohort. Similarly to what was observed with the Wells score, our OR values were significantly lower (*p* value = 0.015) to those observed in the derivation study (Le Gal et al. 2006b). Further analyses of the nine revised Geneva items showed that when patients were assessed within 24 hours, only five items were significant for PE prediction. As for patients assessed ≥24 hours only one item, malignancy, was significant for PE prediction in univariate analyses, however, in multivariate analysis an additional two items were

predictive for PE. As for inpatients, only malignancy was significant for predicting PE in the surgical ward patients. Therefore, the seven and nine items that were independently associated with PE in the derivation studies (Wells et al. 2000, Le Gal et al. 2006b) were not all significantly associated in our study population, especially in inpatient groups. Reasons for this may be due to random error in which the items real association is not detected or other factors confounding the associations resulted in much weaker associations of the items in the FMC study cohort. This highlights that such CPRs should not be readily used in different patient populations.

Other variables, such as clinical signs and symptoms plus types of medications, were also assessed for PE prediction. Similar to the items in both CPRs, the most number of items (four items: dyspnoea, chest pain, hypotension, and hypoxia) were predictive for PE in the patients assessed within 24 hours. Chest pain was the only variable that was independently associated with PE for the whole patient cohort and surgical ward patients. As this was an exploratory analysis, these results need to be viewed with caution. It is not possible to rule out that the other variables assessed were also associated with PE as the number of patients with clinical signs, symptoms, or medications were not large enough to significantly detect any underlying associations. This highlights that further investigation is needed in larger study cohorts with other variables that may be more predictive for PE, focussing on those which may be independently associated with PE in medical or surgical ward patients.

In this study, all patients who did not have a conclusive confirmatory test were followed up over a 3-month period. In this period, 30 patients died with 12 patients remaining inconclusive for PE as insufficient data was not available to determine

cause of death. As a result, the total study population was 1,711. This method is similar to previously reported methods using 3-month follow-up (Kline et al. 2005, Righini et al. 2014, Woller et al. 2014, van Belle et al. 2006). Even when a sensitivity analysis was conducted, where all deaths were PE related, the discrimination for both CPRs was not different from the primary analysis.

In the derivation studies of the Wells and revised Geneva scores the diagnostic test for PE differed. In the Wells' cohort, only V/Q scans were used and in conjunction with leg ultrasound (Wells et al. 2000). In the Le Gal's cohort, a 4-16 slice CTPA was used in addition to the V/Q scan (Le Gal et al. 2006b). Since then, the sensitivity of the CTPA had improved substantially, up to 256–320 slices. This might account for the higher PE prevalence in the low probability categories in the current study with detection of segmental and subsegmental PE's. However, this would also be expected to lead to a higher, rather than lower, prevalence in the high probability category.

This study also highlights that since the implementation of a step-wise approach using algorithms in 2012 for the diagnosis of PE at FMC, staff adherence to these guidelines has been high despite there being relatively minimal educational updates over the study period. This shows that introducing such practice changing guidelines can be effectively implemented at a single centre. Although PE CPRs can be easily implemented, this study raises concerns of the use of such tools if performances of PE CPRs are poor. Further studies are needed to improve these tools but additionally assess for other variables that may be better predictors for PE.

This study has several limitations. As a retrospective observational study of use of the CPRs in a representative hospital population there were associated risks of bias.

Firstly, there were 130 individuals for whom confirmatory imaging for PE was undertaken without being evaluated using the clinical prediction rules and hence were not included in the analysis. Of the 130 patients, there was no substantial difference in the prevalence of PE compared to the study cohort to suggest these patients were systematically different (17.8% vs FMC 15.3%). Additionally, a number of patients had diagnostic imaging that was reported as inconclusive for PE or were missing confirmatory imaging for PE. Secondary care follow-up information was utilized to address this issue, using similar follow-up methods in previously reported studies (Kline et al. 2005, Righini et al. 2014, Woller et al. 2014, van Belle et al. 2006), but this may still have led to some bias. However, it is unlikely that this could explain the degree of poor calibration and discrimination observed. An additional limitation is that our findings represent current practices at a single centre and may not be a true representation of other populations.

This study highlights several concerns regarding the predictive performance of CPRs, the Wells and revised Geneva scores, for use in patients suspected with PE in a hospital setting that utilizes these risk scores as part of routine clinical practice. Both PE predictive scores appear to be less discriminative than previously reported. Future research should address whether it is safe to use PE CPRs within different hospital locations as even with the limited current literature, there is some indication that performance differs in specific hospital locations. Additionally, conducting studies with much larger patient populations could potentially identify other variables that are independently associated with PE. Overall, large multicentre prospective studies of the performance of these scores in routine clinical practice are needed to confirm these findings.

Part B

CLINICAL PREDICTION RULES IN

GERIATRIC MEDICINE

6 PART B - LITERATURE REVIEW

The global population is continuously expanding and aging (WHO 2011). Fertility rates have been ever decreasing from 3.6 babies per woman in 1962 to 1.81 babies per woman in 2015 (ABS 2016). Advances in human health have also led to increased longevity (WHO 2011, ABS 2016). Life expectancy in Australia for females and males has increased from 58.8 years and 55.2 years to current life expectancy of 84.5 years and 80.4 years, respectively (ABS 2014, ABS 2017). This progressive ageing of the population imposes significant public health and financial challenges in Australia and worldwide (Begg 2014). A branch of medicine that covers older adults is known as geriatric medicine or geriatrics (from the Greek geron: old man, and iatros: medicine related) (Luchette and Yelon 2017). This population tends to suffer from unwanted consequences of acute and chronic diseases e.g. reduced quality of life, disability and loss of independence (Nepal and Brown 2013). Introduction of the Comprehensive Geriatric Assessment (CGA) into geriatric care and dedicated wards has improved the standard of care for geriatric patients (Morley 2004). The addition of screening tools being implemented alongside the CGA has furthermore contributed to improved care (Mahoney et al. 1955, Katz et al. 1963, Guigoz et al. 1996, Folstein et al. 1975). The latest trend has led to the development of clinical prediction rules (CPRs) that combine previously established tools for predicting adverse outcome in older adults. This review summarizes the available evidence of the development and limitations of prognostic indices in geriatric care and how well they can predict adverse outcomes in this patient population.

6.1 Co-mobidities and hospitalisations

Over the past 100 years there has been a shift in the leading cause of death from communicable diseases, such as influenza outbreaks, measles, and tuberculosis, to non-communicable diseases and chronic conditions, such as cardiovascular disease, stroke, diabetes, and chronic obstructive pulmonary disease (COPD) (WHO 2011). In Australia, the leading cause of death between 2011 and 2013 was coronary artery disease (CAD) (AIHW 2007). This was followed by dementia and Alzheimer's disease, which affected about 387,000 older Australians (AIHW 2007, Brown et al. 2017).

Burden of disease (BOD) is a measure of combining years of life lost due to premature mortality and years of life lost living with ill-health (disability) (AIHW 2007, WHO 2017). BOD is measured in disability-adjusted life year (DALY), where one DALY represents one year of loss of healthy life from a combination of disease severity and risk factors or premature mortality (AIHW 2007). In 2011, Australians aged 65 and over lost approximately 1.8 million DALY per 1,000 people where 37% of this was contributed by disability (AIHW 2007). The transition between an active and independent lifestyle to loss of independence in activities of daily living, and transfer into a long-term aged care facility are each characterized by a significant increase in health care-associated costs, e.g. adequate staffing (Guralnik et al. 2002). Dementia is one of the leading contributors to BOD and disability with more than 50% of aged-care residents having the disease and approximately 1.2 million people involved in the care of dementia patients in Australia (AIHW 2016).

Hospital admission numbers in Australia have risen by 3.5% each year from 2011-12 to 2015-16 (AIHW 2017). Of the total number of admissions, 41% were for people

who were aged 65 years and older (AIHW 2017). An increase in hospital admissions places a huge economic burden on the health care system where in 2013 to 2014 the average cost per hospital admission was approximately $5,000 (Authority 2016). In addition to financial limitations of the Australian health care system clinicians are ever more expected to accelerate patient turn-over, reduce length of hospital stay and readmission rate, as well as arrange appropriate post-discharge follow-up. Accurately predicting and identifying the most suitable pathways for older inpatients with multiple co-morbidities is problematic. In particular inpatients with dementia present additional challenges and often experience longer hospital stay than patients without dementia (Draper et al. 2011).

Older inpatients are also at risk of potentially devastating complications, in particular falls. Falls in this population is very common, leading to prolonged hospitalization, need for rehabilitation, hip fracture, cerebral bleeding and even death (Bradley 2013). Preventing in-hospital falls, and their associated harm, is a key National Safety and Quality Health Service Standard used for accreditation of healthcare organizations by the Australian Commission on Safety and Quality in Health Care.

6.2 Geriatric inter-variability

One of the most challenging areas of the management of older patients is a wide inter-individual variability in physiological responses (Mangoni and Jackson 2004, Hilmer et al. 2007b). This is characterised by impairment of organ function, homeostatic reserve, and treatment response (Mangoni and Jackson 2004). Many body systems are affected by aging. As we age our body composition changes from higher body water and lean mass to increased body fat (Beaufrere and Morio 2000, Fulop et al. 1985). Other changes are reduction in mass, such as in the liver and

kidneys, reduced absorption in the small intestine, reduced blood flow through organs, and reduced cardiovascular function such as reduced elasticity and compliance of the aorta and great arteries (Mangoni and Jackson 2004). Using current healthcare routine clinical management algorithms, protocols and procedures does not take into account this age variability and identifies an important area of care that should be addressed (Mangoni 2014).

6.3 Medications in geriatric patients

Older adults are poorly represented in clinical trials where they are usually conducted in patients between the ages of 18 and 64 years (Shenoy and Harugeri 2015). This identifies a major limitation of clinical trial evidence for use of such medication in older aged individuals as this group of population is likely to have a high prevalence of chronic conditions and treated with different drugs concurrently (Shenoy and Harugeri 2015). On top of this medication treatment in older adults can be complicated by age-related changes in both pharmacokinetics and pharmacodynamics as described earlier in this chapter (Mangoni and Jackson 2004, Hilmer et al. 2007b). Increased use of medications (polypharmacy defined as ≥5 medications) through high comorbidity or use of specific classes of medications in older frail adults' increases the risk of adverse drug reactions (ADRs) (Routledge et al. 2004, Brahma et al. 2013).

Approximately 2–3% of Australian hospital admissions are medication-related (Roughead and Semple 2009). This equated to approximately 190,000 medicine-related hospital admissions in Australia during 2006 to 2007 and costing an estimated $660 million (Roughead and Semple 2009). ADRs can occur due to medications interacting with other medications (drug-drug interactions), inadequate

monitoring of newer medications, inappropriate use of medication, poor patient adherence to medication, and dose-related reactions such as too much medication given (overdose) (Midlöv et al. 2009).

Increasing evidence shows that certain medications with specific pharmacological effects independently predict physical and cognitive decline and mortality in older adults (Bostock et al. 2010, Ruxton et al. 2015). A number of studies have demonstrated that exposure to medications with anticholinergic and/or sedative effects, assessed with validated scoring systems such as the Anticholinergic Risk Scale (ARS) and the Drug Burden Index (DBI), independently predicts reduced physical and cognitive function, prolonged hospital stay and mortality in older adults (Bostock et al. 2010, Hilmer et al. 2007a, Lowry et al. 2011, Lowry et al. 2012, Mangoni et al. 2013). Importantly, the total number of medications failed to show significant associations in these studies (Hilmer et al. 2007a, Lowry et al. 2011, Lowry et al. 2012, Mangoni et al. 2013).

6.3.1 Anticholinergic scoring systems

A number of anticholinergic drug scoring systems have been developed over the last decade that assesses anticholinergic and sedative drug exposure in patients (Mangoni 2011). The main anticholinergic drug scoring systems are the Anticholinergic Cognitive Burden Scale (ABS) (Boustani et al. 2008), the Anticholinergic Drug Scale (ADS) (Carnahan et al. 2006), Anticholinergic Risk Scale (ARS) Score (Rudolph et al. 2008), and the Drug Burden Index (DBI) (Hilmer et al. 2007a). Refer to Table 6.1 for anticholinergic scoring systems summary.

6.3.1.1 Anticholinergic cognitive burden scale

A systematic literature review by Boustani et al. (2008) developed the ABS of drug

with anticholinergic activity (Table 6.1). In the literature the ABS is also known by the acronym ACB scale. This scale identifies the severity of anticholinergic adverse effects on cognition of prescribed and over-the-counter medications. A team of experts classified medications identified in the literature search as absent, possible, or definite anticholinergic effects. Drugs with no anticholinergic effects are scored as a zero. Measurable serum anticholinergic activity (SAA) or the *in vitro* affinity to muscarinic receptors but with no clinically relevant negative cognitive effects identified drugs with possible anticholinergic effects which were scored as 1. A score of either 2 or 3 were assigned for drugs with recognised and clinically relevant cognitive anticholinergic effects based on the drug blood–brain barrier permeability and its association with the development of delirium. The total added score of different drugs taken by the patient determines the accumulative ABS.

6.3.1.2 Anticholinergic drug scale

The ADS is based on a three-level anticholinergic classification system of 340 medications that was published in 2001 (Han et al. 2001). In 2006, Carnahan et al. validated and renamed this clinician-rated anticholinergic scale as the ADS (Carnahan et al. 2006). The 340 medications were rated for anticholinergic activity and assigned a rank from 0 (none) to 3 (high) according to clinical experience and the pharmacologic characteristics of each medication and the available ratings for the *in vitro* anticholinergic activities of the drugs (Table 6.1). The individual scores of all the drugs taken by a patient are then summed to determine a total ADS score.

6.3.1.3 Anticholinergic risk scale

Rudolph et al. (2008) developed the ARS score based on a review of 500 drugs within the Veterans Affairs Boston Healthcare System (Table 6.1). The dissociation constant for the muscarinic receptor, rates of anticholinergic effects versus placebo

in experimental studies, and literature review on anticholinergic adverse effects was retrieved for each drug. Each drug is ranked on a scale of 0 (limited or none), 1 (moderate), 2 (strong), and 3 (very strong), according to its anticholinergic potential. An ARS score is calculated by the sum of the ARS rankings assigned for each of the prescribed drugs. Topical, ophthalmic, otologic, and inhaled medication preparations were excluded from the ARS score calculations.

6.3.1.4 Drug burden index

The DBI measures a person's total exposure to both anticholinergic and sedative medications (Hilmer et al. 2007a). Medications are characterised with respect to risk into drugs with anticholinergic effects, drugs with sedative effects, and total number of medications (Table 6.1). The DBI uses a number of calculations to determine the medication burden. The anticholinergic component of the DBI is calculated for each patient according to the burden from anticholinergic drugs and DBI for each anticholinergic drug is then calculated using the drug daily dose and the minimum recommended drug daily dose. This is used to define medications with clinically significant anticholinergic effects. Complementary and topical medications were excluded from DBI calculations.

Table 6.1 Summary of anticholinergic drug scoring systems

Method	Year	Basis	Rating scale	Calculation
Anticholinergic Cognitive Burden Scale (ABS)	2008	Expert-based; severity of drug's AC activity on cognition using a scale based on the literature between 1966 and 2007	0 - 3	Sum of all drug scores
Anticholinergic Drug Scale (ADS)	2006	SAA	0 - 3	Sum of all drug scores
Anticholinergic Risk Scale (ARS)	2008	Expert-based; dissociation constant for cholinergic receptors, evidence-based review of all FDA prescribed medication, and AC adverse effects in literature	0 - 3	Sum of all drug scores
Drug Burden Index (DBI)	2007	FDA approved doses	N/A	([Sum of daily doses]/[sum of daily doses + minimum efficacious daily doses])

Abbreviations: AC anticholinergic; FDA food and drug administration; N/A not available; SAA serum anticholinergic activity. Adapted from: (Karimi et al. 2012).

6.4 Comprehensive Geriatric Assessment (CGA)

Modern geriatric medicine was introduced by Dr Marjory Warren who published a paper in 1943 on "Care of the Chronic Sick" (Warren 1943). Warren advocated for practicing geriatrics as a specialist and described the benefits of geriatric care to the hospital system as,

> *"for the proper care of the chronic sick the full facilities of a general hospital are necessary, both for the establishment of a correct diagnosis and for treatment (Warren 1943).*

This included that older patients required more individualised approach in assessing their current state along with any treatment needs, improving the hospital environment to suit patient care, and to rehabilitate such patients to allow them to return home. This was the starting point for what would be known as the comprehensive geriatric assessment (CGA).

6.4.1 What is a CGA

The CGA is widely used across many countries, including Australia, and is a fundamental component of geriatric medicine. The CGA is an individual assessment of a geriatric patient on their medical, psychosocial, functional, social and environmental capacities to aid in a coordinated and integrated treatment plan for maximal health (Ellis and Langhorne 2005, Stuck et al. 1993, Rubenstein 1995). A multidisciplinary team involving physiotherapists, occupational therapists, social workers, nursing staff and geriatricians are involved in the assessment of geriatric patients.

6.5 Components of CGA

The CGA is used to systematically assess frail older patients. Not every older patient will receive a CGA as patients deemed too well or too sick are usually excluded from this assessment, since they are unlikely to benefit from a CGA (Rubenstein 1995). Patients who are transitioning in their living situation, have recent cognitive or physical impairment, or require specialty care would benefit from a CGA (Rubenstein 1995). CGA includes five main components: medical, functional, psychological, social and environmental assessments (Rubenstein 1995). In this review social and environmental assessments are discussed together.

6.5.1 Medical assessment

The medical assessment component is primarily collecting information from the patient and/or care giver and use of past medical notes (Forciea et al. 2004, Ward and Reuben 2013). Table 6.2 lists the information collected.

Table 6.2 Categories of medical assessment collected

Category	Information collected
Demographic data	Full name Age, sex and DOB Marital status Source of history and reliability of historian
Chief complaint	Primary reason for visit Duration of presenting symptoms
Present illness	Chronological narrative of reasons for patient visit. Persistence, change, severity, character, resolution and disabling effects of initial symptoms Presence of new symptoms and/or associated symptoms History of similar symptoms in the past Aggravating and mitigating factors
Past medical history	Previous medical history General state of health Childhood diseases Immunizations Adult medical diseases, injuries and operations Hospitalizations Allergies, including clinical description of exposure Medications, including dosage, duration and indication Diet/Nutrition
Social history	Birthplace and residences Level of education Ethnicity and race Quality of significant relationships and health of partner Occupation, including type of industry, past and present exposures, duration of employment and retirement Hobbies and other interests Habits, including quality of sleep, exercise, recreation, consumption of alcohol and other drugs (including route of administration, if applicable), tobacco use (in pack/yrs), alcohol use, and travel abroad
Family history	Presence of disease with immediate family members i.e. Type 2 diabetes, cancer, osteoporosis, dementia Similar presenting symptoms in family members.
Review of systems	Visual, auditory, cardiovascular, pulmonary, gastrointestinal, genitourinary, musculoskeletal, neurologic/psychiatric, extremities, weight change Physical examination of patient

Abbreviations: DOB: Date of birth; Yrs: Years.

6.5.1.1 Nutrition

Older adults are vulnerable to malnutrition by three main factors: physical/biomedical, psychosocial, and environmental/economic influences (Starr et al. 2015, Leslie and Hankey 2015, Ahmed and Haboubi 2010). Physical and biomedical factors can include age-related decline where they are more vulnerable to adverse health outcomes, obesity due to increased consumption of nutrient poor foods and lack of physical activity, oral health which could be due to limited

dentition or poorly fitted dentures, or the use of different mediations that could reduce a person's appetite (Starr et al. 2015, Leslie and Hankey 2015, Ahmed and Haboubi 2010). Psychosocial factors include mental health where depressive disorders can reduce appetite, cognitive impairment where a person may forget to eat (i.e. dementia), or social isolation and loneliness (Starr et al. 2015, Leslie and Hankey 2015, Ahmed and Haboubi 2010). Environmental and economic factors such as lack of finances, access to food, limitations in food preparation, or lack of transportation can also increase nutritional vulnerability in older adults (Starr et al. 2015, Ahmed and Haboubi 2010).

A number of screening tools have been developed to assess nutritional risk in older adults (Green and Watson 2006, Young et al. 2013). The most common malnutrition screening tools are the Malnutrition Screening Tool (MST; (Ferguson et al. 1999)), Mini-Nutritional Assessment (MNA; (Guigoz 1994)) and shorter version Mini-Nutritional Assessment-Short Form (MNA-SF; (Rubenstein et al. 2001)), Malnutrition Universal Screening Tool (MUST; (Todorovic et al. 2003)), Nutritional Risk Screening (NRS; (Kondrup et al. 2003)), and Subjective Global Assessment (SGA; (Guaitoli et al. 2014)). All tools differ slightly by the number and different risk factors for malnutrition (Green and Watson 2006, Young et al. 2013). Common parameters used in such tools are anthropometric measurements (weight, weight change, BMI), biochemical measures (albumin, cholesterol), dietary intake (overall, specific components, fluid intake, food intake (general appetite), eating problems (self-feeding, cutting food), oral condition (dysphagia), access to food (stores, food preparation), general clinical condition and disease (specific medical conditions i.e. anaemia), medications (polypharmacy), and gut function (Green and Watson 2006).

Of these tools the MNA, MNA-SF, and MUST are commonly used in Australian healthcare (Flanagan et al. 2012). Table 6.3 summarises these three tools. The MNA and MNA-SF have been used in community, and residential aged-care settings, however, validation of such tools in acute care setting are lacking (Young et al. 2013). As for MUST it has been validated in community and aged care settings (Boléo-Tomé et al. 2012).

Table 6.3 Categories of medical assessment collected

Screening tool	Parameters	Score category	Advantages	Disadvantages
MNA	BMI, acute disease, mobility, dementia, depression, weight change, recent intake (food and fluid), MAC, CC	<17 – malnourished 17-23.5 – At risk 24-30 - Normal	Validated in aged care, and community, uses a screening section and full assessment	Takes time to fill out, difficult to obtain anthropometric data, no full action plan
MNA-SF	BMI, acute disease, mobility, dementia, depression, weight change, CC	<8 – malnourished 8-11 – At risk 12-14 - Normal	Validated in aged care, and community, short time to perform, basic action plan	Difficult to obtain anthropometric data
MUST	Weight change, recent intake (food)/acute disease, BMI	<17 – High risk 17-23.5 – Mod. risk 24-30 - Low risk	Validated in community and acute care, short time to perform, basic action plan	Difficult to obtain anthropometric data, does not use recommended BMI of 22-27

Abbreviations: BMI: Body mass index; CC: calf circumference; <: Less than; MAC: mid-arm circumference; MNA: Mini-Nutritional Assessment; MNA-SF: Mini-Nutritional Assessment-Short Form; Mod.: Moderate; MUST: Malnutrition Universal Screening Tool.

6.5.2 Functional assessment

Functional assessment identifies the ability of a person to perform physical activities that would occur in daily living (Rubenstein 1995). Assessment of physical function is often initiated by assessing activities of daily living (ADL), instrumental activities of daily living (IADL), and mobility (Rubenstein 1995, Elsawy and Higgins 2011).

6.5.2.1 ADL

The ADL refer to essential skills that are needed to manage basic physical activities in personal hygiene, toileting/continence, dressing, transfer/ambulating, and feeding (Rubenstein 1995, Katz et al. 1963, Collin et al. 1988, Mlinac and Feng 2016, Mahoney and Barthel 1965). In early life these fundamental skills are learned and entrenched which are preserved if there is a decline in cognitive function compared to higher functioning skills (Mlinac and Feng 2016, Cahn-Weiner et al. 2007). Two commonly used ADL tools are the Katz Index of Independence ADL (Katz et al. 1963) and the Barthel Index (Collin et al. 1988, Mahoney and Barthel 1965). Deficits in these scores are an indicator that a more comprehensive evaluation is needed. Both tools require a short amount of time to complete with any staff member able to conduct the assessment (Table 6.4).

Table 6.4 Comparison of common ADL tools

Screening tool	Parameters	Score category	Advantages	Disadvantages
Katz ADL	Bathing, dressing, toileting, transfer, continence, feeding	Out of 6: 6 – independent 0 – very dependent	Easy to assess, short time to perform	Insensitive to small changes in rehabilitation
Barthel Index	Bowels, bladder, grooming, toileting, feeding, transfer, mobility, dressing, stair, bathing	Out of 20: High scores – independent Low scores – fully dependent	Easy to assess, short time to perform, used by any staff	Lack of consensus of score cut-offs for categorisation, insensitive to small changes

Abbreviations: ADL: Activities of daily living.

6.5.2.2 IADL

IADL differs slightly from ADL as this refers to complex physical activities that are linked to independence at home such as using a telephone, household chores, food preparation, shopping, use of transportation, and ability to manage medications and finances (Mlinac and Feng 2016). These complex skills are more likely to be influenced by a decline in cognitive function such as early stages of dementia or

states of mild cognitive impairment (Mlinac and Feng 2016, Cahn-Weiner et al. 2007). Some commonly known IADL is the Lawton IADL (Lawton and Brody 1970), Nottingham Extended ADL (Nouri and Lincoln 1987), and Frenchay Activities Index (FAI; (Holbrook and Skilbeck 1983)). Refer to Table 6.5 for summary of IADL tools.

Table 6.5 Comparison of common IADL tools

Screening tool	Parameters	Score category	Advantages	Disadvantages
Lawton IADL	Telephone, household cleaning, food preparation, shopping, transportation medications, finances	Out of 8: 8 – independent 0 – very dependent	Easy to assess, short time to perform, sensitive to small changes	Not to be used in institutionalised patients, use of self-reporting if used
Nottingham extended ADL	Mobility, transportation, food preparation, shopping, household cleaning, finances, medications, communication	Out of 22: High scores – independent Low scores – fully dependent	Easy to assess, short time to perform, used by any staff	Use of self-reporting, no guidelines for assigning scores
FAI	Food preparation, shopping, household cleaning, mobility, transportation, reading, work	Out of 60: Assessed at prior 3 months and 6 months High scores – independent Low scores – dependent	Easy to assess, short time to perform, no training required	Requires a proxy, primarily used for stroke patients, gender bias due to higher scores for outdoor activities in men and domestic duties in women

Abbreviations: ADL: Activities of daily living IADL: Instrumental activities of daily living; I-IRR: Inter-rater reliability; FAI: Frenchay activities Index.

6.5.2.3 Mobility

Gait and balance disorders are common in older adults (Salzman 2010). Such disorders increase the likelihood of a fall occurring leading to a loss of independence and quality of life (Pirker and Katzenschlager 2017). Assessing mobility can be done by using a number of different tools. Table 6.6 summarises the differences between some known tools for gait and balance. The Berg Balance Scale (BBS; (Berg et al.

1989)) and Fullerton Advanced Balance Scale (FABS; (Rose et al. 2006)) are two tools that can be used to assess balance while the Performance-Orientated Mobility Assessment (POMA; (Tinetti 1986, Tinetti and Ginter 1988)) and Timed Get Up and Go (Mathias et al. 1986, Podsiadlo and Richardson 1991) tests assess a combination of balance and gait. All of these tools have a high inter-rater reliability (Middleton and Fritz 2013, Steffen et al. 2002, Klein et al. 2011). Two tools, BBS and Timed Get Up and Go, had poor sensitivity where falls were identified in 53% and 44% (Middleton and Fritz 2013, Barry et al. 2014) compared to FABS 85% and POMA 93, respectively (Middleton and Fritz 2013, Jeon and Kim 2017). In contrast, BBS and Timed Get Up and Go had higher specificity of 96% and 71% (Middleton and Fritz 2013, Barry et al. 2014) compared to FABS 65% and POMA 11%, respectively (Middleton and Fritz 2013, Jeon and Kim 2017).

Table 6.6 Comparison of common gait and balance tools

Screening tool	Assessing	Description	Advantages	Disadvantages
BBS	Functional balance	14 item scale with variations: sit to stand vice versa, standing with eye open and shut or on one foot, retrieving objects, turning. Out of 56: <45 – balance impairment	Static and dynamic assessment of balance, used by any staff, I-RR 98%, specificity 96%	Takes time to conduct test, not suitable for active older adults due to simplicity of tasks, sensitivity 53%
FABS	Functional balance	10 item scale with variations: standing with eye open and shut or on one foot, retrieving objects, turning, moving over obstacles, tandem walking, jumping Out of 40: >25-40 – low fall risk ≤25 – high fall risk	Suitable for active older adults due to advanced level of tasks, used by any staff, I-RR 95%, sensitivity 85%	Takes time to conduct test, specificity 65%
POMA	Balance and gait	16 item scale with variations: sit to stand vice versa, standing with eye open and shut or on one foot, retrieving objects, turning, walking distance with gait assessed. Out of 28: 25-28 – low fall risk 19-24 – medium fall risk <19 – high fall risk	Different parts of balance and gait assessed, used by any staff, I-RR 85%, sensitivity 93%	Takes time to conduct test, may not be sensitive to changes in balance, specificity 11%
Timed Get Up and Go	Balance and gait	Stand up from chair, walk 3 meters, turn around, walk back to the chair and sit. 10 s- Normal >10-20 s – Normal frail older adult/disabled >20 s – functional impairment	Easy to assess, short time to perform, used by any staff, sensitive to change over time, I-RR 98%, specificity 71%	Difficult to use in cognitive impaired adults, not a comprehensive assessment of balance, sensitivity 44%

Abbreviations: BBS: Berg Balance Scale; FAB: Fullerton Advanced Balance Scale; I-IRR: Inter-rater reliability; POMA: Performance-Orientated Mobility Assessment; s: seconds.

6.5.3 Psychological assessment

Older adults are more susceptible to suffer from cognitive impairment, delirium, dementia and depressive disorders (Ward and Reuben 2013). The psychological assessment contains two parts: cognitive and mood (Ward and Reuben 2013).

6.5.3.1 Cognitive assessment

Assessing cognition involves the examination of higher cortical functions of perception, attention/concentration, orientation, language, functions of planning and praxis (practice) (Young et al. 2011). Dementia is related to several adverse outcomes such as poor physical function, longer periods of stay in hospitals, institutionalisation and greater home care needs (Zekry et al. 2009, Fong et al. 2012). There are a number of cognitive tools available summarised in Table 6.7. Commonly used tools in Australia are the Abbreviated Mental Test (AMT; (Hodkinson 1972)), clock drawing test (Brodaty and Moore 1997), Mini mental state examination (MMSE; (Folstein et al. 1975)), Montreal Cognitive Assessment (MoCA; (Nasreddine et al. 2005)), and Rowland Universal Dementia Assessment Scale (RUDAS; (Storey et al. 2004)). Other tools are the General Practitioner assessment of Cognition (GPCOG; (Brodaty et al. 2002)), Mini-Cognition (Mini-Cog; (Borson et al. 2000)), and Short Portable Mental Status Questionnaire (SPMSQ; (Pfeiffer 1975)). All of these tools have reasonable to excellent specificity and sensitivity (Storey et al. 2004, Sheehan 2012, Malhotra et al. 2013).

Table 6.7 Comparison of common cognitive assessment tools

Screening tool	Description	Score category	Advantages	Disadvantages
AMT	10 items: age, time, address recall, year, place, recognition, DOB, dates of war, present prime minister, countdown from 20	Out of 10: <8 – Cog. Imp.	Short time to perform, simple, used by any staff, specificity 84%, sensitivity 81%	Cannot reliably identify delirium, life event of war to recall isn't as significant in present time, hard to assess in language barrier patients, culturally specific test
Clock drawing	1 item: draw a clock face with hands to represent a specific time	Many versions of scoring Out of 10: <6 Cog. Imp.	Short time to perform, used by any staff, specificity 96%, sensitivity 86%	Poor at distinguishing types of dementia, other conditions such as stroke can affect assessment
GPCOG	Step 1: clock drawing, date, remembering recent event, address recall Step 2: comparison from 5-10 years ago on remembering recent things, recall conversations, difficulty in using right words, managing finances and medications, assistance with transportation	For step 1 out of 9 >8 no further testing 5-8 proceed with step 2 <5 Cog. Imp.	Short time to perform step 1, used by any staff, multicultural specificity 83%, sensitivity 82%	Takes time to conduct for intermediate patients, limited to use in primary care, conditions such as stroke can affect assessment
Mini-Cog	2 items: memory recall, clock drawing	Out of 5: <3 higher likelihood of dementia	Short time to perform step 1, used by any staff, multicultural specificity 89%, sensitivity 76%	Cannot rule out Cog. Imp. with scores above 2, conditions such as stroke can affect assessment
MMSE	11 items: year, season, day, month, place, identify objects with recall, countdown from 100 by 7 or spell backwards, repeat phrases, instructions, writing, drawing shapes	Out of 30: 25-30 – normal 21-24 – mild Cog. Imp. 10-20 – moderate Cog. Imp. <10 severe Cog. Imp.	Used by any staff, can be used for monitoring Cog. Imp. progress, specificity 95%, sensitivity 79%	Takes longer to conduct, insensitive to subtle Cog. Imp., hard to assess in language barrier patients, culturally specific test
MoCA	11 items: drawing and clock drawing, naming objects, recall, instructions, language, abstraction, date, month, year, day, place, city	Out of 30: 27-30 – normal <26 - Cog. Imp.	Used by any staff, sensitive to subtle Cog. Imp. changes, specificity 95%, sensitivity 79%	Takes longer to conduct, hard to assess in language barrier patients, culturally specific test

Screening tool	Description	Score category	Advantages	Disadvantages
RUDAS	6 items: item recall, identification of body parts, instruction of movement, drawing of shape, judgement, listing items	Out of 30: <23 Cog. Imp.	Short time to perform, used by any staff, multicultural specificity 98%, sensitivity 89%	Hard to assess in language barrier patients
SPMSQ	10 items: date, day of week, place, address, age, DOB, present and past prime minister, mother's maiden name, countdown from 20 by 3	Out of 10: <8 – Cog. Imp.	Short time to perform, used by any staff, specificity 75%, sensitivity 78%	Hard to assess in language barrier patients, culturally specific test, insensitive to subtle Cog. Imp.

Abbreviations: AMT: Abbreviated Mental Test; Cog. Imp.: Cognitive impairment; GPCOG: General Practitioner assessment of Cognition; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; RUDAS: Rowland Universal Dementia Assessment Scale; SPMSQ: Short Portable Mental Status Questionnaire.

6.5.3.2 Mood assessment

Mood disorders are frequent in older adults with associations to negative outcomes related to comorbidities, cognitive impairment, increased suicide risk and mortality (Trevisan 2015, Valiengo et al. 2016). Depression is the most common form of mood disorder, however, late life depression still remains underdiagnosed (Ward and Reuben 2013, Trevisan 2015). Some known mood assessment tools are the Geriatric Depression Scale (GDS; (Yesavage et al. 1982)), Centre for Epidemiology Studies Depression scale (CES-D; (Radloff 1977)), Hamilton Rating Scale for Depression (HRSD; (Hamilton 1960)), Geriatric Anxiety Inventory (GAI; (Pachana et al. 2007)), and Geriatric Anxiety Scale (GAS; (Segal et al. 2010)), Patient Health Questionnaire 2 (PHQ2; (Whooley et al. 1997, Kroenke et al. 2003)) (refer to Table 6.8). All tools for assessing depression had good to excellent specificity (Yesavage et al. 1982, Blank et al. 2004, Strik et al. 2001, Kroenke et al. 2003, Gerolimatos et al. 2013, Gould et al. 2014). Sensitivity was poor for the GAS with 60% of patients correctly classified with depression (Gould et al. 2014) while other tools had higher sensitivity ranging from 75% to 92% (Yesavage et al. 1982, Blank et al. 2004, Strik et al. 2001,

Kroenke et al. 2003, Gerolimatos et al. 2013).

Table 6.8 Comparison of common mood assessment tools.

Screening tool	Assessing	Score category	Advantages	Disadvantages
GDS	Depression – 30 questions	Out of 30: 0-9 – normal 10-19 mild depression 20-30; severe depression	Short time to perform, specificity 89%, sensitivity 92%	Not assess suicidality, not suitable for moderate and severe dementia patients
CES-D	Depression – 20 questions	Out of 60: Higher scores - depression	Short time to perform, specificity 76%, sensitivity 75%	Not suitable for assessing changes in severity of depression
HRSD	Depression – 21 questions	Out of 50: 0-7 – normal 8-13 - mild depression 14-18 moderate depression 19-22 severe depression ≥23 very severe depression	Measure severity and change of depression, specificity 92%, sensitivity 86%	Takes time to perform, need trained clinician
PHQ2	Depression – 2 questions	Out of 6: <4 depression	Short time to perform, for major depression specificity 92%, sensitivity 83%	Only a screening tool not for monitoring or diagnosis
GAI	Anxiety – 20 questions	Out of 20: Higher scores – anxiety symptoms	Short time to perform, used by any staff, specificity 84%, sensitivity 75%	Assesses only anxiety symptoms in general
GAS	Anxiety – 30 questions	Out of 25: Higher scores - anxiety	Wide range of anxiety symptoms, specificity 75%, sensitivity 60%	Need trained clinician for unassessed questions

Abbreviations: CES-D: Centre for Epidemiology Studies Depression scale; GAI: Geriatric Anxiety Inventory; GAS: Geriatric Anxiety Scale; GDS: Geriatric Depression Scale; HRSD: Hamilton Rating Scale for Depression PHQ2: Patient Health Questionnaire 2.

6.5.4 Social and environmental assessment

Social assessment includes using the information collected from the social history in the medical assessment component and expanding on whether the geriatric patient is capable of living at home with or without any support or needs placement in an institution (Rubenstein 1995). Identifying any problems in social support can assist

in the planning and development of referrals to appropriate resources i.e. home care packages depending on the level of care required (2017). Another important part is to screen any caregivers for symptoms of depression or burnout and refer them to appropriate counselling or support groups (Rubenstein 1995). Understanding the financial situation of an older adult is important to assess as they may qualify for government or community support services depending on their income (Rubenstein 1995).

Environmental assessment looks at an older adult's home situation and access to transport (Martin 2010). Social workers can assess if the patient requires any support at home such as modifications to the home (i.e. hand rails or ramps) or can set up access transport for shopping or appointments in the community (2017). Clinicians may also evaluate if a patient is able to retain their drivers licence. This is another important factor to consider support if the patient requires community transport.

6.6 Benefits of CGA

The use of CGA in older patients has shown good evidence in improving better clinical outcomes. A meta-analysis, which included randomised control trials (RCT) of geriatric inpatient rehabilitation, showed that patient who had undergone a CGA had improved functional status (OR 1.75, 95% CI 1.31 to 2.35), reduced admission to nursing homes (RR 0.64, 95% CI 0.51 to 0.81) and reduced mortality (RR 0.72, 95% CI 0.55 to 0.95) (Bachmann et al. 2010). In another meta-analysis, patients who received a CGA were more likely to return to their own home (OR 1.16, 95% CI 1.05 to 1.28) and less likely to live in aged care facilities (OR 0.78, 95% CI 0.69 to 0.88) (Ellis et al. 2011). This meta-analysis included RCT where older patients were admitted as an emergency (Ellis et al. 2011). A recent meta-analysis of RCT on

geriatric patients who were admitted for a surgical emergency showed that patient who had undergone a CGA had a reduced loss of function (RR 0.92, 95% CI 0.88 to 0.97), reduced 1-year mortality (RR 0.76, 95% CI 0.65 to 0.88), and reduced length of stay (mean difference -1.17, 95% CI -1.63 to -0.88) (Eamer et al. 2017). All the studies included in the meta-analyses compared patients with or without a CGA. A limitation of using the CGA is that this method does not provide an objective, consistent and quantifiable method for risk prediction and patient stratification. Using a quantifiable method would allow a more effective and improved management in this vulnerable patient population.

6.7 CGA based tools for geriatric patients

A number of tools have been developed based on the CGA while other tools use partial information from the CGA. In this review, comprehensive tools for geriatric assessment will be discussed. Four comprehensive tools based on the CGA are the Frailty Index based on CGA (FI-CGA; (Jones et al. 2005)), Multidimensional Frailty Score (MFS; (Kim et al. 2014)), Multidimensional Prognostic Index (MPI; (Pilotto et al. 2008)), and Reported Edmonton Frail Scale (REFS; (Hilmer et al. 2009)). Table 6.9 summarises characteristics of these tools.

Table 6.9 Comparison of common CGA based geriatric tools.

Tool	No. of domains	Components	Score breakdown	Score category
FI-CGA	12	Cognition (MMSE), emotion (GDS), communication (speech, hearing, vision), mobility (timed get up and go), balance (FR or falls), bladder and bowel continence, nutrition (weight change), ADL, cohabitation status, CIRS	Each impairment index domain (n=10) has a score out of 0, 0.5, or 1. CIRS – out of 4 Total score is impairment domain plus CIRS score divided by 14	<7 - mild risk 7-13 - moderate risk >13 - high risk
MFS	9	Malignant disease, CCI, albumin levels, ADL, IADL, cognition (MMSE), delirium (Nu-DESC), MNA, MAC	Each domain has a score out of 0, 1, or 2 (if applicable) Total score - 15	≤5 - low risk >5 - high risk
MPI	8	Cohabitation status, medication (total), ADL, IADL, SPMSQ, ESS, CIRS, MNA	Each domain has a score out of 0, 0.5, or 1. Total score divided by 8 Total score - 1	0.0-0.33 - mild risk 0.34-0.66 - moderate risk 0.67-1.0 - high risk
REFS	9	Cognition (clock drawing), general health status, IADL, social support, medication use, nutrition (weight change), mood, continence, self-reported performance	Each domain has a score out of 0, 1, or 2 (if applicable) Total score - 18	0-5 - not frail 6-7 - apparently vulnerable 8-9 – mildly frail 10-11 – moderate frailty 12-18 – severe frailty

Abbreviations: ADL: Activities of Daily Living; CCI: Charlson Comorbidity Index; CIRS: Cumulative Illness Rating Scale; ESS: Exton-Smith Scale; FI-CGA: Frailty Index based on Comprehensive Geriatric Assessment; FR: Functional Reach; GDS: Geriatric Depression Scale; MAC: Mid-Arm Circumference; MFS: Multidimensional Frailty Score; MMSE: Mini mental state examination; MNA: Mini Nutritional Assessment; MPI: Multidimensional Prognostic Index; Nu-DESC: Nursing Delirium Screening Scale; REFS: Reported Edmonton Frail Scale; SPMSQ: Short Portable Mental Status Questionnaire.

Three of the tools were developed to assess clinical outcomes, either short- or long-term outcomes (Jones et al. 2005, Kim et al. 2014, Pilotto et al. 2008). The MFS show good predictive ability for 1-year mortality (AUC 0.82, 95% CI: not reported), post-operative complications (AUC 0.73, 95% CI: not reported), and patients being admitted to nursing home (AUC 0.77, 95% CI: not reported) (Kim et al. 2014). However, in a fully adjusted multiple logistic regression model the MFS failed to predict post-operative complications (OR 1.17, 95% CI 0.92 to 1.49; *p* value = 0.210) (Kim et al. 2014). For the FI-CGA, patients with higher scores of frailty were

associated with higher risk of 1-year all-cause mortality (HR 1.23, 95% CI 1.18 to 1.29) and being institutionalised (HR 1.20, 95% CI 1.10 to 1.32) (Kim et al. 2014). As for the MPI, good predictive ability was shown for 6-month (AUC 0.75, 95% CI: 0.70 to 0.80) and 1-year mortality (AUC 0.75, 95% CI: 0.71 to 0.80) (Pilotto et al. 2008). Predictive outcomes for the REFS were not reported as the study focused on validating the REFS against the Geriatrician's Clinical Impression of Frailty (GCIF) tool (Hilmer et al. 2009). For the remaining of the review, emphasis will be on the development, validation, and limitations of CGA based tool, the MPI.

6.8 Multidimensional Prognostic Index

The recently developed Multidimensional Prognostic Index (MPI) (Pilotto et al. (2008) is a quantifiable CGA-based tool, used to estimate short- and medium-term adverse outcomes in older patients. The MPI index score of between 0 and 1 is based on averaging the scores obtained from the eight cores of the CGA domains (refer to Table 6.10). The eight domains are ADL, IADL, SPMSQ, MNA, ESS, CIRS, total number of medications, and social support network (co-habitation status). Each domain is separated three ways where 0 is given for no problems, 0.5 for minor problems, and 1 for major problems. This was based on conventional cut-offs reported in the literature or by observing the frequency distribution identify points of separation for co-morbidities or number of medications. The overall MPI score is calculated by dividing the sum of each score of the eight CGA domains. Patients are then stratified into low (MPI $\leq$0.33), medium (MPI 0.33-0.66) and high (MPI >0.66) risk. The MPI can be completed in 20 to 30 minutes however this depends on the state of the patient at the time of assessment.

Table 6.10 MPI score assigned to each domain based on severity and calculation of the total MPI

Assessment score	Tripartite score		
	No (value = 0)	Minor (value = 0.5)	Major (value = 1)
ADL	6-5	4-3	2-0
IADL	8-6	5-4	3-0
SPMSQ	0-3	4-7	8-10
CIRS	0	1-2	≥3
MNA	≥24	17-23.5	<17
ESS	16-20	10-15	5-9
Medications	0-3	4-6	≥7
Social support	Living with family	Institutionalized	Living alone
	Total MPI score: (sum of tripartite scores assigned to each domain/8)		
MPI risk categories	**Mild risk**	**Moderate risk**	**Severe risk**
Range	0 to 0.33	0.34 to 0.66	0.67 to 1.0
MPI Example:	**MPI domains**	**Domain score**	**Tripartite score**
	ADL score	4	0.5
	IADL score	5	0.5
	SPMSQ score	2	0
	CIRS score	4	1
	MNA score	23	0.5
	ESS score	17	0
	Medication	4	0.5
	Social support	Living with family	0.5
	Total score		**3.5/8 = 0.438 Moderate risk**

Abbreviations: ADL: Activities of daily living; CIRS: Cumulative index rating scale; ESS: Exton-Smith Scale; IADL: Instrumental activities of daily living; SPMSQ: Short portable mental status questionnaire; MNA: Mini nutritional assessment; MPI: Multidimensional prognostic index.

6.8.1 Derivation of MPI

The MPI was derived from a prospective cohort from a single centre that included patients aged 65 years and older admitted to a Geriatric Unit for acute disease or relapse of a chronic disease (Pilotto et al. 2008). A cluster analysis based on the development patient population was performed to identify any CGA domains for predicting mortality. Three sets of correlated variables were identified: ADL, IADL, SPMSQ, ESS and MNA as one set; the CIRS, medication use, ADL, IADL, SPMSQ, ESS and MNA as a second set; and medication use and cohabitation status as the third set of correlations. Based on these correlated sets, the MPI initially used three domains; ADL, medication use, and cohabitation status. Using a Cox regression analysis, survival curves of patients grouped into three categories (mild, moderate and severe risk of mortality) showed suitable separation, however in the logistic

regression this MPI (as a continual variable) did not indicate significant prediction for 1-year mortality (OR 0.64, 95% CI 0.14 to 2.87). A forward selection stepwise regression method was conducted where each of the remaining domains of the CGA were added to the model one by one. For each additional CGA domain added Cox regression and logistic regression analyses were performed. Pilotto et al. (2008) identified eight domains (63 items) of the CGA that resulted in the best prognostic index for 1-year mortality: ADL, IADL, SPMSQ, ESS, CIRS, MNA, total number of drugs, and social support.

Cut-off points were assigned to each of the domains as by either using previously reported cut-offs or by identifying points of separation through observing frequency distribution of patients at different levels (refer to Table 6.10). As previously described the total score is the total of each domain score divided by eight giving a number between 0 and 1. As the MPI classifies patients into risk categories, a sequence of cut-off points along with degree of separation between the curves, produced cut-off points of 0.33 and 0.66 (refer to Table 6.11).

An issue with the MPI is the interview can take up to 30 minutes to complete per person. In a large prospective singe-centre study a modified version of the MPI (m-MPI) was developed using a shorter MNA version (Sancarlo et al. 2011). This m-MPI still had the eight domains but 12 items less than the original MPI. All cut-off points remained the same as the original MPI (refer to Table 6.11).

As the MPI was derived in an inpatient population another version was developed to use in the community including nursing homes (Pilotto et al. 2013). The MPI-Standardised Multidimensional Assessment Schedule (MPI-SVaMA) differs from the MPI by including nine domains (55 items): age, sex, main diagnosis, nursing care

needs, cognitive status (SPMSQ), pressure sore risk (ESS), ADL, mobility (Barthel Index), and social support (refer to Table 6.11). Another difference is the individual domains are not equally weighted as seen in the original MPI. An algorithm was used to identify subgroups of patients at different risks for mortality for both 1-month and 12-month mortality. This gave two separate cut-off scores for MPI-SVaMA based on 1-month and 12-months (refer to Table 6.11).

Another version of the MPI has been developed for the use in oncology patients (Brunello et al. 2016). The Oncology-MPI (Onco-MPI) was derived in a small oncology patient population from a single institute. Of all the MPI versions the Onco-MPI has the greatest number of domains (refer to Table 6.11). Like the MPI-SVaMA, weighted domains were used using estimates from a multivariable Cox proportional hazard model and then an algorithm applied to identify three risk groups for 1-year mortality.

Table 6.11 Versions of the MPI items and cut-off scores

Rule	MPI	m-MPI	MPI-SVaMA	Onco-MPI
Authors	Pilotto et al. 2008	Sancarlo et al. 2011	Pilotto et al. 2013	Brunello et al. 2016
Domains	ADL IADL SPMSQ CIRS MNA ESS Medications Social support	ADL IADL SPMSQ CIRS MNA-SF ESS Medications Social support	ADL Mobility SPMSQ NCN Main diagnosis ESS Social support Age Sex	Age Sex BMI ADL IADL CIRS MMSE Psychiatric disease Cancer stage Cancer treatment Medications ECOG performance status Caregiver status GDS (15-item) Syndromes Tumour site
Cut-off scores	≤0.33 – Mild risk 0.33-0.66 – Mod. risk >0.66 – Severe risk	≤0.33 – Mild risk 0.33-0.66 – Mod. risk >0.66 – Severe risk	1-month: ≤0.41 – Mild risk 0.42-0.53 – Mod. risk >0.53 – Severe risk 12-month: ≤0.33 – Mild risk 0.34-0.47 – Mod. risk >0.47 – Severe risk	≤0.46 – Mild risk 0.47-0.63 – Mod. risk >0.63 – Severe risk

ADL: Activities of daily living; BMI: Body Mass Index; CIRS: Cumulative index rating scale; ECOG: Eastern Cooperative Oncology Group; ESS: Exton-Smith Scale; GDS: Geriatric Depression Scale; IADL: Instrumental activities of daily living; MMSE: Mini Mental State Examination; MNA: Mini nutritional assessment; MNA-SF: Mini nutritional assessment- Short Form; Mod.: Moderate; MPI: Multidimensional Prognostic Index; m-MPI: Modified-Multidimensional Prognostic Index; MPI-SVaMA: Multidimensional Prognostic Index - Standardised Multidimensional Assessment Schedule; Onco-MPI: Oncology- Multidimensional Prognostic Index; NCN: Nursing Care Needs; SPMSQ: Short portable mental status questionnaire.

A number of studies have investigated the use of the MPI in a number of patient populations and settings. Table 6.12 and Table 6.13 summarises the studies for MPI, m-MPI, MPI-SVaMA and Onco-MPI which can be found at the end of this chapter.

6.8.2 Validation of MPI

The MPI study (Pilotto et al. 2008) prospectively validated their tool in a separate patient cohort to the derived cohort. The prevalence for 1-year mortality was 5.7%, 23.2%, and 45.1% for mild, moderate, and severe risk, respectively. Similar results were obtained for 6-month mortality with slightly lower prevalence of 4.2%, 17.1%, and 36.9% for each risk category. The MPI in the validation cohort showed good predictive ability for both 6-months (AUC 0.75, 95% CI: 0.70 to 0.80) and 1-year

mortality (AUC 0.75, 95% CI: 0.71 to 0.80). The MPI has been validated in a number of studies in different sub-populations and setting (Pilotto et al. 2012a, Sancarlo et al. 2011, Sancarlo et al. 2012, Pilotto et al. 2007, Pilotto et al. 2009a, Pilotto et al. 2009b, Fontana et al. 2013, Pilotto et al. 2010, Pilotto et al. 2012b, Pilotto et al. 2009c) (refer to Table 6.12 and Table 6.13).

6.8.2.1 MPI in hospitalised patients

6.8.2.1.1 All geriatric patients and all-cause mortality

Three studies (Sancarlo et al. 2011, Fontana et al. 2013, Pilotto et al. 2012b) have assessed the MPI with the same patient population characteristics to the original study (Pilotto et al. 2008). Sancarlo et al. (2011) assessed the use of the MPI as well as their modified version, the m-MPI. The MPI observed mortality for mild, moderate, and severe risk was 2.8%, 8.9%, and 21.9% for 1-month mortality and 10.8%, 27.3%, and 52.8% for 1-year mortality, respectively (Sancarlo et al. 2011). This is similar to the original study mortality prevalence for 1-year (Pilotto et al. 2008). The MPI in this cohort showed good predictive ability for both 1-month (AUC 0.76, 95% CI: 0.73 to 0.79) and 1-year mortality (AUC 0.72, 95% CI: 0.70 to 0.74). A study by Pilotto et al. (2012b) assessed the MPI against other frailty tools such as the FI-CGA, Frailty Index derived from the Study of Osteoporotic Fractures (FI-SOF), and Frailty Index based on Cumulative Deficits (FI-CD). All frailty tools were significantly associated with 1-month and 1-year mortality (Pilotto et al. 2012b) (refer to Table 6.12 for MPI HR and 95% CI). The AUC for the MPI was good for predicting mortality at 1-month (AUC 0.77, 95% CI: 0.72 to 0.80) and 1-year mortality (AUC 0.75, 95% CI: 0.72 to 0.78). Another study (Fontana et al. 2013) evaluated the MPI in hospitalised geriatric patient to identify biomarkers associated with increased frailty and mortality. The MPI observed mortality for mild, moderate,

and severe risk was 1.0%, 4.6%, and 16.7% for 1-month mortality and 5.6%, 19.7%, and 43.5% for 1-year mortality, respectively (Fontana et al. 2013). The use of four biomarkers, C-reactive protein (CRP), haemoglobin, glycaemia, and Insulin-like growth factor-1 (IGF-1), were shown to improve predictive performance of the MPI for both 1-month (MPI alone: AUC 0.76, 95% CI: 0.70 to 0.82; MPI with biomarkers: AUC 0.80, 95% CI: 0.74 to 0.87) and 1-year mortality (MPI alone: AUC 0.70, 95% CI: 0.66 to 0.75; MPI with biomarkers: AUC 0.75, 95% CI: 0.71 to 0.79).

6.8.2.1.2 Geriatric patients with different medical conditions and all-cause mortality

Six studies have used the MPI in assessing mortality in a number of different medical conditions including gastrointestinal (GI) bleeding patients (Pilotto et al. 2007, Pilotto et al. 2009a), liver cirrhosis (Pilotto et al. 2009a), community acquired pneumonia (CAP) (Pilotto et al. 2009b), heart failure (HF) (Pilotto et al. 2010), chronic kidney disease (CKD) (Pilotto et al. 2012a), transient ischaemic attack (TIA) (Sancarlo et al. 2012), and dementia patients (Pilotto et al. 2009c) (refer to Table 6.12). For GI bleeding patients, the MPI was used in small sample of inpatients in two studies (Pilotto et al. 2007, Pilotto et al. 2009a). One of the studies assessed the MPI and long-term outcome of 2-year mortality (Pilotto et al. 2007). This study showed 2-year mortality prevalence for mild, moderate, and severe risk groups as 12.5%, 41.6%, and 83.3%, respectively (Pilotto et al. 2007). The other study assessed the MPI for 1-month mortality (Pilotto et al. 2009a). The MPI observed 1-month mortality for mild, moderate, and severe risk was 4.1%, 15.7%, and 30.4%, respectively (Pilotto et al. 2009a). This was similar to the predicted MPI 1-month mortality estimates. The AUC for the MPI was good for predicting mortality at 1-

month (AUC 0.76, 95% CI: 0.58 to 0.94). This study also assessed the MPI in patients with liver cirrhosis (Pilotto et al. 2009a). The MPI observed mortality for mild, moderate, and severe risk was 0.0%, 4.8%, and 27.6% for 1-month mortality and 12.5%, 31.0%, and 41.4% for 1-year mortality, respectively. The MPI showed very good predictive ability for 1-year mortality (AUC 0.90, 95% CI: 0.85 to 0.96). One study has investigated the use of the MPI in predicting short-term and long-term mortality in a small population of patients admitted to hospital with CAP (Pilotto et al. 2009b). The mortality prevalence was 3.4% at 1-month, 11.9% at 6-months, and 44.1% at 1-year for the mild risk category, 6.9% at 1-month, 21.4% at 6-months, and 50.0% at 1-year for the moderate risk category, and 10.3% at 1-month, 33.3% at 6-months, and 52.9% at 1-year for the severe risk category (Pilotto et al. 2009b). The predictive performance of the MPI for each 1-month (AUC 0.83, 95% CI: 0.75 to 0.87), 6-month (AUC 0.79, 95% CI: 0.71 to 0.85), and 1-year (AUC 0.80, 95% CI: 0.72 to 0.86) mortality was good. In a small study cohort that assessed the MPI in dementia patients the prevalence of mortality was consistently higher for each risk category at 1-month, 6-month, and 1-year (Pilotto et al. 2009c) (refer to Table 6.12). The MPI predictive performance was the same for 1-month and 6-months (AUC 0.79, 95% CI: 0.73 to 0.84) and similar for 1-year mortality (AUC 0.78, 95% CI: 0.72 to 0.83). The use of the MPI in predicting 1-month mortality for HF patients showed higher prevalence in men for all three risk categories compared to women (Pilotto et al. 2010). The predictive performance of the MPI based on sex was similar for men (AUC 0.83, 95% CI: 0.76 to 0.90) and women (AUC 0.80, 95% CI: 0.71 to 0.89). Pilotto et al. (2012a) also assessed the MPI in addition with the estimated Glomerular Filtration Rate (eGFR) in predicting 2-year mortality (Pilotto et al. 2012a). Two-year mortality prevalence was 11.3%, 22.4%, and 39.7% for mild,

moderate, and severe MPI risk categories. This study showed that using eGFR with the MPI compared to eGFR by itself improved predictive performance (eGFR: AUC 0.58, 95% CI: 0.55 to 0.61; eGFR and MPI: AUC 0.65, 95% CI: not reported). Interestingly, using the MPI alone (AUC 0.65, 95% CI: 0.62 to 0.68) had similar results to the combining of eGFR and MPI (Pilotto et al. 2012a). Another study used the MPI with patients who had been admitted to hospital and diagnosed with a TIA (Sancarlo et al. 2012). In this moderate sized cohort the prevalence of mortality was consistently higher for each risk category at 1-month, 6-month, and 1-year (Sancarlo et al. 2012) (refer to Table 6.12). The MPI showed good predictive performance for 1-month (AUC 0.82, 95% CI: 0.75 to 0.89), 6-month (AUC 0.80, 95% CI: 0.74 to 0.86), and 1-year mortality (AUC 0.77, 95% CI: 0.72 to 0.82) (Sancarlo et al. 2012).

6.8.2.1.3 All geriatric patients and in-hospital mortality

Two studies have assessed the use of the MPI in predicting in-hospital mortality (Volpato et al. 2015, Pilotto et al. 2016a) (refer to Table 6.12). Both of these studies had large prospective cohorts of older adults admitted to a Geriatric Unit. The prevalence of in-hospital mortality in one study was 1.08%, 4.27%, and 9.56% for mild, moderate, and severe risk categories (Volpato et al. 2015). Patients included in the severe risk category was eight times (HR 8.31, 95% CI 2.54 to 27.19) at higher risk of death within hospital than patients in the mild risk category. For patients in the moderate risk category this risk of in-hospital mortality was three times (HR 3.48, 95% CI 1.02 to 11.88) higher than mild risk category patients. Good predictive performance was observed for the MPI and in-hospital mortality (AUC 0.85, 95% CI: 0.79 to 0.91). In the other study, prevalence of in-hospital mortality rates as events per 100 person-months was 6.4%, 12.3%, and 48.9% for mild, moderate, and severe risk categories (Volpato et al. 2015). Hazard ratios were lower in this study

with one and a half times (HR 1.52, 95% CI 0.79 to 2.92) increased risk of in-hospital mortality for patients in the moderate risk group compared to mild category and five times (HR 5.69, 95% CI 3.08 to 10.50) increased risk for severe risk patients compared to mild risk patients. Compared to the other study (Volpato et al. 2015) predictive performance was lower for this study (Pilotto et al. 2016a) for the MPI and in-hospital mortality (AUC 0.76, 95% CI: 0.71 to 0.82).

6.8.2.1.4 All geriatric patients and hospital Length of stay

Both of the studies assessing in-hospital mortality also assessed the MPI in predicting length of stay (LOS) in geriatric patients (Volpato et al. 2015, Pilotto et al. 2016a) (refer to Table 6.12). After excluding the patients who had died during hospital admission the LOS ranged from 9.71 days (95% CI 8.7 to 10.6), 11.9 days (95% CI 10.9 to 12.9), and 12.0 days (95% CI 11.2 to 12.8) for mild, moderate, and severe risk categories, respectively. The other study had slightly increased LOS with 10.1 days (95% CI 8.6 to 11.8), 12.5 days (95% CI 10.7 to 14.6), and 13.4 days (95% CI 11.5 to 15.7) for mild, moderate, and severe risk categories, respectively (Pilotto et al. 2016a). MPI was a good predictor for longer (greater than 10 days) LOS (AUC 0.74, 95% CI: 0.71 to 0.77).

6.8.2.1.5 Geriatric patients and depression

A study has looked at the use of the MPI and treatment of late life depression with Selective Serotonin Reuptake Inhibitor (SSRI) (Pilotto et al. 2012c) (refer to Table 6.12). Patients were grouped into responders, poor responders and non-responders based on their reduction of the 21-item HRSD (Pilotto et al. 2012c). No change in depressive symptoms was observed for the non-responders group over a 6-month follow-up. For the responders and poor responders groups, SSRI treatment increased

more patients assigned to mild risk MPI category (12.9% and 10.3%) and reduced the number of patients in both moderate (11.2% and 16.8%) and severe (32.7% and 2%) risk groups over a 6-month period. Good predictive performance was observed for the MPI and SSRI treatment response (AUC 0.79, 95% CI: Not stated).

6.8.2.2 MPI in community and outpatients

6.8.2.2.1 All geriatric patients and all-cause mortality

Five studies have validated the use of the MPI in community and outpatient settings (Bureau et al. 2017, Giantin et al. 2013, Pilotto et al. 2015a, D'onofrio et al. 2015, Angleman et al. 2015) (refer to Table 6.13). Giantin et al. (2013) used the MPI to predict 6-month and 1-year mortality risk in patients aged ≥70 years with inoperable or metastatic solid cancer. Hazard ratios were higher for 6-month follow-up in the moderate risk group with four times (HR 4.36, 95% CI 2.27 to 8.27) increased risk of mortality compared to mild category and eight times (HR 8.09, 95% CI 3.75 to 17.48) increased risk for severe risk group patients compared to mild risk patients (Giantin et al. 2013). At 1-year, higher HR was seen in the severe risk (HR 5.66, 95% CI 2.87 to 11.16) patients group than patients in the moderate risk (HR 3.57, 95% CI 2.11 to 6.01) group at 1-year. The predictive performance of the MPI for 6-months and 1-year follow-up were 0.81 (95% CI: 0.74 to 0.88) and 0.78 (95% CI: 0.71 to 0.85).

6.8.2.2.2 Dementia patients and all-cause mortality or multidimensional impairment

Another study used the MPI in frail older adults living in the community with dementia and the role of anti-dementia treatment on mortality rates and impairment (Pilotto et al. 2015a) (refer to Table 6.13). This study had a large cohort with patients followed up for nine years. This study showed that patients who were not receiving

anti-dementia treatment had a higher risk of death (HR 2.65, 95% CI 2.27 to 3.09). Multidimensional impairment was also higher in patients in the severe risk (HR 5.37, 95% CI 4.76 to 6.06) group than in the moderate risk (HR 2.26, 95% CI 2.16 to 2.43) group (Pilotto et al. 2015a). D'Onofrio et al. (2015) also assessed the use of the MPI in dementia patients in an outpatient setting. This small randomised controlled trial had patients either with a medicated transdermal patch or the patch with cognitive stimulation sessions (D'onofrio et al. 2015). Patients who received the patch and sessions showed at 6-months to have more patients shifting from the moderate risk group to the mild risk group (N=14, 31.1%) compared to patients only receiving the patch (N=5, 11.1%). Therefore, patients in the former group had significant improvement of multidimensional impairment.

6.8.2.2.3 Geriatric patients with different medical conditions and all-cause mortality

A study evaluated the MPI in predicting mortality in patients who underwent cardiovascular surgery for transcatheter aortic valve implantation (TAVI) (Bureau et al. 2017) (refer to Table 6.13). Prevalence of mortality was higher for severe risk group at 1-month, 6-month, and 1-year follow-up. Due to the very low number of patients in the severe risk group this study combined this with the moderate risk group for estimating survival rate. At one year, 91.1% (±4.2%) and 74.4% (±4.2%) were estimated to survive for mild risk group patients and combined moderate/severe risk patient groups, respectively (Bureau et al. 2017).

Angleman et al. (2015) used a six-domain MPI in assessing future mortality and number of in-hospital days (refer to Table 6.13). In this study results were stratified by age in decades (starting from 66). The mean number of days in hospital during a

1-year period was significantly lower in patients in their sixties; however, no significance was observed for patients aged 70 or older (Angleman et al. 2015). When comparing each MPI risk group, higher risk groups were associated with longer mean in-hospital days for all age groups. When compared to mild risk group, patients in moderate and severe MPI risk categories had a shorter median time to death in years for all age categories (Angleman et al. 2015).

6.8.2.3 Validation of m-MPI

The m-MPI study internally validated the m-MPI in a large hospitalised patient cohort (Sancarlo et al. 2011) (refer to Table 6.12). Mortality prevalence increased with each risk category for 1-month (mild: 2.8%, moderate: 9.0%, severe: 21.9%) and 1-year (mild: 10.5%, moderate: 28.0%, severe: 52.7%) follow-up. Good predictive performance was observed at both 1-month (AUC 0.75, 95% CI: 0.72 to 0.78) and 1-year (AUC 0.71, 95% CI: 0.69 to 0.73). Currently, no further studies have validated the m-MPI.

6.8.2.4 Validation of Onco-MPI

Brunello et al. (2016) who developed the Onco-MPI are the only study which has validated the use of the Onco-MPI in an outpatient setting of cancer patients (refer to Table 6.13). The prevalence for 1-year mortality was 2.1%, 17.7%, and 80.8% for mild, moderate, and severe risk, respectively (Brunello et al. 2016). Very good predictive performance was seen with an AUC of 0.87 (95% CI: 0.84 to 0.90).

6.8.2.5 Validation of MPI-SVaMA

Four studies have validated the use of the MPI-SVaMA in a number of different medical conditions including diabetes, coronary artery disease (CAD), and patients with atrial fibrillation (AF) (Pilotto et al. 2013, Pilotto et al. 2016c, Pilotto et al. 2015b, Pilotto et al. 2016b) (refer to Table 6.13). In the original study that developed

the MPI-SVaMA, a validation cohort was also used to assess the MPI-SVaMA in older community patients (Pilotto et al. 2013). Hazard ratios for 1-month mortality were six times (HR 6.12, 95% CI 4.24 to 8.85) and twenty-five times (HR 25.71, 95% CI 18.33 to 36.06) higher for moderate and severe risk groups compared to mild risk group, respectively (Pilotto et al. 2013). At one year, lower HR were seen for both moderate (HR 3.29, 95% CI 2.84 to 3.81) and severe (HR 11.55, 95% CI 10.11 to 13.20) risk groups compared to mild risk group. Predictive performance of the MPI-SVaMA was shown to be good for both 1-month (AUC 0.83, 95% CI: 0.82 to 0.85) and 1-year (AUC 0.79, 95% CI: 0.78 to 0.80) follow-up. In a retrospective study, the MPI-SVaMA was used to estimate 3-year mortality risk of statin drug treatment in older frail adults who have diabetes mellitus (Pilotto et al. 2015b). Patients on statin treatment were associated with lower MPI-SVaMA risk scores (mild: 39%, moderate: 36%, severe: 25%). This study showed that satin use was significantly associated with lower 3-year mortality irrespective of MPI-SVaMA group (mild HR: 0.19, 95% CI: 0.14 to 0.27, moderate HR: 0.28, 95% CI: 0.21 to 0.36, severe HR: 0.26, 95% CI: 0.20 to 0.34). Another retrospective study assessed the relationship of statin use and mortality using the MPI-SVaMA in community older adults with CAD (Pilotto et al. 2016b). This study showed that patients with CAD and treated with a statin drug had reduced 3-year mortality for all MPI-SVaMA risk groups (mild HR: 0.45, 95% CI: 0.37 to 0.55, moderate HR: 0.44, 95% CI: 0.36 to 0.53, severe HR: 0.28, 95% CI: 0.21 to 0.39). Finally, a retrospective study used the MPI-SVaMA in community older adults treated with warfarin in patients with AF (Pilotto et al. 2016c). This study showed that patients with AF and treated with warfarin had reduced 2-year mortality for all MPI-SVaMA risk groups (mild HR: 0.64, 95% CI: 0.50 to 0.82, moderate HR: 0.68, 95% CI: 0.55 to 0.85, severe HR:

0.55, 95% CI: 0.44 to 0.67).

6.8.3 Limitations

In the current literature, the use of the MPI and its modified versions has their limitations. In the original study of the MPI (Pilotto et al. 2008), the eight domains that were included in the overall MPI had equal weighting, indicating that the MPI consists of a single construct. However, for the other modified versions of the MPI, the domains were assigned different weightings. Therefore, an approach is to assess the underlying dimensionality of the MPI through an exploratory and confirmatory factor analysis to confirm the MPI as a single construct or identify several different constructs.

Another limitation is the medications domain of the MPI. The MPI collects information regarding the total number of medications a patient is currently taking (Pilotto et al. 2008). As already discussed in part 8.3 Medications in geriatric patients, patients taking ≥5 medications, known as polypharmacy, have been shown to independently predict adverse outcomes such as falls and mortality in older adults (Routledge et al. 2004, Brahma et al. 2013). However, studies have shown that the total number of medications failed to show such significant associations with the previously mentioned adverse outcomes (Hilmer et al. 2007a, Lowry et al. 2011, Lowry et al. 2012, Mangoni et al. 2013). Assessing patient's exposure to drugs with anticholinergic and/or sedative effects with validated scoring systems such as the ARS could identify an area of the MPI to further improve the predictive accuracy.

A limitation of the MPI is the use of the SPMSQ in the assessment of cognitive function (Pilotto et al. 2008). The use of such tool in a cultural diverse patient population may reduce the accuracy of the assessment of cognitive function due to

certain items in the SPMSQ that rely on known cultural knowledge. Using a cognitive assessment tool that is not influenced by language, gender or educational status such as the RUDAS might allow a more accurate assessment of cognitive function (Basic et al. 2009).

Finally, the MPI is limited with the number of current studies in the literature that have validated the tool in an external population to the original study and with a fully independent investigator. Current studies have primarily been conducted within the same area of Italy (Pilotto et al. 2008, Pilotto et al. 2012a, Sancarlo et al. 2011, Sancarlo et al. 2012, Pilotto et al. 2007, Pilotto et al. 2009a, Pilotto et al. 2009b, Fontana et al. 2013, Pilotto et al. 2010, Pilotto et al. 2012b, Pilotto et al. 2009c, Volpato et al. 2015, Pilotto et al. 2012c, Pilotto et al. 2016a, Giantin et al. 2013, Pilotto et al. 2015a, Pilotto et al. 2013, Pilotto et al. 2016b, Pilotto et al. 2016c, Pilotto et al. 2015b, Brunello et al. 2016, D'onofrio et al. 2015) with the exception of two studies that were conducted in France (Bureau et al. 2017) and Sweden (Angleman et al. 2015). The latter study has its own limitations as only six of the domains were used for predicting mortality and in-hospital stay in days (Angleman et al. 2015). Most of the studies have been by the same primary investigator, Alberto Pilotto; therefore require more independent investigators to assess the predictive accuracy of the MPI. Another reason for the need of validating the MPI in different geographical settings is due to the variances in admission thresholds under different health care settings. Some health care settings may have a relatively high threshold resulting in more severely ill patients being admitted into hospital. This may result in vast differences in the predictive accuracy of the MPI for adverse outcomes compared to the original study.

6.9 Conclusion

Due to the complexity of treatment and management in older adults the implementation of a comprehensive assessment in geriatric patients identified patients who required additional needs. The use of such prediction tools to assess patients in different CGA domains has also improved patient care in this older population. Using such tools, that are more comprehensive, have an important place in identifying the risks of mortality in older adults. However, these tools have their limitations in their applicability across different care settings; components may be culturally sensitive leading to possible higher risk scores, and lack of validation that is external from the developed tools. Therefore, further studies should explore these issues to determine if they can be appropriately used in different geographical population by an independent investigator and to identify/modify the MPI to minimise the effects of cultural learning and language diversity.

6.10 The research problem

There are several important issues with current clinical practice and optimising the hospital management of an increasingly vulnerable and diverse patient population:

- Clinicians are increasingly expected to accelerate throughput, reduce length of hospital stay and readmission rate, as well as arrange appropriate post-discharge follow-up.
    - Not all geriatric patients are able to have a complete CGA at the time of admission, therefore missing potential patients who would benefit from a full assessment.
    - Although completion of the CGA is associated with improved outcomes it does not provide an objective, consistent and quantifiable

method for risk prediction and patient stratification.

- Older inpatients, either with or without dementia, are also at risk of potentially devastating complications, e.g. falls. The latter are common in this population, leading to prolonged hospitalisation, need for rehabilitation, hip fracture, cerebral bleeding and even death.

6.11 Rationale

6.11.1 Significance of the study

No information is currently available about the applicability, predictive accuracy and validity of the MPI in Australian cohorts of older inpatients either with or without dementia. The information provided by the CGA can be subjective and, more importantly, cannot be quantified and used to predict key adverse clinical outcomes and stratify risk in this complex patient population.

At Flinders Medical Centre (FMC), geriatric patients are allocated to either general medical wards (long-stay) or for the more chronic patients to the ACE ward. The ACE ward admits patients based on a priority list:

1. High priority patients
    a. With significant age related cognitive impairment
    b. With behavioural and psychological symptoms of dementia
2. Medium priority patients
    a. Who may not have high priority criteria but likely to benefit from interdisciplinary care and functional maintenance
3. Low priority patients
    a. Aged 65 years and older from high level care and no behavioural and psychological symptoms of dementia

Based on previous and current patient volume, approximately 3,600 older medical patients are admitted within a 12-month period. Access to this number of patients at one facility is an invaluable source where it can be linked with other clinical data such as biochemical parameters and medication prescribing information. Therefore, this study will allow rigorous assessment, refinement, and validation of an MPI in older Australian inpatients in terms of risk stratification and predictive accuracy towards key short- and medium-term adverse clinical outcomes.

6.11.2 The objectives of the study

- To test the predictive accuracy of the MPI in predicting 6-month all-cause mortality in older medical patients aged ≥ 65 years admitted to an acute medical unit (AMU) at FMC.
- To test the predictive accuracy of the MPI on previously validated outcomes in predicting
    - in-hospital mortality,
    - length of stay (LOS),
    - 1- and 3-month all-cause mortality

  in older medical patients aged ≥ 65 years admitted to an acute medical unit (AMU) at FMC.

- To test the predictive accuracy of the MPI on exploratory outcomes i.e. in-hospital falls, in-hospital delirium, readmission rate at 30 days and re-admissions within 3 and 6 months in older medical patients aged ≥ 65 years admitted to an acute medical unit (AMU) at FMC.
- To assess the underlying dimensionality of the MPI for single or multiple constructs using a factor analysis.

- To assess whether anticholinergic drugs, using the Anticholinergic Risk Scale (ARS) score, enhance the predictive accuracy of the MPI.
- To assess whether the Rowland Universal Dementia Assessment Scale (RUDAS), a cognitive assessment tool that includes frontal lobe assessment and is suitable for a multicultural population, enhances the predictive accuracy of the MPI.

Table 6.12 Summary of study characteristics and results for different MPI scores and adverse outcomes in hospital setting.

Study	Data	Population	CPR	No.	Age cut-off, yrs	Mean age, yrs	Sex (%F)	Outcome	FU (M)	No. (%) of participants in each risk level In each level No. (%)				MPI categories Results per level		
										Mild	*Mod.*	*Severe*	*Measured Units*	*Mild*	*Mod.*	*Severe*
Pilotto et al. 2007	P	**GI bleeding patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2004	MPI	36	≥65	82.8 (7.9)	55.6	Mortality	24	18 (50)	12 (33.3)	6 (16.6)	%	12.5	41.6	83.3
Pilotto et al. 2008	P; D	**All patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2004	MPI	838	≥65	79.2 (7.3)	55.4	Mortality	6 & 12	477 (53.3)	262 (31.2)	129 (15.4)	% (95% CI)	6M: 5.3 (3.3-7.3) 12M: 8.2 (5.7-10.7)	6M: 16.8 (12.5-21.1) 12M: 22.3 (17.4-27.2)	6M: 35.0 (27.0-43.0) 12M: 48.2 (39.6-56.8)
Pilotto et al. 2008	P;V	**All patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2005	MPI	856	≥65	78.3 (7.1)	53	Mortality	6 & 12	471 (55.0)	263 (30.7)	122 (14.2)	% (95% CI)	6M: 4.1 (2.3-5.9) 12M: 5.7 (3.5-7.9)	6M: 17.7 (13.2-22.2) 12M: 24.6 (19.5-29.7)	6M: 43.8 (35.0-52.6) 12M: 55.9 (46.9-64.9)
Pilotto et al. 2009a	P	**GI bleeding patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy unknown date	MPI	91	≥65	79.9 (8.9)	44	Mortality	1	49 (53.8)	19 (20.8)	23 (25.3)	%	4.1	15.7	30.4
Pilotto et al. 2009a	P	**Liver cirrhosis patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy unknown date	MPI	154	≥65	75.6 (6.4)	NA	Mortality	NA	NA	NA	NA	% (95% CI)	1M: reference group 12M: 15.5 (7.9-23.1)	1M: 4.8 (4.4-14.4) 12M: 32.0 (18.9-45.1)	1M: 30.3 (14.1-46.2) 12M: 41.0 (24.3-57.7)

Study	Data	Population	CPR	No.	Age cut-off, yrs	Mean age, yrs	Sex (%F)	Outcome	FU (M)	No. (%) of participants in each risk level In each level No. (%)				MPI categories Results per level		
Pilotto et al. 2009b	P	**CAP patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2004-2006	MPI	134	≥65	78.7 (8.8)	34	Mortality	1, 6 & 12	58 (43)	42 (31)	34 (25)	HR (95% CI)	1M: 0.039 (-0.03-0.10) 6M: 0.074 (0.00-0.15) 12M: 0.110 (0.02-0.19)	1M: 0.096 (0.01-0.18) 6M: 0.204 (0.07-0.33) 12M: 0.318 (0.18-0.45)	1M: 0.485 (0.33-0.64) 6M: 0.623 (0.47-0.78) 12M: 0.693 (0.48-0.80)
Pilotto et al. 2009c	P	**Dementia patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2004-2006	MPI	262	≥65	80.8 (6.7)	65.6	Mortality	1, 6 & 12	73 (27.9)	116 (44.3)	73 (27.9)	%	1M: 0, 6M: 2.7, 12M: 2.7	1M: 5.2, 6M: 11.2, 12M: 18.2	1M: 13.7, 6M: 28.8, 12M: 35.6
Pilotto et al. 2010	P	**HF patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2005-2007	MPI	376	≥65	80.5 (7.3)	56.6	Mortality	1	130 (34.6)	179 (47.6)	67 (17.8)	%	Male: 2.8 Female: 0	Male: 15.3 Female: 6.5	Male: 47.4 Female: 14.6
Sancarlo et al. 2011	P	**All patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2005-2007	MPI	4088	≥65	78.1 (7.1)	51.8	Mortality	1 & 12	2198 (53.8)	1519 (37.1)	371 (9.1)	% (95% CI)	1M: 2.8 (2.2-3.4) 12M: 10.8 (9.4-12.0)	1M: 8.9 (7.5-10.3) 12M: 27.3 (25.1-29.5)	1M: 21.9 (17.9-25.9) 12M: 52.7 (47.5-57.9)
Pilotto et al. 2012a	P	**CKD patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2005-2007	MPI	1198	≥65	80.5 (6.8)	55.5	Mortality	N/A	543 (45.3)	525 (43.8)	130 (10.9)	Per 100 persons-month; HR (95% CI)* adjusted	11.3; reference group	22.4; Adjusted: 1.96 (1.59-2.41)	39.7; Adjusted: 3.35 (2.55-4.40)
Pilotto et al. 2012b	P	**All patients** in Geriatric Units of 20 Hospitals, Italy 2008-2009	MPI	2033	≥65	79.8 (7.8)	57	Mortality	1 & 12	NA	NA	NA	HR (95% CI)	1M, 12M: reference group	1M: 2.05 (1.40-3.00) 12M: 2.00 (1.64-2.45)	1M: 7.70 (5.73-10.34) 12M: 5.70 (4.49-7.22)

Study	Data	Population	CPR	No.	Age cut-off, yrs	Mean age, yrs	Sex (%F)	Outcome	FU (M)	No. (%) of participants in each risk level In each level No. (%)				MPI categories Results per level		
Sancarlo et al. 2012	P	**TIA patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2005-2007	MPI	654	≥65	79.3 (6.5)	53.2	Mortality	1, 6 & 12	316 (48.3)	235 (35.9)	103 (15.7)	HR (95% CI)	1M, 6M, 12M: reference group	1M: 14.13 91.80-110.58) 6M: 3.86 (1.53-9.77) 12M: 2.56 (1.39-4.71)	1M: 26.17 (3.25-210.42) 6M: 9.78 (3.87-24.75) 12M: 6.73 (3.44-11.78
Fontana et al. 2013	P	**All patients with biomarkers** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy unkown dates	MPI	594	≥65	78.7 (7.1)	61.1	Mortality	1 & 12	201 (33.8)	201 (33.8)	192 (32.4)	1M: Per 100 persons-month; 12M: Per 100 persons-yr	1M: 1 12M: 5.6	1M: 4.6 12M: 19.7	1M: 16.7 12M: 43.5
Sancarlo et al. 2011	P	**All patients** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2005-2007	m-MPI	4088	≥65	78.1 (7.1)	51.8	Mortality	1 & 12	2206 (53.9)	1512 (37.0)	370 (9.1)	% (95% CI)	1M: 2.8 (2.2-3.4) 12M: 10.5 (9.3-11.7)	1M: 9.0 (7.6-10.4) 12M: 28.0 (25.8-30.2)	1M: 21.9 (17.9-25.9) 12M: 52.8 (47.6-58.0)
Pilotto et al. 2016a	P	**All patients** in 20 acute geriatric wards, Italy 2008		2033	≥65	79.8 (7.8)	57	In-hospital Mortality	N/A	851 (41.9)	743 (36.5)	439 (21.6)	HR (95% CI)	reference group	Adjusted: 1.52 (0.79-2.92)	Adjusted: 5.69 (3.08-10.5)
Volpato et al. 2015	P	**All patients** in 20 acute geriatric wards North-Eastern Hospitals, Italy 2012	MPI	1178	≥65	85.0 (6.8)	59.6	In-hospital Mortality	N/A	278 (23.6)	398 (33.8)	502 (42.6)	Per 100 persons-month; HR (95% CI)	3.39; reference group	10.92; Adjusted: 3.48 (1.02-11.9)	24.34; Adjusted: 8.31 (2.54-27.2)
Volpato et al. 2015	P	**All patients** in 20 acute geriatric wards North-Eastern Hospitals, Italy 2012		1178	≥65	85.0 (6.8)	59.6	LOS	N/A	278 (23.6)	398 (33.8)	502 (42.6)	Mean days (95% CI)	Unadjusted: 9.71 (8.7-10.6) Adjusted: 11.3 (9.3-13.7)	Unadjusted: 11.9 (10.9-12.9) Adjusted: 13.7 (11.3-16.7)	Unadjusted: 12.0 (11.2-12.8) Unadjusted: 15.3 (12.6-18.6)
Pilotto et al. 2016a	P	**All patients** in 20 acute geriatric wards, Italy 2008	MPI	2033	≥65	79.8 (7.8)	57	LOS	N/A	851 (41.9)	743 (36.5)	439 (21.6)	Mean days (95% CI)	Adjusted: 10.1 (8.6-11.8)	Adjusted: 12.5 (10.7-14.6)	Adjusted: 13.4 (11.5-15.7)

Study	Data	Population	CPR	No.	Age cut-off, yrs	Mean age, yrs	Sex (%F)	Outcome	FU (M)	No. (%) of participants in each risk level In each level No. (%)			MPI categories Results per level		
Pilotto et al. 2012c	P	**Major depressive disorder patients with SSRI's** in Geriatric Unit, Casa Sollievo della Sofferenza Hospital, Italy 2007-2009	MPI	485	≥65	77.2 (6.6)	72.2	Multi-dimensional impairment	6	272 (56.1)	161 (33.2)	52 (10.7)	Baseline; 6M: No. in each category (%)	Baseline: Responders: 208 (64.2) Poor responders: 59 (48) Non-responders: 5 (13.2) 6M: Responders: 243 (75) Poor responders: 87 (70.7) Non-responders: 6 (15.8)	Baseline: Responders: 78 (24.1) Poor responders: 57 (46.3) Non-responders: 26 (68.4) 6M: Responders: 60 (18.5) Poor responders: 30 (24.4) Non-responders: 27 (71.1)	Baseline: Responders: 38 (11.7) Poor responders: 7 (5.7) Non-responders: 7 (18.4) 6M: Responders: 21 (6.5) Poor responders: 6 (4.9) Non-responders: 5 (13.2)

Abbreviations: CAP: Community acquired pneumonia; CI: Confidence interval; CKD: Chronic kidney disease; CPR: Clinical prediction rule; F: Female; FU: Follow-up; GI: Gastrointestinal; HF: Heart failure: HR: Hazard ratio; LOS: Length of stay (in days); M: Months; Mod.: Moderate; MPI: Multidimensional prognostic index; No.: Number; SSRI: Selective serotonin re-uptake inhibitor; TIA: Transient ischaemic attack.

Table 6.13 Summary of study characteristics and results for different MPI scores and adverse outcomes in community and outpatient settings.

Study	Data	Population	CPR	No.	Age cut-off, yrs	Mean age, yrs	Sex (%F)	Outcome	FU (M)	No. (%) of participants in each risk level In each level No. (%)				MPI categories Results per level		
										Mild	*Mod.*	*Severe*	*Measured Units*	*Mild*	*Mod.*	*Severe*
Giantin et al. 2013	P	**Oncology patients** from Geriatric, Surgery, Medical Oncology Clinics, Padua Hospital, Italy 2008-2011	MPI	160	≥70	79.4 (5.7)	55	Mortality	6 & 12	96 (60)	48 (30)	16 (10)	HR (95% CI)	6M, 12M: reference group	6M: 4.36 (2.27-8.27) 12M: 3.57 (2.11-6.01)	6M: 8.09 (3.75-17.48) 12M: 5.66 (2.87-11.16)
Pilotto et al. 2015a	P	**Dementia in community patients**, Italy unknown dates	MPI	6712	≥65	N/A	N/A	Mortality	108	N/A	N/A	N/A	HR (95% CI)* adjusted	Anti-dementia drug use 108M: reference group	Anti-dementia drug use 108M: 2.26 (2.16-2.43)	Anti-dementia drug use 108M: 5.37 (4.76-6.06)
Bureau et al. 2017	P	**TAVI outpatients**, Poitiers University Hospital, France 2013-2015	MPI	225	≥75	86.2 (4.2)	49.1	Mortality	1, 6 & 12	45 (38.8)	68 (58.6)	3 (2.6)	%	1M: 8.9 6M: 8.9 12M: 9.5	1M: 8.8 6M: 16.2 12M: 24.2	1M: 33.3 6M: 66.7 12M: 66.7
Angleman et al. 2015	R	**SNAC-K study**, Stockholm, Sweeden 2001-2004	MPI – missing domains	2472	≥66	N/A	N/A	Mortality	12, 36 & 120	N/A	N/A	N/A	Median time till death in years (95% CI)* adjusted	Age 72-78, Age 81-87, Age 90-99: Reference group	Age 72-78: -2.6 (-4.2- -0.9) Age 81-87: -3.6 (-4.5- -2.8) Age 90-99: -2.2 (-3.7- -0.7)	Age 72-78: -9.0 (-10.0- -8.1) Age 81-87: -7.2 (-8.8- -5.6) Age 90-99: -3.8 (-5.3- -2.3)
Pilotto et al. 2013	P;D	**All community patients**, Padova Health district, Veneto, Italy	MPI-SVaMA	7876	≥65	81.8 (8.1)	63.1	Mortality	1 & 12	N/A	N/A	N/A	HR (95% CI)	1M, 12M: Reference group	1M: 6.01 (4.61-7.85)	1M: 26.17 (20.5-33.4)

Study	Data	Population	CPR	No.	Age cut-off, yrs	Mean age, yrs	Sex (%F)	Outcome	FU (M)	No. (%) of participants in each risk level In each level No. (%)				MPI categories Results per level		
		2004-2010													12M: 3.38 (3.04-3.76)	12M: 11.81 (10.71-13.02)
Pilotto et al. 2013	P;V	**All community patients**, Padova Health district, Veneto, Italy 2004-2010	MPI-SVaMA	4144	≥65	82.0 (7.8)	63.7	Mortality	1 & 12	N/A	N/A	N/A	HR (95% CI)	1M, 12M: Reference group	1M: 6.12 (4.24-8.85) 12: 3.29 (2.84-3.81)	1M: 25.71 (18.33-36.06) 12M: 11.55 (10.11-13.20)
Pilotto et al. 2015b	R	**Diabetes mellitus community patients**, Italy 2005-2013	MPI-SVaMA	1712	≥65	81.1 (7.3)	56.8	Mortality	12, 24 & 36	603 (35.2)	662 (38.7)	447 (26.1)	HR (95% CI)	36M Statin use: 0.19 (0.14-0.27)	36M Statin use: 0.28 (0.21-0.36)	36M Statin use: 0.26 (0.20-0.34)
Pilotto et al. 2016b	R	**CAD community patients**, Italy 2005-2013	MPI-SVaMA	2597	≥65	83.9 (7.4)	55.5	Mortality	12, 24 & 36	785 (30.2)	1096 (42.2)	716 (27.6)	HR (95% CI)*	Statin use: 0.45 (0.37-0.55)	Statin use: 0.44 (0.36-0.53)	Statin use: 0.28 (0.21-0.39)
Pilotto et al. 2016c	R	**AF community patients**, Italy 2005-2013	MPI-SVaMA	1827	≥65	84.4 (7.1)	64.3	Mortality	12, 24 & 36	705 (38.6)	634 (34.7)	488 (26.7)	HR (95% CI)*	Warfarin use: 0.5 (0.4-0.7)	Warfarin use: 0.5 (0.4-0.7)	Warfarin use: 0.4 (0.3-0.5)
Brunello et al. 2016	P;D	**Oncology outpatients**, Institute Veneto Oncology, Padova, Italy 2004-2011	Onco-MPI	658	≥70	77.2 (5.1)	65.8	Mortality	12	N/A	N/A	N/A	%	2.1	17.7	80.8
Angleman et al. 2015	R	**SNAC-K study**, Stockholm, Sweeden 2001-2004	MPI – missing domains	2472	≥66	N/A	N/A	LOS	12, 36 & 120	N/A	N/A	N/A	Mean days (95% CI)*	Age 66: 2.9 (1.8-3.9)	Age 66: 9.0 (3.3-14.6)	Age 66: NA Age 72-78: 30.1 (6.3-53.9)

Study	Data	Population	CPR	No.	Age cut-off, yrs	Mean age, yrs	Sex (%F)	Outcome	FU (M)	No. (%) of participants in each risk level In each level No. (%)			MPI categories Results per level			
														Age 72-78: 4.3 (3.3-5.3) Age 81-87: 7.8 (3.5-12.1) Age 90-99: 11.0 (7.4-14.5)	Age 72-78: 13.3 (9.0-17.6) Age 81-87: 18.9 (14.7-23.1) Age 90-99: 24.5 (20.7-28.3)	Age 81-87: 28.2 (16.3-40.0) Age 90-99: 30.7 (22.4-39.0)
D'Onofrio et al. 2015	P	**Alzheimer's Disease outpatients**, Alzheimer's Evaluation Unit,Casa Sollievo della Sofferenza Hospital, Italy 2011-2012	MPI	90	≥65	78.19 (4.8)	53.3	Cognitive function	6	48 (53.3)	42 (46.7)	0 (0)	Baseline; 6M: Number in each category (%) Group 1 – transdermal patch and cognitive stimulation; Group 2 – transdermal patch only	Baseline: Group 1: 31 (68.9) Group 2: 17 (37.8) 6M: Group 1: 45 (100) Group 2: 22 (48.9)	Baseline: Group 1: 14 (31.1) Group 2: 28 (62.2) 6M: Group 1: 0 (-) Group 2: 23 (51.1)	Baseline: Group 1: 0 (-) Group 2: 0 (-) 6M: Group 1: 0 (-) Group 2: 0 (-)

Abbreviations: AF: Atrial fibrillation; CAD: Coronary artery disease; CI: Confidence interval; CPR: Clinical prediction rule; F: Female; FU: Follow-up: HR: Hazard ratio; LOS: Length of stay (in days); M: Months; Mod.: Moderate; MPI: Multidimensional prognostic index; MPI-SVaMA: Standardized Multidimensional Assessment Schedule for Adults and Aged Persons; N/A: Not available; No.: Number; Onco-MPI: Oncology multidimensional prognostic index; SNAC-K: Swedish National study on Aging and Care in Kungsholmen; TAVI: Transcatheter aortic valve implantation.

7 PART B - METHODS

7.1 Research study design

This was a prospective cohort study conducted at Flinders Medical Centre (FMC), in Adelaide, South Australia. Patients presenting to the Emergency Department and then admitted to hospital between 14th September 2015 and 17th February 2017 were included. Patients were followed for 6 months from MPI assessment date.

7.2 Ethics

Approval for the study was obtained from the Southern Adelaide Clinical Human Research Ethics Committee on 19th August 2015 (Appendix D).

7.3 Study Population

A consecutive series of inpatients that were admitted at FMC under either General Medical or Acute Care of the Elderly (ACE) wards were eligible to participate in the study.

7.4 Participant selection

All eligible patients were identified daily from general medical wards (4A, 4D and 6G) and ACE wards (6B). Inclusion criteria were the following: age ≥65 years, ability to provide informed consent or ability of a proxy for informed consent, willingness to participate in the study, no previous diagnosis of dementia, and assessed within the first three days of hospital admission. Participants were able to withdraw from the study at any time.

7.5 Patient bedside interview

Patients went through a preliminary cognitive screen test, the abbreviated mental test

(AMT) to identify if a proxy was needed to provide consent ((Hodkinson 1972); refer to Appendix E). A score of less than 7 identified those patients requiring a proxy. Patient recruitment process is shown in Figure 7.1.

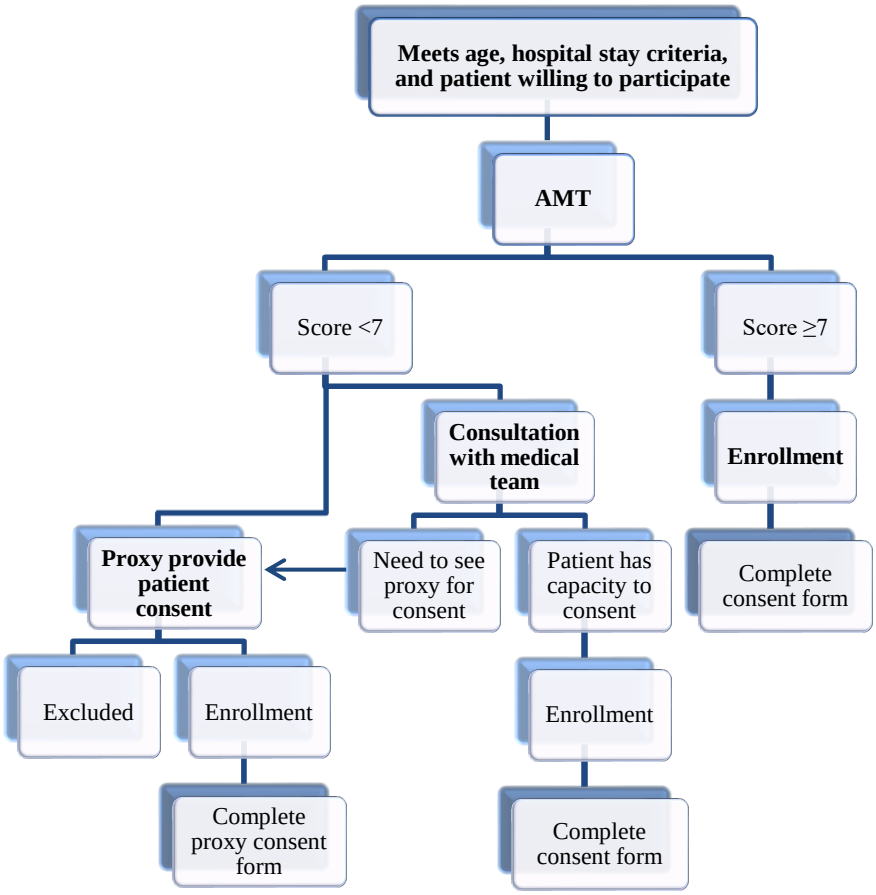


Figure 7.1 Patient recruitment process at FMC.

7.5.1 RUDAS

The 6-item RUDAS was used as an additional assessment for cognitive function (Storey et al. 2004) (refer to Appendix F). Due to the array of cultural, religious, and language backgrounds in the Australian population this tool has been specifically designed to minimise these effects and gain a more accurate assessment of cognitive function. The questionnaire takes approximately 10 minutes to conduct.

7.5.2 MPI

The 63-item MPI, a prognostic tool based on a standard CGA, was assessed in all

study participants (Pilotto et al. 2008) (refer to Appendix G). A printable version was used for bedside interviews, with minor adaptations to SPMSQ domain where 'President' was changed to 'Prime Minister'. The questionnaire takes approximately 25 minutes to conduct.

7.6 Data collection techniques

All data were entered into a database and captured data from the following sources: The State-wide Clinical Information System (OACIS), and individual patient medical records. Mortality rates were via through the death registry and added to the database. The database was housed on a university server located in the Department of Clinical Pharmacology, FMC. Data collection was conducted between 14th September 2015 and 30th September 2017. Table 7.1 describes all parameters collected.

Table 7.1 List of parameters collected for each patient at FMC.

Hospital Demographics		
Location in FMC		
	Inpatients	Ward 4A, 4D, 6B, 6G
Hospital stay		
	Admission/discharge date	
	Length of stay (days)	
	Hospital transfers	
Patient Demographics		
General		
	Age, DOB	
	Gender	
	Past medical history	
Clinical		
	Blood studies	
		Haemoglobin
		CRP
		Sodium
		Urea
		Serum creatinine
		eGFR
		Albumin
	Medications	
		Total number of medications
		Total number of regular medications
		Total number of PRN medications
		Total number of mediations on discharge
		Anticholinergics
		Sedatives
	In-hospital outcomes	
		Falls
		Delirium
		Mortality
Interview related		
	AMT	
		10 question cognitive test
	RUDAS	
		6 question cognitive test
	MPI (8 domains)	
		Co-habitation status
		ADL's
		IADL's
		SPMSQ
		ESS
		CIRS
		MNA
Follow-up (3- and 6-months)		
	Re-admission	
	All-cause mortality	

Abbreviations: ADL: Activities of daily living; AMT: abbreviated metal test; CIRS: Cumulative illness rating scale; CRP: C-reactive protein; DOB: date of birth; eGFR: estimated glomerular filtration rate; ESS: Exton-Smith scale; IADL: Instrumental Activities of daily living; MNA: Mini nutritional assessment; MPI: Multidimensional prognostic index; PRN: pro re nata; RUDAS: Rowland Universal Dementia Assessment Scale; SPMSQ: Short portable mental status questionnaire.

7.6.1 Medications

For each patient, the total number of medications given on the day of assessment was collected using medication charts and clinical notes found in patient medical records. Pro re nata (PRN; “as needed”) medications were also collected for day of assessment and discharge medications.

7.6.1.1 Medications with anticholinergic effects

In addition to collection of total medications, medication was further characterised by identifying specific drugs with anticholinergic effects, using the validated exposure scoring system Anticholinergic Risk Scale (ARS) (Rudolph et al. 2008, Hilmer et al. 2007a).

7.6.1.1.1 Anticholinergic risk scale score

The ARS ranks the anticholinergic effect of each drug on a scale of 0 (limited or none), 1 (moderate), 2 (strong) and 3 (very strong), based on the dissociation constant for the muscarinic receptor, rates of anticholinergic effects vs. placebo in experimental studies and a literature review on anticholinergic adverse effects. The ARS score is calculated by summing the ARS rankings assigned for each of the prescribed drugs in a patient (Rudolph et al. 2008). A list of medications generic names used in the ARS score is found in Table 7.2.

Table 7.2 Anticholinergic Risk Scale Score medication list used within Australia using generic names.

Anticholinergic Risk Scale Categories		
Score 3	**Score 2**	**Score 1**
Amitriptyline	Amantadine	Carbidopa-Levodopa
Atropine products	Baclofen	Entacapone
Chlorphenamine	Cetirizine	Haloperidol
Chlorpromazine	Cimetidine	Methocarbamol
Cyproheptadine	Clozapine	Metoclopramide
Cyclizine	Loperamide	Mirtazapine
Dicycloverine	Loratadine	Paroxetine
Diphenhydramine	Nortriptyline	Pramipexole
Fluphenazine	Olanzapine	Quetiapine
Hydroxyzine	Prochlorperazine	Ranitidine
Imipramine	Pseudoephedrine	Risperidone
Ipratropium	Tiotropium	Selegiline
Oxybutynin	Tolterodine	Trazodone
Perphenazine		
Promethazine		
Tizanidine		
Trifluoperazine		

Note: A higher score indicates drugs with stronger anticholinergic activity.

7.7 Outcome measures

The primary outcome was all-cause mortality at 6-months. All-cause mortality was defined as all deaths that occur within the study cohort, regardless of the cause of death. Death date and location were collected.

A number of secondary outcomes were included. In-hospital outcomes involved all-cause mortality, falls, and delirium. In-hospital falls were defined as any fall reported in the medical notes. The number of falls during the assessment admission was collected along with days till first fall and consequences of the fall (none, soft tissue damage, fracture). Delirium was identified as present if the medical team stated this diagnosis in the medical notes. Occurrence of delirium was collected to determine if delirium was present pre-admission or developed during admission. Any uncertainties were discussed with a qualified clinician (A.A.M.). Other secondary outcomes were length of hospital stay (in days) and hospital re-admission rates for

30 days, as well as 3- and 6-months.

7.8 Data analysis

Data analyses were performed using the STATA statistical software Version 15 (StataCorp©, Texas, USA).

7.8.1 Sample size

Based on Pilotto's derivation study, a sample size of n=750 patients without dementia was sufficient to provide an 80% statistical power to detect an odds ratio of 1.55 for each category increase in the MPI using a 2-sided Type 1 error rate of $P<0.05$, assuming a 12-month mortality rate of 5.7% in the lowest MPI category (Pilotto et al. 2008). Due to time constraints, 12-month mortality was not assessed. However, 6-month mortality was assessed as mortality rates for the lowest MPI category was higher (8.8% versus 5.7%) than the 12-month mortality rate in derivation study (Pilotto et al. 2008) indicating appropriate sample size.

7.8.2 Descriptive statistics

The characteristics of the patient cohort were described with simple descriptive statistics including percentages, means, and standard deviations. This included the number of patients grouped into the three different MPI categories, length of stay, number of re-admissions, falls, delirium, and total cohort all-cause mortality.

7.8.3 Inferential statistics

7.8.3.1 Summary of cohort

A number of different statistical analysis models were used to summarise baseline study characteristics. A Mann-Whitney U Test was used for comparison of male to females in the FMC study cohort for items of the MPI, RUDAS, AMT, in-hospital mortality, and mortality at 1-, 3-, and 6-months. The Kruskall-Wallis analysis of

ranks test was used for comparison of age, gender, in-hospital mortality, mortality at 1-, 3-, and 6-months, falls, and delirium across the MPI risk categories.

Intra-observer reliability was assessed by interviewing a small sample of patients twice on the same day at different times. This was assessed using a mixed effects linear regression model and determining the within patient variance in scores.

7.8.3.2 Model validation

Univariate and multivariate logistic regression adjusted for age and sex was conducted to assess the prognostic value of the individual MPI domains and the total MPI on in-hospital falls, in-hospital mortality, and 1-, 3-, and 6-month mortality. In order to assess whether the prognostic value of the total MPI was superior to that of its individual domains, and the ARS, a logistic regression model and resultant C-statistics was conducted. Age, ADL, IADL, SPMSQ, RUDAS, CIRS, MNA, EES, total number of drugs, and ARS were evaluated as continuous variables, while cohabitation status and total MPI were assessed as ordinal variables, based on the assumption of equidistance between single unit values. A competing risk analysis was used for assessing readmission rate (within 30 days, 3-, and 6-month re-admissions) across the MPI risk groups with death as the competing risk. Univariate and multivariate Poisson regression were conducted to compare incidence of in-hospital falls, readmissions within 3- and 6-months across the MPI risk groups. Length of stay was assessed using Cox proportional hazards analysis for MPI.

7.8.3.3 Model optimisation

Three models were assessed:

1. MPI with number of medications replaced with the ARS score. Cut-off points were applied to the ARS score with a 0 score for patients not on any

anticholinergics, 0.5 points for patients on 1-2 anticholinergics, and 1 point for patients taking >2 anticholinergics.

2. MPI with SPMSQ replaced with the RUDAS score. Cut-off points were applied to the RUDAS score with a 0 score for patients not on any anticholinergics, 0.5 points for patients on 1-2 anticholinergics, and 1 point for patients taking >2 anticholinergics.
3. MPI with both the ARS and RUDAS scores using the above cut-off points.

The same analyses as the model validation were performed on MPI optimisation models.

7.8.3.4 Factor analysis

A confirmatory factor analysis (CFA) of the eight MPI domains was performed for testing the dimensionality of the MPI. Due to poor model fit with a one-dimensional model, an exploratory factor analysis (EFA) was then conducted to a) identify the numbers of latent constructs and the underlying factor structures and b) reduce the number of variables required. Maximum-likelihood estimation was adopted with varimax rotations. A Kaiser-Meyer-Olkin value ≥0.6 indicated the appropriateness of principal axis factoring. The CFA and EFA were assessed with multiple model fit tests. The fit criteria include the Chi-square (χ^2) test where a statistical significant value indicates that a significant proportion of the variance in the data remains unexplained by the model; however, a statistically significant χ^2 can often be produced through large sample size and small variations in the data (Bentler and Bonett 1980). Another fit test was the Root Mean Square Error of Approximation (RMSEA) and 90 % confidence intervals (Steiger 1990). A value of <0.05 represents good fit or errors of approximation of up to 0.08 are considered an acceptable absolute fit. The Comparative Fit Index (CFI; (Bentler 1990)) and Tucker Lewis

Index (TFI; (Tucker and Lewis 1973)) with a value of >0.95 indicates a good model fit. The Akaike information criterion (AIC; (Akaike 1987)) and the Bayesian information criterion (BIC; (Schwarz 1978) allows comparisons between models with the lower value indicating a better model. The standardized root mean square residual (SRMR; (MacCallum et al. 1996) is an absolute measure of fit with a value of <0.05 indicating good model fit.

8 PART B - RESULTS

8.1 Study patient characteristics

Study characteristics of FMC patients included in the study, divided according to gender are reported in Table 8.1. From September 14, 2015 to February 17, 2017, 760 patients received a MPI assessment at FMC. Twenty-two patients were excluded because of a diagnosis of dementia prior to admission and one patient was excluded due to incomplete MPI. The final study cohort included 737 older patients, 367 men and 370 women, with a mean age of 79.6 ± 8.4, and an age range between 65 to 102 years.

Table 8.1 Characteristics of FMC patient cohort according to gender.

	Whole cohort n=737	**Male n=367**	**Female n=370**	***p* value**
Patients, %	100	49.8	50.2	
Age, years	79.6 ± 8.4	79 ± 8.2	80.2 ± 8.6	*0.0411*
Age range	65 - 102	65 - 99	65 - 102	
AMT, score	8.7 ± 1.3	8.7 ± 1.4	8.7 ± 1.3	*0.1547*
RUDAS, score	25.5 ± 3.8	25.5 ± 4.1	25.4 ± 3.4	*0.2014*
MPI, score				
ADL	5.2 ± 1.4	5.3 ± 1.4	5.1 ± 1.4	*0.008*
IADL	5.3 ± 2.4	5.2 ± 2.3	5.3 ± 2.4	*0.4412*
SPMSQ	1.5 ± 1.6	1.4 ± 1.5	1.6 ± 1.7	*0.136*
ESS	17.6 ± 2.2	17.9 ± 2.1	17.2 ± 2.3	*<0.0001*
CIRS-CI	6.5 ± 2.1	6.7 ± 2.1	6.4 ± 2.1	*0.0485*
CIRS-SI	2.5 ± 0.4	2.5 ± 0.4	2.4 ± 0.4	*0.0162*
MNA	20.1 ± 4.3	20.7 ± 4.4	19.6 ± 4.2	*0.0001*
Number of drugs	9.4 ± 4.3	9.3 ± 4.4	9.4 ± 4.2	*0.6367*
Prognostic index, score	0.42 ± 0.15	0.39 ± 0.15	0.44 ± 0.15	*<0.0001*
Mortality, n (%)				
In-hospital	25 (3.4)	15 (4.1)	10 (2.7)	*0.2995*
1-month	35 (4.8)	21 (5.7)	14 (3.8)	*0.2164*
3-month	65 (8.8)	38 (10.4)	27 (7.3)	*0.1437*
6-month	137 (18.6)	82 (22.3)	55 (14.9)	*0.0091*
Fall, n (%)	21 (2.9)	11 (3.0)	10 (2.7)	*0.8102*
Delirium, n (%)	71 (9.6)	42 (11.4)	29 (7.8)	*0.0973*
Re-admission rate, %				
30 days	13.5	14.2	12.8	*0.5877*
3-month	29.5	31.5	27.5	*0.2383*
6-month	41.9	43.5	40.3	*0.3889*
LOS, in days	9.44 ± 10.5	9.43 ±10.1	9.45 ± 11.0	*0.9033*

Note: results in table are means with standard deviations, unless otherwise stated. Abbreviations: AMT: Abbreviated Mental Test; ADL: Activity of daily living; CIRS-CI: Cumulative illness rating scale-illness severity score; CIRS-CI: Cumulative illness rating scale-comorbidity index; ESS: Exton-Smith scale; IADL: Instrumental activities of daily living; LOS: length of stay; MNA: Mini nutritional assessment; MPI: Multidimensional prognostic index; n: number; RUDAS: Rowland University dementia assessment score; SPMSQ: Short portable mental status questionnaire.

In terms of patient allocation into the MPI scores categories (Table 8.2), most patients were in the moderate risk category (57.8%) while a third were in the mild risk category (33.9%) and only a few in the severe risk category (8.3%). Higher MPI scores were significantly associated with older age (*p* value = 0.0001), female sex (*p* value = 0.0002), delirium (*p* value = 0.0001), in-hospital mortality (*p* value = 0.0001), longer LOS (*p* value = 0.0001), and higher mortality after 1-month, 3-, and 6-months mortality (*p* value = 0.0001). Re-admission within 3 months (*p* value = 0.006) and 6 months (*p* value = 0.005) were significantly different for MPI risk groups. Re-admission rates for 30 days did not significantly differ between MPI risk groups (*p* value = 0.1483).

Table 8.2 Characteristics FMC patient cohort by MPI category.

Characteristics	Mild risk (0.0-0.33)	Moderate risk (0.34-0.66)	Severe risk (0.67-1.0)
Patients, n. (%)	250 (33.9)	426 (57.8)	61 (8.3)
Women, n (%) **	101 (40.4)	230 (54.0)	39 (63.9)
Males, n (%)	149 (59.6)	196 (46.0)	22 (36.1)
Prognostic index score			
Range	0.06-0.31	0.38-0.63	0.69-0.88
Mean ± SD*	0.26 ± 0.06	0.47 ± 0.08	0.73 ± 0.05
Age			
Range	65-96	65-101	67-102
Mean ± SD*	76.4 ± 7.8	80.7 ± 8.1	85.5 ± 7.6
Mortality, n (%)			
In-hospital*	1 (0.4)	16 (3.8)	8 (13.1)
1 month*	3 (1.2)	20 (4.7)	12 (19.7)
3 month*	7 (2.8)	42 (9.9)	16 (26.2)
6 month*	22 (8.8)	95 (22.3)	20 (32.8)
Fall n (%)	5 (2.0)	11 (2.6)	5 (8.2)
Delirium n (%)*	15 (6.0)	36 (8.5)	20 (32.8)
Re-admission rate, %			
30 days	10.8	15.6	9.4
3-month	22.1	33.9	30.2
6-month	33.7	46.6	43.4
LOS, in days*	7.43 ± 9.7	9.62 ± 10.1	12.2 ± 10.0

Note: * *p* value = 0.0001, ***p* value =0.0002. Abbreviations: LOS: length of stay; n: number; SD: Standard deviation.

8.2 Validation of current MPI

8.2.1 Primary outcome

8.2.1.1 6-month all-cause mortality

In univariate analysis, the MPI as a continuous variable was associated with 6-month mortality (OR 2.34, 95% CI 1.69 to 3.24). The MPI as a categorical variable was also associated with 6-month mortality (Mild: OR reference group; moderate: OR 2.97, 95% CI 1.82 to 4.87; severe: OR 5.06, 95% CI 2.53 to 10.09). Table 8.3 shows MPI univariate logistic regression analyses for 6-month mortality.

Table 8.3 Six-month mortality univariate and multivariate logistic regression of MPI items, age, and sex.

	6-Month Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI Continuous	0.2696	0.8503	2.3403	1.6912	3.2384	*<0.0001*
MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.2835	1.0901	2.9745	1.8159	4.8721	*<0.0001*
Severe	0.2351	1.6205	5.0554	2.5336	10.0873	*<0.0001*
Multivariate						
MPI Continuous	0.2437	0.7710	2.1620	1.5384	3.0384	*<0.0001*
Age	0.0808	0.0182	1.0184	0.9943	1.0430	*0.135*
MPI Continuous	0.2958	0.9492	2.5836	1.8506	3.6070	*<0.0001*
Sex	0.1810	0.6933	2.0003	1.3493	2.9652	*0.001*
MPI Continuous	0.2683	0.8651	2.3751	1.6793	3.3593	*<0.0001*
Age	0.0914	0.0210	1.0212	0.9968	1.0462	*0.089*
Sex	0.1860	0.7159	2.0459	1.3767	3.0406	*<0.0001*
MPI Categorical						
Moderate	0.2629	1.0140	2.7565	1.6667	4.5591	*<0.0001*
Severe	0.2110	1.4584	4.2992	2.0902	8.8428	*<0.0001*
Age	0.0809	0.0184	1.0186	0.9946	1.0431	*0.131*
MPI Categorical						
Moderate	0.3061	1.1973	3.3112	2.0073	5.4623	*<0.0001*
Severe	0.2584	1.8119	6.1222	3.0157	12.4288	*<0.0001*
Sex	0.1797	0.6944	2.0026	1.3530	2.9640	*0.001*
MPI Categorical						
Moderate	0.2846	1.1189	3.0615	1.8404	5.0930	*<0.0001*
Severe	0.2326	1.6397	5.1535	2.4746	10.7325	*<0.0001*
Age	0.0919	0.0213	1.0215	0.9972	1.0465	*0.084*
Sex	0.1849	0.7181	2.0506	1.3818	3.0429	*<0.0001*

Abbreviations: β: beta; LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

In terms of discrimination, the area under the ROC curve for 6-month mortality was 0.63 (95% CI: 0.58 to 0.67) for the MPI (Figure 8.1).

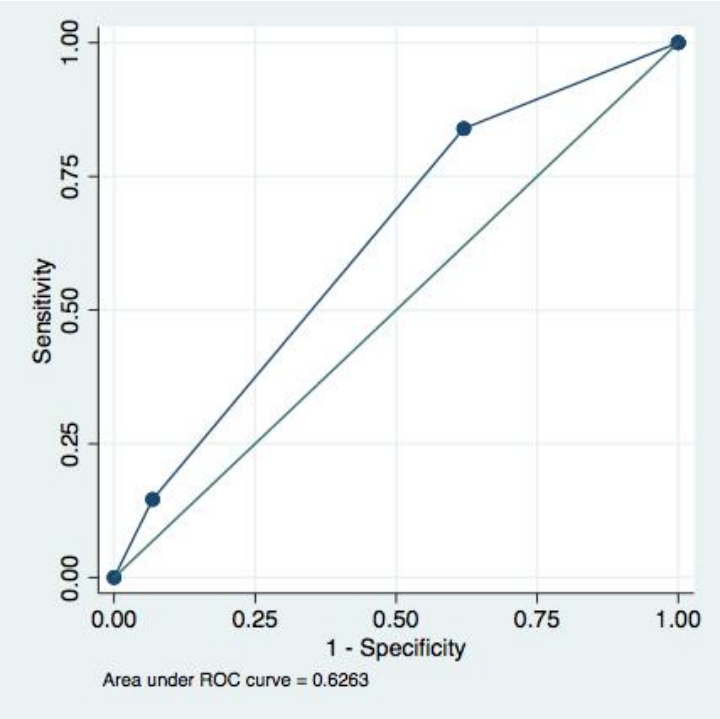


Figure 8.1 ROC curve for unadjusted MPI for 6-month mortality.

In multivariate analysis, the MPI as a continuous variable showed sex was a significant predictor for 6-month mortality (*p* value <0.001), however age was not (*p* value = 0.135). Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.131; Sex: *p* value = 0.001). Refer to Table 8.3 for MPI multivariate logistic regression results and 6-month mortality.

For assessing discrimination, the area under the ROC curve for the MPI adjusted for age, or sex, or age and sex was 0.65 (95% CI: 0.60 to 0.70), 0.67 (95% CI: 0.62 to 0.72), and 0.680 (95% CI: 0.63 to 0.73), respectively (Figure 8.2).

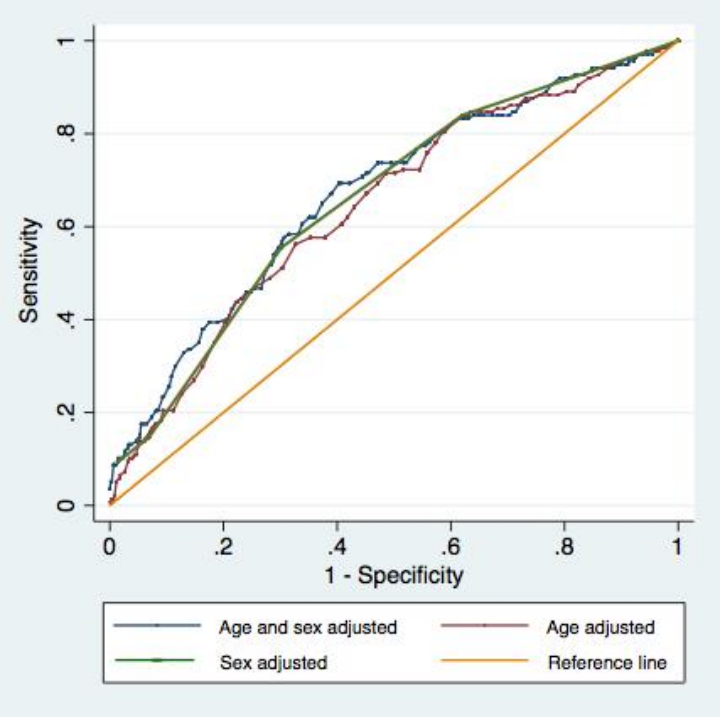


Figure 8.2 Six-month mortality ROC curve for MPI adjusted for age and sex.

8.2.2 Secondary outcomes

8.2.2.1 All-cause mortality

8.2.2.1.1 3-month all-cause mortality

In univariate analysis, the MPI as a continuous variable was associated with 3-month mortality (OR 3.47, 95% CI 2.21 to 5.44). The MPI as a categorical variable was also associated with 3-month mortality (Mild: OR reference group; moderate: OR 3.80, 95% CI 1.68 to 8.59; severe: OR 12.34, 95% CI 4.81 to 31.71). Table 8.4shows MPI univariate logistic regression analyses for 3-month mortality.

Table 8.4 Three-month mortality univariate and multivariate logistic regression of MPI items, age, and sex.

	3-Month Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI Continuous	0.3788	1.2429	3.4657	2.2069	5.4424	*<0.0001*
MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.3346	1.3342	3.7969	1.6788	8.5874	*0.001*
Severe	0.3516	2.5131	12.3429	4.8050	31.7058	*<0.0001*
Multivariate						
MPI Continuous	0.3453	1.1384	3.1217	1.9460	5.0077	*<0.0001*
Age	0.1016	0.0238	1.0241	0.9906	1.0588	*0.160*
MPI Continuous	0.3996	1.3291	3.7778	2.3822	5.9910	*<0.0001*
Sex	0.1611	0.6398	1.8960	1.1059	3.2508	*0.020*
MPI Continuous	0.3642	1.2210	3.3907	2.1016	5.4704	*<0.0001*
Age	0.1149	0.0274	1.0278	0.9939	1.0629	*0.109*
Sex	0.1696	0.6787	1.9713	1.1441	3.3967	*0.014*
MPI Categorical						
Moderate	0.3079	1.2340	3.4349	1.5007	7.8620	*0.003*
Severe	0.3209	2.3049	10.0235	3.7446	26.8305	*<0.0001*
Age	0.1011	0.0239	1.0241	0.9907	1.0587	*0.159*
MPI Categorical						
Moderate	0.3524	1.4244	4.1555	1.8283	9.4450	*0.001*
Severe	0.3707	2.6857	14.6691	5.6096	38.3598	*<0.0001*
Sex	0.1601	0.6391	1.8948	1.1062	3.2453	*0.020*
MPI Categorical						
Moderate	0.3246	1.3229	3.7544	1.6350	8.6209	*0.002*
Severe	0.3382	2.4711	11.8354	4.3753	32.0153	*<0.0001*
Age	0.1144	0.0275	1.0278	0.9939	1.0629	*0.109*
Sex	0.1684	0.6781	1.9702	1.1447	3.3908	*0.014*

Abbreviations: β: beta; LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

In terms of discrimination, the area under the ROC curve for 3-month mortality was 0.68 (95% CI: 0.62 to 0.74) for the MPI (Figure 8.3).

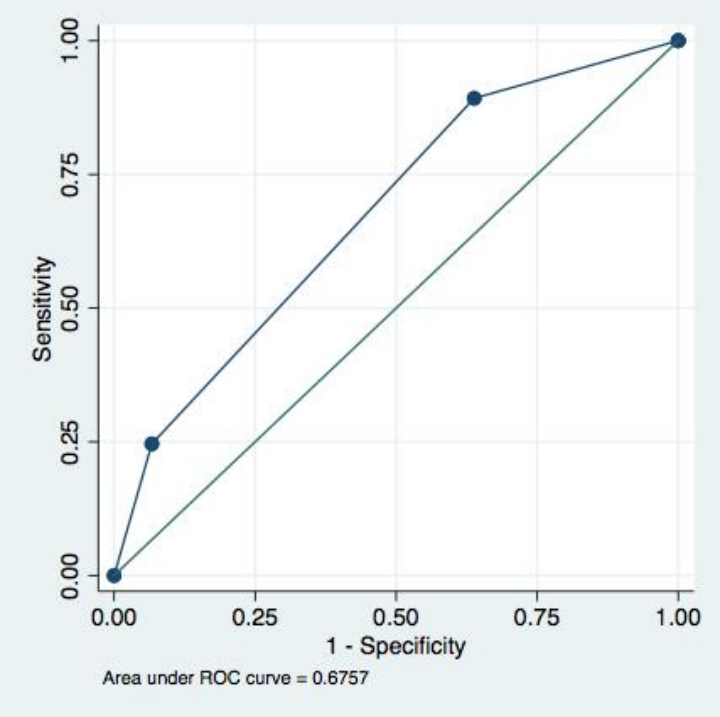


Figure 8.3 ROC curve for unadjusted MPI and 3-month mortality.

In multivariate analysis, the MPI as a continuous variable showed sex was a significant predictor for 3-month mortality (*p* value = 0.020), however age was not (*p* value = 0.160). Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.159; Sex: *p* value = 0.020). Refer to Table 8.4 for MPI multivariate logistic regression results and 3-month mortality.

For assessing discrimination, the area under the ROC curve for the MPI adjusted for age, or sex, or age and sex was 0.70 (95% CI: 0.63 to 0.77), 0.70 (95% CI: 0.63 to 0.76), and 0.71 (95% CI: 0.64 to 0.78), respectively (Figure 8.4).

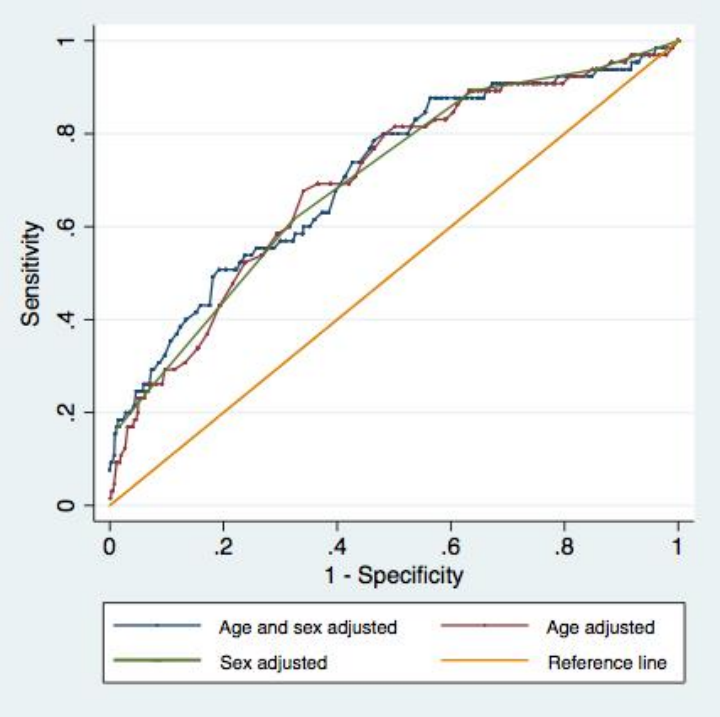


Figure 8.4 Three-month mortality ROC curve for MPI adjusted for age and sex.

8.2.2.1.2 1-month mortality

In univariate analysis, the MPI as a continuous variable was associated with 1-month mortality (OR 4.67, 95% CI 2.56 to 8.50). The MPI as a categorical variable was also associated with 1-month mortality (Mild: OR reference group; moderate: OR 4.06, 95% CI 1.19 to 13.79; severe: OR 20.16, 95% CI 5.49 to 74.11). Table 8.5 shows all MPI univariate logistic regression analyses for 1-month mortality.

Table 8.5 One-month mortality univariate and multivariate logistic regression of MPI items, age, and sex.

	1-Month Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI Continuous	0.4523	1.5402	4.6655	2.5602	8.5019	*<0.0001*
MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.3438	1.4002	4.0558	1.1929	13.7895	*0.025*
Severe	0.4115	3.0039	20.1633	5.4855	74.1147	*<0.0001*
Multivariate						
MPI Continuous	0.4288	1.4630	4.3188	2.2989	8.1137	*<0.0001*
Age	0.0705	0.0171	1.0173	0.9731	1.0634	*0.450*
MPI Continuous	0.4730	1.6378	5.1438	2.7859	9.4975	*<0.0001*
Sex	0.1800	0.7438	2.1039	1.0218	4.3320	*0.044*
MPI Continuous	0.4453	1.5506	4.7144	2.4948	8.9090	*<0.0001*
Age	0.0896	0.0222	1.0225	0.9775	1.0695	*0.333*
Sex	0.1882	0.7822	2.1863	1.0544	4.5333	*0.036*
MPI Categorical						
Moderate	0.3251	1.3273	3.7709	1.0930	13.0103	*0.036*
Severe	0.3897	2.8521	17.3249	4.4562	67.3561	*<0.0001*
Age	0.0711	0.0171	1.0172	0.9730	1.0635	*0.451*
MPI Categorical						
Moderate	0.3620	1.5002	4.4825	1.3123	15.3110	*0.017*
Severe	0.4310	3.2015	24.5685	6.5475	92.1901	*<0.0001*
Sex	0.1820	0.7451	2.1066	1.0214	4.3448	*0.044*
MPI Categorical						
Moderate	0.3402	1.4183	4.1301	1.1949	14.2749	*0.025*
Severe	0.4055	3.0302	20.7017	5.2821	81.1348	*<0.0001*
Age	0.0904	0.0222	1.0224	0.9774	1.0696	*0.334*
Sex	0.1903	0.7835	2.1892	1.0540	4.5472	*0.036*

Abbreviations: β: beta; LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

In terms of discrimination, the area under the ROC curve for 1-month mortality was 0.71 (95% CI: 0.64 to 0.79) for the MPI (Figure 8.5).

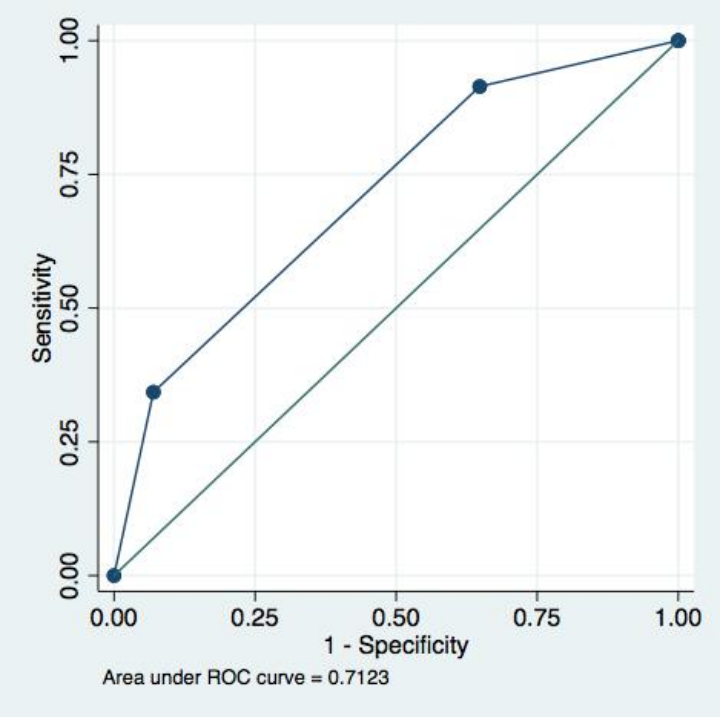


Figure 8.5 ROC curve for unadjusted MPI and 1-month mortality.

In multivariate analysis, the MPI as a continuous variable showed sex was a significant predictor for 1-month mortality (*p* value = 0.044), however age was not (*p* value = 0.450). Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.451; Sex: *p* value = 0.044). Refer to Table 8.5 for MPI multivariate logistic regression results and 1-month mortality.

For assessing discrimination, the area under the ROC curve for the MPI adjusted for age, or sex, or age and sex was 0.72 (95% CI: 0.63 to 0.81), 0.73 (95% CI: 0.65 to 0.82), and 0.74 (95% CI: 0.66 to 0.82), respectively (Figure 8.6).

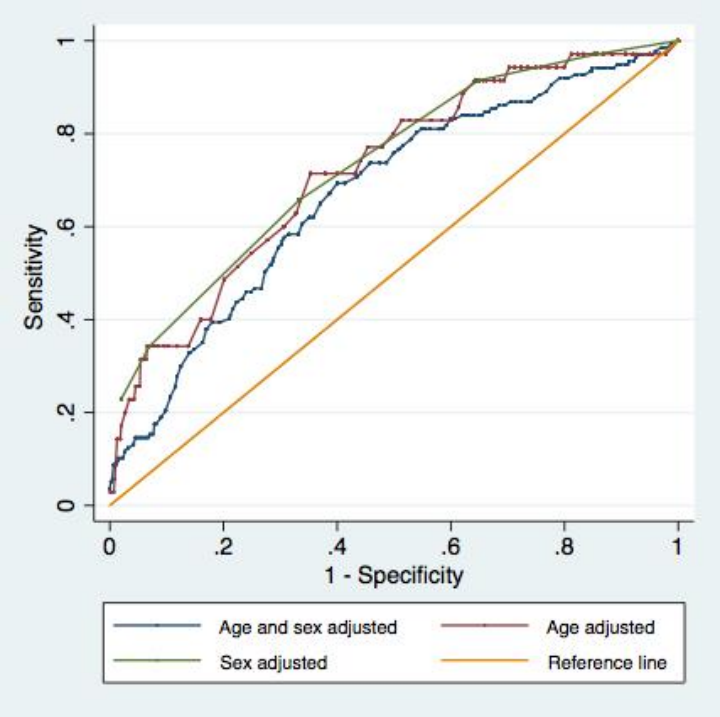


Figure 8.6 One-month mortality ROC curve for MPI adjusted for age and sex.

8.2.2.2 In-hospital Outcomes

8.2.2.2.1 In-hospital all-cause mortality

In univariate analysis, the MPI as a continuous variable was associated with in-hospital mortality (OR 4.82, 95% CI 2.40 to 9.68). The MPI as a categorical variable was also associated with in-hospital mortality (Mild: OR reference group; moderate: OR 9.72, 95% CI 1.28 to 73.72; severe: OR 37.59, 95% CI 4.60 to 306.89). Table 8.6 shows all MPI univariate logistic regression analyses for in-hospital mortality.

Table 8.6 In-hospital mortality univariate and multivariate logistic regression of MPI items, age, and sex.

	In-hospital Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI Continuous	0.4599	1.5728	4.8202	2.4000	9.6809	*<0.0001*
MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.5149	2.2739	9.7171	1.2808	73.7217	*0.028*
Severe	0.4582	3.6266	37.5849	4.6030	306.8918	*0.001*
Multivariate						
MPI Continuous	0.4294	1.4735	4.3647	2.0964	9.0871	*<0.0001*
Age	0.0902	0.0220	1.0223	0.9702	1.0771	*0.408*
MPI Continuous	0.4794	1.6653	5.2872	2.5997	10.7531	*<0.0001*
Sex	0.1773	0.7352	2.0858	0.8985	4.8423	*0.087*
MPI Continuous	0.4450	1.5587	4.7529	2.2740	9.9342	*<0.0001*
Age	0.1103	0.0275	1.0279	0.9748	1.0838	*0.309*
Sex	0.1878	0.7853	2.1931	0.9357	5.1403	*0.071*
MPI Categorical						
Moderate	0.4919	2.1797	8.8436	1.1516	67.9133	*0.036*
Severe	0.4319	3.4303	30.8849	3.6049	264.6078	*0.002*
Age	0.0847	0.0221	1.0224	0.9706	1.0769	*0.404*
MPI Categorical						
Moderate	0.5297	2.3719	10.7183	1.4079	81.5988	*0.022*
Severe	0.4750	3.8125	45.2636	5.4660	374.8276	*<0.0001*
Sex	0.1657	0.7328	2.0810	0.9009	4.8070	*0.086*
MPI Categorical						
Moderate	0.5031	2.2709	9.6877	1.2602	74.4764	*0.029*
Severe	0.4453	3.6021	36.6760	4.2668	315.2528	*0.001*
Age	0.1035	0.0275	1.0279	0.9751	1.0835	*0.306*
Sex	0.1755	0.7822	2.1862	0.9381	5.0947	*0.070*

Abbreviations: β: beta; LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

In terms of discrimination, the area under the ROC curve was 0.72 (95% CI: 0.65 to 0.80) for the MPI (Figure 8.7).

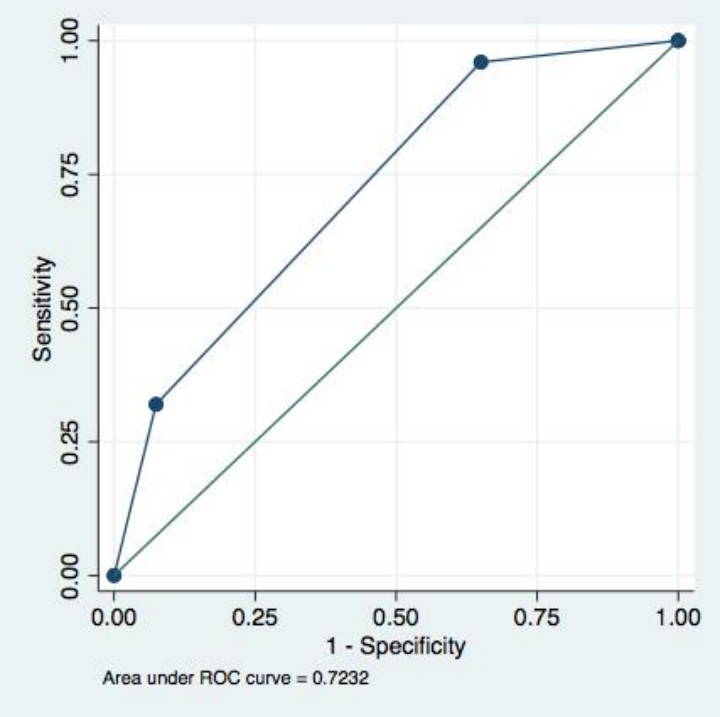


Figure 8.7 ROC curve for unadjusted MPI and in-hospital mortality.

In multivariate analysis, the MPI as a continuous variable, neither age (*p* value = 0.408) nor sex (*p* value = 0.087) were significant predictors for in-hospital mortality Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.404; Sex: *p* value = 0.086). Refer to Table 8.6 for MPI multivariate logistic regression results and in-hospital mortality.

For assessing discrimination, the area under the ROC curve for the MPI adjusted for age, or sex, or age and sex was 0.73 (95% CI: 0.63 to 0.83), 0.75 (95% CI: 0.66 to 0.83), and 0.75 (95% CI: 0.66 to 0.85), respectively (Figure 8.8).

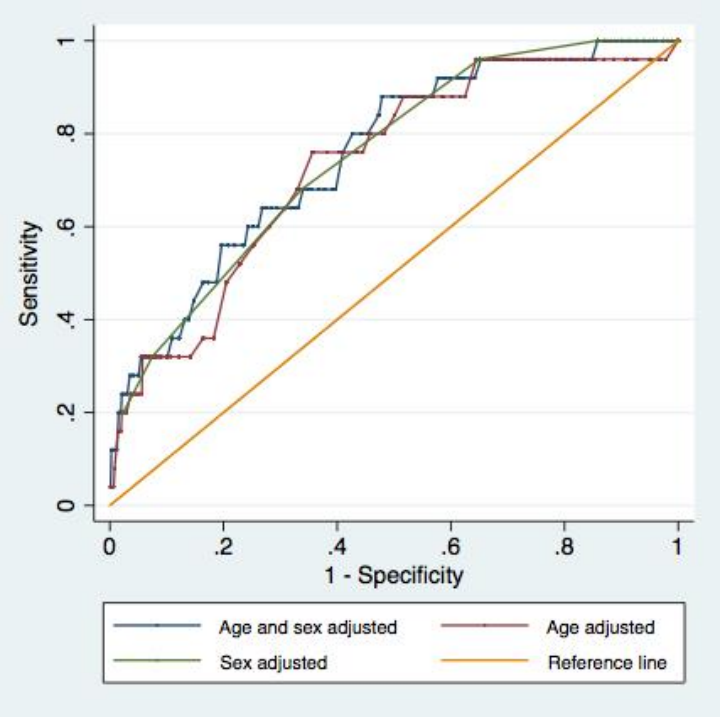


Figure 8.8 In-hospital mortality ROC curve for MPI adjusted for age and sex.

8.2.2.2.2 Falls

In a univariate analysis, the MPI as a continuous variable was associated with in-hospital falls (OR 2.08, 95% CI 1.01 to 4.27). The MPI as a categorical variable was associated with in-hospital falls for the severe risk group (OR 4.38, 95% CI 1.22 to 15.63), but not for the moderate risk group (OR 1.30, 95% CI 0.45 to 3.78). Table 8.7 shows all MPI univariate logistic regression analyses for in-hospital falls.

Table 8.7 In-hospital fall univariate and multivariate logistic regression of MPI items, age, and sex.

	In-hospital Falls					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI Continuous	0.2337	0.7300	2.0751	1.0078	4.2726	*0.048*
MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.0697	0.2614	1.2988	0.4460	3.7821	*0.632*
Severe	0.2196	1.4759	4.3750	1.2248	15.6276	*0.023*
Multivariate						
MPI Continuous	0.1846	0.5824	1.7903	0.8360	3.8336	*0.134*
Age	0.1478	0.0332	1.0337	0.9776	1.0932	*0.245*
MPI Continuous	0.2425	0.7589	2.1359	1.0300	4.4292	*0.041*
Sex	0.0647	0.2416	1.2733	0.5277	3.0725	*0.591*
MPI Continuous	0.1945	0.6155	1.8507	0.8607	3.9794	*0.115*
Age	0.1524	0.0343	1.0349	0.9785	1.0946	*0.230*
Sex	0.0737	0.2785	1.3211	0.5441	3.2074	*0.538*
MPI Categorical						
Moderate	0.0314	0.1190	1.1263	0.3762	3.3725	*0.832*
Severe	0.1740	1.1819	3.2605	0.8333	12.7566	*0.090*
Age	0.1483	0.0331	1.0337	0.9772	1.0934	*0.248*
MPI Categorical						
Moderate	0.0780	0.2932	1.3407	0.4573	3.9302	*0.593*
Severe	0.2275	1.5322	4.6284	1.2722	16.8388	*0.020*
Sex	0.0634	0.2354	1.2655	0.5220	3.0681	*0.602*
MPI Categorical						
Moderate	0.0408	0.1551	1.1678	0.3881	3.5136	*0.783*
Severe	0.1829	1.2465	3.4782	0.8790	13.7637	*0.076*
Age	0.1530	0.0343	1.0349	0.9782	1.0948	*0.233*
Sex	0.0728	0.2734	1.3144	0.5383	3.2095	*0.548*

Abbreviations: β: beta; LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

In terms of discrimination, the area under the ROC curve was 0.60 (95% CI: 0.48 to 0.72) for the MPI (Figure 8.9).

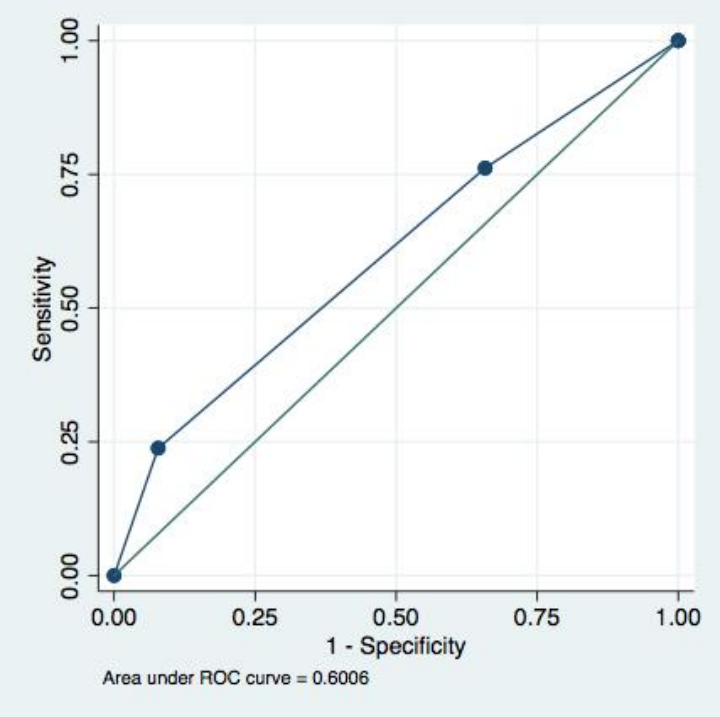


Figure 8.9 ROC curve for unadjusted MPI and in-hospital falls.

In multivariate analysis, after adjusting for continuous MPI, neither age (*p* value = 0.245) nor sex (*p* value = 0.591) were significant predictors for in-hospital falls. Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.248; Sex: *p* value = 0.602). Refer to Table 8.7 for MPI multivariate logistic regression results and in-hospital falls.

For assessing discrimination, the area under the ROC curve for the MPI adjusted for age, or sex, or age and sex was 0.64 (95% CI: 0.51 to 0.77), 0.59 (95% CI: 0.46 to 0.72), and 0.63 (95% CI: 0.49 to 0.77), respectively (Figure 8.10).

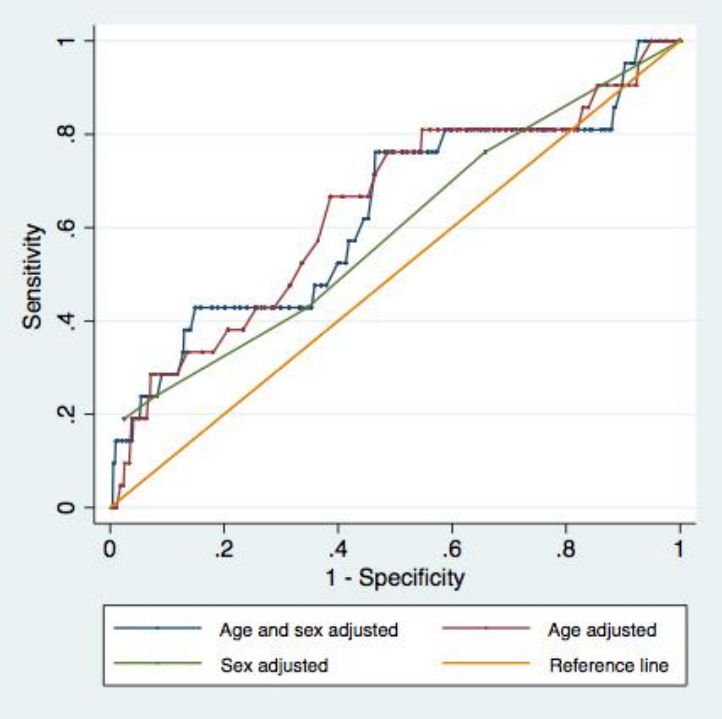


Figure 8.10 In-hospital fall ROC curve for MPI adjusted for age and sex.

Among the 20 (2.85%) patients who had a fall in-hospital, 19 (2.58%) were single fallers and 1 (0.14%) was a recurrent faller (≥ 2 falls). In Poisson regression analysis, the Incidence-Rate Ratio (IRR) for the MPI as a continuous variable (IRR 0.87, 95% CI 0.42 to 1.76) was not associated with number of in-hospital falls. The MPI as a categorical variable (Mild: IRR reference group; moderate: IRR 0.66, 95% CI 0.23 to 1.88; severe: IRR 0.79, 95% CI 0.21 to 2.93) was also not associated with number of in-hospital falls. Additionally, in a multivariate analysis, the MPI as a continuous variable, neither age (*p* value = 0.439) nor sex (*p* value = 0.765) were not predictors for number of in-hospital falls. Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.534; Sex: *p* value = 0.577). Refer to Table 8.8 for MPI univariate and multivariate Poisson regression results and number of in-hospital falls.

Table 8.8 Number of in-hospital falls univariate and multivariate Poisson regression of MPI items, age, and sex.

Risk factors	IRR	Number of Falls Standard error	LCI	UCI	*p* value
Univariate					
MPI Continuous	0.8682	0.3169	0.4245	1.7756	*0.699*
MPI Categorical					
Mild	1.00	reference group	-	-	
Moderate	0.6624	0.3526	0.2334	1.8803	*0.439*
Severe	0.7871	0.5280	0.2114	2.9311	*0.721*
Multivariate					
MPI Continuous	1.1088	0.5357	0.4301	2.8580	*0.831*
Age	0.9696	0.0387	0.8966	1.0485	*0.439*
MPI Continuous	0.8803	0.3289	0.4233	1.8309	*0.733*
Sex	0.8767	0.3862	0.3699	2.0789	*0.765*
MPI Continuous	1.1307	0.5556	0.4316	2.9622	*0.803*
Age	0.9689	0.0390	0.8954	1.0485	*0.433*
Sex	0.8653	0.3814	0.3647	2.0583	*0.743*
MPI Categorical					
Moderate	0.8740	0.6136	0.2207	3.4603	*0.848*
Severe	1.1601	1.0821	0.1864	7.2191	*0.874*
Age	0.9748	0.0401	0.8993	1.0566	*0.534*
MPI Categorical					
Moderate	0.6255	0.3390	0.2163	1.8092	*0.387*
Severe	0.8479	0.5812	0.2213	3.2495	*0.810*
Sex	0.7670	0.3644	0.3022	1.9462	*0.577*
MPI Categorical					
Moderate	0.8159	0.5794	0.2028	3.2820	*0.775*
Severe	1.2182	1.1382	0.1952	7.6038	*0.833*
Age	0.9758	0.0405	0.8997	1.0584	*0.555*
Sex	0.7805	0.3712	0.3073	1.9824	*0.602*

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; UCI: upper confidence interval.

8.2.2.2.3 Delirium

In univariate analysis, the MPI as a continuous variable was associated with in-hospital delirium (OR 2.79, 95% CI 1.82 to 4.27). The MPI as a categorical variable was associated with in-hospital delirium for the severe risk group only (Mild: OR reference group; moderate: OR 1.45, 95% CI 0.78 to 2.70; severe: OR 7.64, 95% CI 3.62 to 16.13). Table 8.9 shows all MPI univariate logistic regression analyses for in-hospital delirium.

Table 8.9 In-hospital delirium univariate and multivariate logistic regression of MPI items, age, and sex.

	In-hospital Delirium					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI Continuous	0.3203	1.0268	2.7920	1.8249	4.2717	*<0.0001*
MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.0966	0.3689	1.4462	0.7751	2.6983	*0.246*
Severe	0.2969	2.0337	7.6423	3.6203	16.1324	*<0.0001*
Multivariate						
MPI Continuous	0.2474	0.8119	2.2522	1.4417	3.5183	*<0.0001*
Age	0.2199	0.0514	1.0527	1.0188	1.0878	*0.002*
MPI Continuous	0.3418	1.1108	3.0367	1.9679	4.6859	*<0.0001*
Sex	0.1630	0.6325	1.8822	1.1246	3.1502	*0.016*
MPI Continuous	0.2705	0.9056	2.4735	1.5749	3.8848	*<0.0001*
Age	0.2312	0.0551	1.0567	1.0222	1.0922	*0.001*
Sex	0.1774	0.7089	2.0318	1.2020	3.4346	*0.008*
MPI Categorical						
Moderate	0.0376	0.1474	1.1589	0.6097	2.2026	*0.653*
Severe	0.2286	1.6059	4.9823	2.2546	11.0098	*<0.0001*
Age	0.2261	0.0522	1.0536	1.0192	1.0892	*0.002*
MPI Categorical						
Moderate	0.1175	0.4556	1.5771	0.8406	2.9589	*0.156*
Severe	0.3181	2.2115	9.1297	4.2256	19.7255	*<0.0001*
Sex	0.1679	0.6431	1.9023	1.1240	3.2193	*0.017*
MPI Categorical						
Moderate	0.0613	0.2451	1.2778	0.6691	2.4403	*0.458*
Severe	0.2511	1.8004	6.0520	2.6924	13.6039	*<0.0001*
Age	0.2368	0.0558	1.0574	1.0225	1.0935	*0.001*
Sex	0.1819	0.7187	2.0517	1.1996	3.5092	*0.009*

Abbreviations: β: beta; LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

In terms of discrimination, the area under the ROC curve was 0.64 (95% CI: 0.57 to 0.70) for the MPI (Figure 8.9).

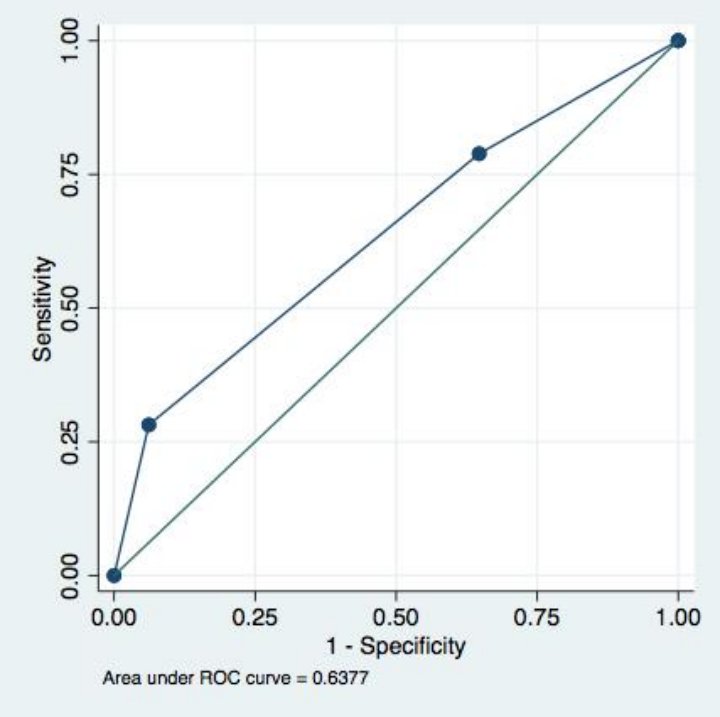


Figure 8.11 ROC curve for unadjusted MPI and in-hospital delirium.

In multivariate analysis, the MPI as a continuous variable, both age (*p* value = 0.002) and sex (*p* value = 0.016) were significant predictors for in-hospital delirium. Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.002; Sex: *p* value = 0.017). Refer to Table 8.9 for MPI multivariate logistic regression results and in-hospital delirium.

For assessing discrimination, the area under the ROC curve for the MPI adjusted for age, or sex, or age and sex was 0.70 (95% CI: 0.63 to 0.77), 0.66 (95% CI: 0.59 to 0.73), and 0.71 (95% CI: 0.63 to 0.78), respectively (Figure 8.12).

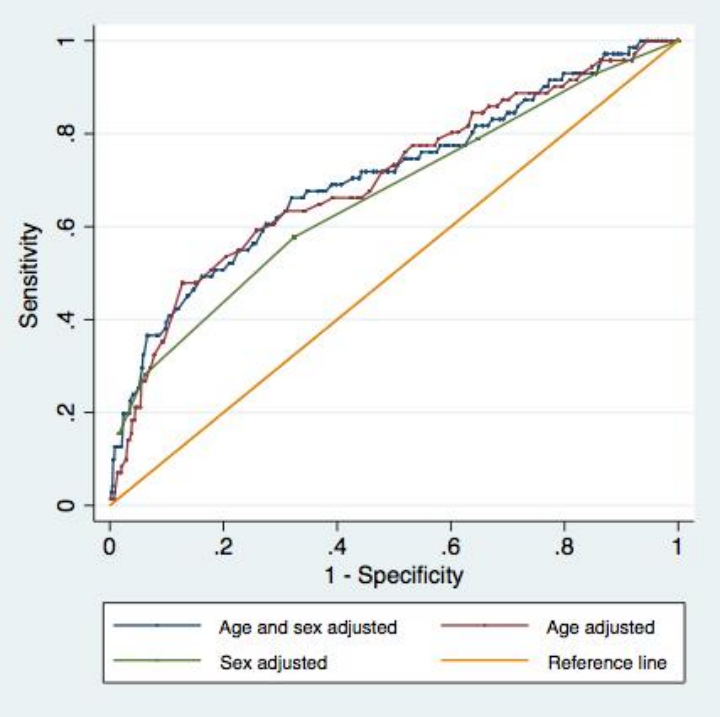


Figure 8.12 In-hospital delirium ROC curve for MPI adjusted for age and sex.

8.2.2.2.4 Length of stay

The mean LOS for patients in the mild, moderate and severe MPI risk groups were 7.43 days (SD: 9.66), 10.14 days (SD: 10.95), and 12.79 days (SD: 9.73), respectively (Figure 8.13).

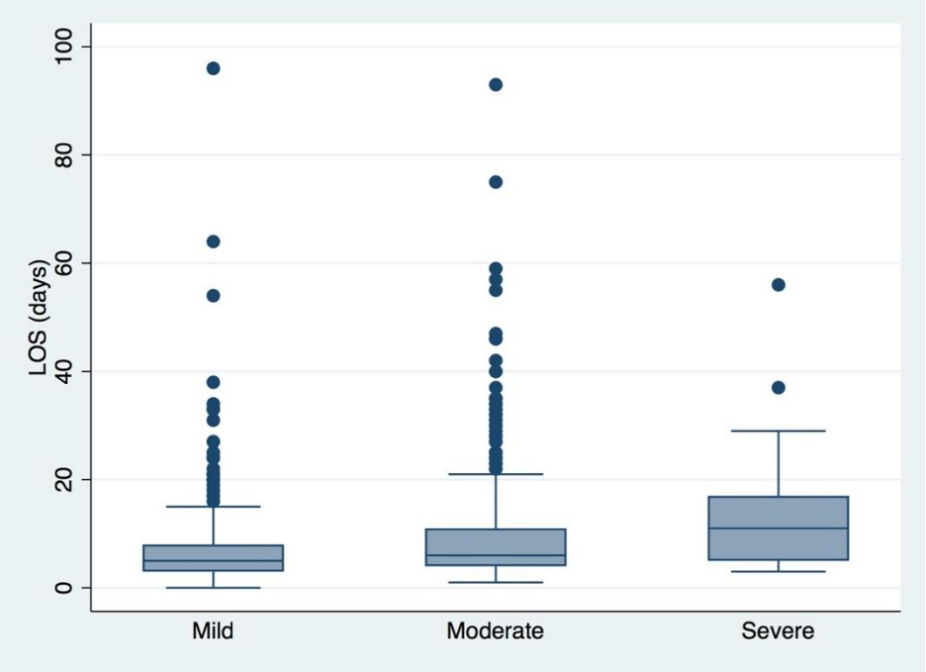


Figure 8.13 Boxplot for LOS in days according to MPI risk categories.

The results of Cox univariate and multivariate proportional hazards analyses with the MPI severe risk group included as a time-varying covariate in order to meet the proportional hazards assumption are summarized in Table 8.10. Each of the MPI risk groups were associated with LOS in days (Mild: HR 5.12, 95% CI 2.22 to 11.85; Moderate: HR 3.90, 95% CI 1.69 to 9.00; Severe: HR 1.71, 95% CI 1.20 to 2.45). Patients in the mild risk group were five times at risk to be discharged earlier (*p* value <0.0001) while moderate and severe risk group, patients were four times (*p* value = 0.001) and one time (*p* value = 0.003) at risk to be discharged earlier. Figure 8.14 shows the survival curves for the three MPI risk groups. Adjusting for both age and sex did not substantially modify the HR for the MPI risk groups (Mild: HR 4.71, 95% CI 2.02 to 11.02; Moderate: HR 3.71, 95% CI 1.60 to 8.60; Severe: HR 1.69, 95% CI 1.18 to 2.42).

Table 8.10 Length of stay univariate and multivariate Cox proportional hazards of MPI items, age, and sex.

Risk factors	HR	Length of stay Standard error	LCI	UCI	*p* value
Univariate					
MPI Categorical					
Mild (Y vs N)	5.1241	2.1914	2.2161	11.8480	*<0.0001*
Moderate (Y vs N)	3.8986	1.6639	1.6890	8.9990	*0.001*
Severe x Ln(follow-up)	1.7145	0.3128	1.1991	2.4514	*0.003*
Multivariate					
MPI Categorical					
Mild	4.5314	1.9455	1.9533	10.5122	*<0.0001*
Moderate	3.5830	1.5267	1.5543	8.2593	*0.003*
Severe	1.6652	0.3026	1.1662	2.3778	*0.005*
Age	0.9908	0.0046	0.9819	0.9998	*0.046*
MPI Categorical					
Mild	5.3259	2.3003	2.2842	12.4176	*<0.0001*
Moderate	4.0291	1.7334	1.7339	9.3628	*0.001*
Severe	1.7404	0.3203	1.2133	2.4964	*0.003*
Sex	0.9428	0.0717	0.8123	1.0942	*0.438*
MPI Categorical					
Mild	4.7141	2.0429	2.0162	11.0222	*<0.0001*
Moderate	3.7082	1.5924	1.5982	8.6037	*0.002*
Severe	1.6919	0.3102	1.1812	2.4235	*0.004*
Age	0.9907	0.0046	0.9817	0.9997	*0.043*
Sex	0.9373	0.0713	0.8076	1.0879	*0.395*

Note: Reference group for the Mild and Moderate risk groups were categorical Yes versus No. Severe risk group was time varying covariate of natural log times follow-up Abbreviations: HR: hazard ratio; LCI: lower confidence interval; Ln: Natural log; MPI: Multidimensional Prognostic Index; N: No; UCI: upper confidence interval; Vs: Versus; Y: Yes.

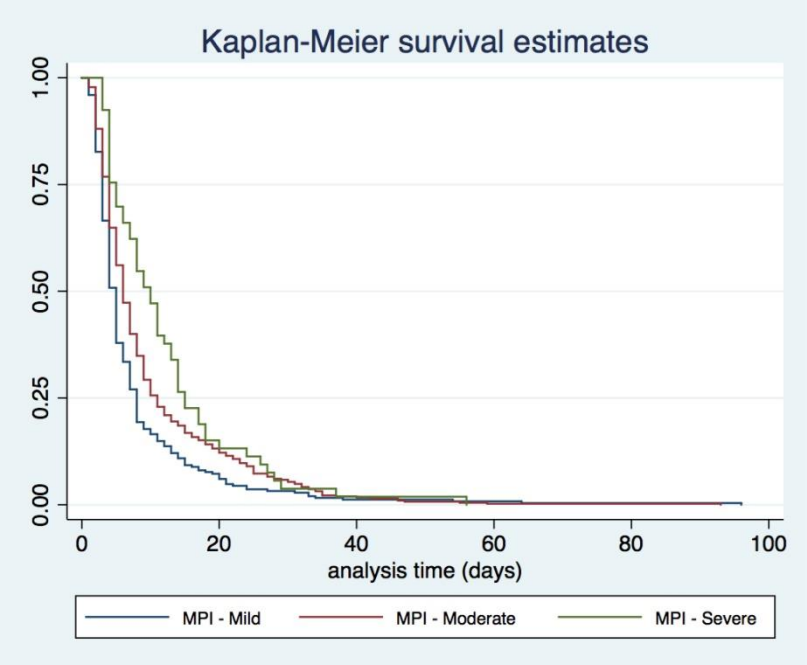


Figure 8.14 Unadjusted Kaplan-Meier survival cure for LOS in days according to MPI risk categories.

8.2.2.3 Re-admission

8.2.2.3.1 30-day re-admission rate

In a competing risk analysis – with death as the competing risk, the sub-hazard ratio for MPI as a continuous variable was not significant for 30-day re-admission rate (SHR 1.05, 95% CI 0.78 to 1.40). The sub-hazard ratio for the MPI as a categorical variable was not significant for the moderate risk group (SHR 1.34, 95% CI 0.88 to 2.04) and the severe risk group (SHR 0.65, 95% CI 0.24 to 1.78). Table 8.11 shows all MPI univariate competing risk regression analyses for 30-day re-admission rate.

Neither age (*p* value = 0.650) nor sex (*p* value = 0.614) were predictors for 30-day re-admission rate for MPI as a continuous variable. Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.636; Sex: *p* value = 0.610). Refer to Table 8.11 for MPI multivariate competing risk regression analyses for 30-day re-admission rate.

Table 8.11 Thirty-day re-admission rate univariate and multivariate competing risk regression of MPI items, age, and sex.

	30-day re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI Continuous	1.0470	0.1542	0.7845	1.3975	*0.755*
MPI Categorical					
Mild	1.00	reference group		-	-
Moderate	1.3389	0.2874	0.8790	2.0393	*0.174*
Severe	0.6526	0.3338	0.2395	1.7784	*0.404*
Multivariate					
MPI Continuous	1.0227	0.1628	0.7486	1.3972	*0.888*
Age	1.0056	0.0123	0.9817	1.0301	*0.650*
MPI Continuous	1.0620	0.1598	0.7908	1.4263	*0.689*
Sex	1.1028	0.2141	0.7538	1.6135	*0.614*
MPI Continuous	1.0374	0.1673	0.7563	1.4230	*0.820*
Age	1.0057	0.0124	0.9818	1.0303	*0.641*
Sex	1.1056	0.2154	0.7547	1.6195	*0.606*
MPI Categorical					
Moderate	1.3076	0.2894	0.8474	2.0177	*0.226*
Severe	0.6214	0.3317	0.2183	1.7689	*0.373*
Age	1.0057	0.0122	0.9822	1.0299	*0.636*
MPI Categorical					
Moderate	1.3583	0.2939	0.8888	2.0756	*0.157*
Severe	0.6714	0.3471	0.2437	1.8494	*0.441*
Sex	1.1031	0.2123	0.7565	1.6084	*0.610*
MPI Categorical					
Moderate	1.3266	0.2950	0.8579	2.0513	*0.204*
Severe	0.6395	0.3438	0.2229	1.8344	*0.406*
Age	1.0059	0.0122	0.9823	1.0301	*0.629*
Sex	1.1054	0.2133	0.7574	1.6134	*0.603*

Abbreviations: LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; SHR: sub-hazard ratio; UCI: upper confidence interval.

8.2.2.3.2 3-month re-admission

In a competing risk analysis – with death as the competing risk, the sub-hazard ratio for MPI as a continuous variable was not significant for 3-month re-admission rate (SHR 1.17, 95% CI 0.96 to 1.42). The sub-hazard ratio for the MPI as a categorical variable was significant for the moderate risk group (SHR 1.37, 95% CI 1.04 to 1.80) 3-month re-admission rate, however not for the severe risk group (SHR 0.67, 95% CI 0.67 to 1.88). Table 8.12 shows all MPI univariate competing risk regression analyses for 3-month re-admission rate.

Neither age (*p* value = 0.201) nor sex (*p* value = 0.345) were predictors for 3-month re-admission rate for MPI as a continuous variable. Similar results were observed for

the MPI as a categorical variable (Age: *p* value = 0.197; Sex: *p* value = 0.332). Refer to Table 8.12 for MPI multivariate competing risk regression analyses for 3-month re-admission rate.

Table 8.12 Three-month re-admission rate univariate and multivariate competing risk regression of MPI items, age, and sex.

	3-month re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI Continuous	1.1718	0.1166	0.9641	1.4242	*0.111*
MPI Categorical					
Mild	1.00	reference group		-	-
Moderate	1.3673	0.1930	1.0369	1.8029	*0.027*
Severe	1.1269	0.2957	0.6738	1.8848	*0.649*
Multivariate					
MPI Continuous	1.1236	0.1185	0.9137	1.3817	*0.269*
Age	1.0103	0.0081	0.9946	1.0263	*0.201*
MPI Continuous	1.1915	0.1206	0.9771	1.4529	*0.083*
Sex	1.1269	0.1424	0.8796	1.4437	*0.345*
MPI Continuous	1.1435	0.1225	0.9269	1.4107	*0.211*
Age	1.0102	0.0081	0.9945	1.0263	*0.204*
Sex	1.1260	0.1427	0.8784	1.4435	*0.349*
MPI Categorical					
Moderate	1.3115	0.1909	0.9859	1.7446	*0.062*
Severe	1.0357	0.2831	0.6062	1.7697	*0.898*
Age	1.0103	0.0080	0.9947	1.0262	*0.197*
MPI Categorical					
Moderate	1.3925	0.1996	1.0515	1.8443	*0.021*
Severe	1.1646	0.3072	0.6944	1.9531	*0.564*
Sex	1.1300	0.1424	0.8828	1.4465	*0.332*
MPI Categorical					
Moderate	1.3366	0.1976	1.0004	1.7859	*0.05*
Severe	1.0726	0.2944	0.6263	1.8368	*0.799*
Age	1.0102	0.0080	0.9946	1.0261	*0.201*
Sex	1.1284	0.1425	0.8811	1.4453	*0.339*

Abbreviations: LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; SHR: sub-hazard ratio; UCI: upper confidence interval.

Among the 210 (28.49%) patients who had a re-admission within 3 months, 19 (218.59%) were single re-admitters and 73 (9.90%) were recurrent re-admitters (≥ 2 re-admissions). In Poisson regression analysis, the Incidence-Rate Ratio (IRR) for the MPI (IRR 1.16, 95% CI 0.97 to 1.39) as a continuous variable was not associated with number of re-admissions within 3 months (Table 8.13). The IRR for the MPI as a categorical variable for number of re-admissions within 3 months when compared to mild risk group was significant for the moderate risk group (IRR 1.53, 95% CI

1.19 to 1.97), however not for the severe risk group (IRR 0.92, 95% CI 0.56 to 1.51).

In a multivariate Poisson regression analysis, the MPI as a continuous variable, neither age (*p* value = 0.442) and sex (*p* value = 0.184) were predictors for number of re-admissions within 3 months. Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.476; Sex: *p* value = 0.168). Refer to Table 8.13 for MPI univariate and multivariate Poisson regression results and number of re-admissions within 3 months.

Table 8.13 Number of re-admissions within 3 months univariate and multivariate Poisson regression of MPI items, age, and sex.

	Number of re-admissions within 3 months				
Risk factors	**IRR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI Continuous	1.1625	0.1073	0.9703	1.3928	*0.103*
MPI Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.5327	0.1955	1.1937	1.9680	*0.001*
Severe	0.9161	0.2325	0.5571	1.5064	*0.730*
Multivariate					
MPI Continuous	1.1905	0.1159	0.9838	1.0083	*0.073*
Age	0.9947	0.0069	0.9812	1.4214	*0.442*
MPI Continuous	1.1841	0.1103	0.9864	1.4214	*0.070*
Sex	1.1605	0.1302	0.9315	1.4459	*0.184*
MPI Continuous	1.2098	0.1184	0.9987	1.4657	*0.052*
Age	0.9950	0.0069	0.9815	1.0087	*0.472*
Sex	1.1570	0.1298	0.9285	1.4415	*0.194*
MPI Categorical					
Moderate	1.5652	0.2049	1.2111	2.0229	*0.001*
Severe	0.9582	0.2505	0.5739	1.5996	*0.870*
Age	0.9951	0.0069	0.9817	1.0087	*0.476*
MPI Categorical					
Moderate	1.5650	0.2010	0.1217	2.0130	*<0.0001*
Severe	0.9501	0.2424	0.5762	1.5664	*0.841*
Sex	1.1669	0.1306	0.9371	1.4532	*0.168*
MPI Categorical					
Moderate	1.5947	0.2968	1.2325	2.0635	*<0.0001*
Severe	0.9892	0.2594	0.5916	1.6539	*0.967*
Age	0.9954	0.0069	0.9820	1.0090	*0.508*
Sex	1.1637	0.1303	0.9344	1.4494	*0.176*

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; UCI: upper confidence interval.

8.2.2.3.3 6-month re-admission

In a competing risk analysis – with death as the competing risk, the sub-hazard ratio for MPI as a continuous variable was not significant for 6-month re-admission rate (SHR 1.03, 95% CI 0.86 to 1.22). The sub-hazard ratio for the MPI as a categorical variable was not significant for the moderate risk group (SHR 1.07, 95% CI 0.85 to 1.36) and the severe risk group (SHR 0.99, 95% CI 0.64 to 1.51). Table 8.14 shows all MPI univariate competing risk regression analyses for 6-month re-admission rate.

Neither age (*p* value = 0.888) nor sex (*p* value = 0.619) were predictors for 6-month re-admission rate for MPI as a continuous variable. Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.879; Sex: *p* value = 0.621). Refer to Table 8.14 for MPI multivariate competing risk regression analyses for 6-month re-admission rate.

Table 8.14 Six-month re-admission rate univariate and multivariate competing risk regression of MPI items, age, and sex.

	6-month re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI Continuous	1.0246	0.0933	0.8571	1.2248	*0.789*
MPI Categorical					
Mild	1.00	reference group		-	-
Moderate	1.0724	0.1294	0.8465	1.3586	*0.563*
Severe	0.9845	0.2138	0.6432	1.5069	*0.943*
Multivariate					
MPI Continuous	1.0208	0.0964	0.8484	1.2282	*0.828*
Age	1.0010	0.0069	0.9875	1.0146	*0.888*
MPI Continuous	1.0171	0.0935	0.8494	1.2180	*0.853*
Sex	0.9471	0.1035	0.7644	1.1734	*0.619*
MPI Continuous	1.0137	0.0964	0.8413	1.2215	*0.886*
Age	1.0009	0.0069	0.9874	1.0145	*0.899*
Sex	0.9474	0.1038	0.7644	1.1743	*0.622*
MPI Categorical					
Moderate	1.0683	0.1309	0.8402	1.3583	*0.590*
Severe	0.9763	0.2194	0.6284	1.5166	*0.915*
Age	1.0010	0.0069	0.9876	1.0147	*0.879*
MPI Categorical					
Moderate	1.0644	0.1296	0.8385	1.3513	*0.608*
Severe	0.9705	0.2114	0.6332	1.4874	*0.891*
Sex	0.9474	0.1035	0.7649	1.1735	*0.621*
MPI Categorical					
Moderate	1.0607	0.1310	0.8327	1.3512	*0.633*
Severe	0.9631	0.2170	0.6193	1.4977	*0.867*
Age	1.0010	0.0069	0.9875	1.0146	*0.890*
Sex	0.9478	0.1037	0.7649	1.1745	*0.624*

Abbreviations: LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; SHR: sub-hazard ratio; UCI: upper confidence interval.

Among the 298 (40.43%) patients who had a re-admission within 6 months, 166 (22.52%) were single re-admitters and 132 (17.91%) were recurrent re-admitters (≥ 2 re-admissions). In Poisson regression analysis, the Incidence-Rate Ratio (IRR) for the MPI (IRR 1.23, 95% CI 1.08 to 1.41) as a continuous variable was associated with number of re-admissions within 6 months (Table 8.15). The IRR for the MPI as a categorical variable for number of re-admissions within 6 months when compared to mild risk group was significant for the moderate risk group (IRR 1.64, 95% CI 1.36 to 1.99), however not for the severe risk group (IRR 1.08, 95% CI 0.75 to 1.54).

In a multivariate Poisson regression analysis, the MPI as a continuous variable, age (*p* value = 0.026) was a significant predictor for number of re-admissions within 6

months, however sex (*p* value = 0.128) was not. Similar results were observed for the MPI as a categorical variable (Age: *p* value = 0.032; Sex: *p* value = 0.112). Refer to Table 8.15 for MPI univariate and multivariate Poisson regression results and number of re-admissions within 6 months.

Table 8.15 Number of re-admissions within 6 months univariate and multivariate Poisson regression of MPI items, age, and sex.

	Number of re-admissions within 6-months				
Risk factors	**IRR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI Continuous	1.2319	0.0855	1.0752	1.4115	0.003
MPI Categorical					
Mild	1.00	reference group		-	-
Moderate	1.6440	0.1613	1.3565	1.9926	<0.0001
Severe	1.0755	0.1987	0.7488	1.5446	0.694
Multivariate					
MPI Continuous	1.2977	0.0952	1.1240	1.4982	<0.0001
Age	0.9884	0.0052	0.9783	0.9986	0.026
MPI Continuous	1.2516	0.0878	1.0908	1.4361	0.001
Sex	1.1372	0.0961	0.9635	1.3421	0.128
MPI Continuous	1.3144	0.0969	1.1376	1.5188	<0.0001
Age	0.9887	0.0052	0.9785	0.9989	0.031
Sex	1.1287	0.0954	0.9564	1.3321	0.152
MPI Categorical					
Moderate	1.7237	0.1733	1.4155	2.0991	<0.0001
Severe	1.1908	0.2272	0.8194	1.7307	0.360
Age	0.9889	0.0052	0.9788	0.9991	0.032
MPI Categorical					
Moderate	1.6741	0.1653	1.3795	2.0317	<0.0001
Severe	1.1100	0.2062	0.7713	1.5976	0.574
Sex	1.1437	0.0965	0.9694	1.3493	0.112
MPI Categorical					
Moderate	1.7502	0.1767	1.4360	2.1331	<0.0001
Severe	1.2218	0.2338	0.8397	1.7777	0.295
Age	0.9892	0.0052	0.8397	0.9994	0.038
Sex	1.1357	0.0958	0.9626	1.3400	0.131

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; MPI: Multidimensional Prognostic Index; UCI: upper confidence interval.

8.3 Optimisation of MPI

For optimisation of the MPI, two items (number of medications and SPMSQ) of the MPI were replaced. The number of medications was substituted for the ARS score and the SPMSQ was substituted for the RUDAS. Cut-off points were applied to each replacement item as shown in Table 8.16. The MPI with ARS and RUDAS score will be referred to as Optimised MPI (OPT-MPI).

Table 8.16 Cut-off values for the ARS score and RUDAS.

Item	Score given to each item		
	Low (value = 0)	Middle (value = 0.5)	High (value = 1)
ARS score	0	1 – 2	≥3
RUDAS	≥26	25 - 17	<17

Abbreviations: ARS: anticholinergic risk scale; RUDAS: Rowland University dementia assessment scale.

For the ARS score, most patients had a score of zero (n=440, 59.7%) followed by a score of >2 (n=162, 22.0%) and a score of one (n=135, 18.3%). For the RUDAS score categories, most patients had a score of ≥26 (n=432, 58.6%) with just over a third with a score between 25 and 17 (n=284, 38.5%) and only a few with a score of <17 (n=21, 2.9%).

8.3.1 Patient study characteristics

Patient study characteristics for separate analyses with the ARS score or the RUDAS score can be found in Appendix H (Table 11.1 and Table 11.2).

In terms of patient allocation into the OPT-MPI scores categories (Table 8.17), patients were mainly in the mild risk category (46.5%) and moderate risk category (47.4%) and only a few in the severe risk category (6.1%). This was similar to the patient allocation for the MPI at the beginning of this chapter (Table 8.2) and MPI with RUDAS score (Appendix H - Table 11.2). Higher OPT-MPI scores were significantly associated with older age (*p* value = 0.0001), female sex (*p* value =

0.0002), delirium (*p* value = 0.0001), in-hospital mortality (*p* value = 0.0001), longer LOS (*p* value = 0.0001), and higher mortality after 1-month, 3-, and 6-months mortality (*p* value = 0.0001). Re-admission rate for 6 month (*p* = 0.0241) was significantly different for MPI risk groups. Re-admission rates for 30 days (*p* value = 0.4255), 3-month re-admission rate (*p* = 0.1778) and falls (*p* value = 0.1930) did not significantly differ between MPI risk groups.

Table 8.17 Characteristics FMC patient cohort using OPT-MPI categories.

Characteristics	Mild risk 0.0-0.33	Moderate risk 0.34-0.66	Severe risk 0.67-1.0
Patients, n (%)	343 (46.5)	349 (47.4)	45 (6.1)
Women, n (%)**	144 (42.0)	201 (42.4)	25 (55.6)
Men, n (%)	199 (58.0)	148 (57.6)	20 (44.4)
Prognostic index score			
Range	0.06-0.31	0.38-0.63	0.66-0.88
Mean ± SD*	0.24 ± 0.07	0.46 ± 0.08	0.74 ± 0.06
Age			
Range	65-96	65-101	73-102
Mean ± SD*	78.2 ± 7.9	80.3 ± 8.6	85.3 ± 7.9
Mortality n. (%)			
In-hospital*	3 (0.9)	16 (4.6)	6 (13.3)
1 month*	6 (1.8)	20 (5.7)	9 (20.0)
3 month*	14 (4.1)	39 (11.2)	12 (26.7)
6 month*	39 (11.4)	83 (23.8)	15 (33.3)
Fall n (%)	7 (2.0)	11 (3.2)	3 (6.7)
Delirium n (%)*	18 (5.3)	36 (8.5)	17 (37.8)
Re-admission rate, %			
30 days	13.4	13.5	6.7
3-month	26.2	32.4	33.3
6-month	36.8	47.2	41.0
LOS, in days*	7.8 ± 10.2	10.6 ± 10.7	13.1 ± 10.2

Note: * p value = 0.0001, **p=0.0002. Abbreviations: LOS: length of stay; n: number.

8.3.2 Primary Outcome

8.3.2.1 6-month all-cause mortality

Separate univariate and multivariate logistic regression analyses for the MPI with either the ARS score or RUDAS score or the OPT-MPI for 6-month mortality can be found in Appendix H - Table 11.3, Table 11.4, and Table 11.5.

In univariate analysis, the MPI with ARS (OR 2.33, 95% CI 1.71 to 3.19) or MPI with RUDAS (OR 2.35, 95% CI 1.70 to 3.26) or OPT-MPI (OR 2.13, 95% CI 1.57

to 2.89) as a continuous variable were associated with 6-month mortality. The MPI with ARS or MPI RUDAS score as a continuous variable were similar to the original MPI (Table 8.3).

The MPI with ARS (Mild: OR reference group; moderate: OR 2.64, 95% CI 1.77 to 3.94; severe: OR 4.39, 95% CI 2.03 to 9.53), MPI with RUDAS (Mild: OR reference group; moderate: OR 2.78, 95% CI 1.65 to 4.70; severe: OR 5.48, 95% CI 2.79 to 10.76), and OPT-MPI (Mild: OR reference group; moderate: OR 2.43, 95% CI 1.61 to 3.68; severe: OR 3.90, 95% CI 1.93 to 7.88) as a categorical variable were also associated with 6-month mortality. Refer to Appendix H - Table 11.3, Table 11.4, and Table 11.5 for all optimised versions of the MPI univariate logistic regression analyses for 6-month mortality. The MPI with RUDAS score as a categorical variable was similar to the original MPI (Table 8.3).

Separate unadjusted 6-month mortality ROC curves for the MPI with either the ARS score or RUDAS score or the OPT-MPI can be found in Appendix H - Figure 11.1, Figure 11.2, and Figure 11.3. In terms of discrimination, the area under the ROC curve for 6-month mortality was 0.63 (95% CI: 0.58 to 0.68) for the MPI with the ARS (Figure 11.1), 0.62 (95% CI: 0.58 to 0.67) for the MPI with the RUDAS (Figure 11.2), and 0.62 (95% CI: 0.57 to 0.67) for the OPT-MPI (Figure 11.3). These figures are similar to the original MPI (Figure 8.1).

In multivariate analysis, the MPI with ARS score and OPT-MPI as a continuous variable showed age was a significant predictor for 6-month mortality (MPI-ARS: *p* value = 0.038; OPT-MPI: *p* value = 0.038) MPI with RUDAS score showed age was not a significant predictor for 6-month mortality (*p* value = 0.132). This is similar to the original MPI (Table 8.3). As for sex, this was a significant predictor for 6-month

mortality for all optimised versions of the MPI (p value = 0.001) and comparable to the original MPI (Table 8.3). Refer to Appendix H - Table 11.3, Table 11.4, and Table 11.5 for all optimised versions of the MPI multivariate logistic regression results and 6-month mortality.

Separate adjusted 6-month mortality ROC curves for the MPI with ARS score, MPI with RUDAS score and OPT-MPI adjusted for age or sex or both can be found in Appendix H - Figure 11.4, Figure 11.5, and Figure 11.6. For assessing discrimination, the area under the ROC curve for each optimised version of the MPI is summarised in Table 8.18. The predictive performance for optimised versions of the MPI did not substantially differ when compared the original MPI for 6-month mortality (Figure 8.2).

Table 8.18 Summary of AUC for MPI with ARS, MPI with RUDAS and OPT-MPI for 6-month mortality.

6-month	Adjusted	AUC	LCI	UCI
MPI-ARS				
	Age	0.65650	0.60540	0.70767
	Sex	0.65910	0.60742	0.71082
	Age & Sex	0.67270	0.61994	0.72553
MPI-RUDAS				
	Age	0.64430	0.59283	0.69570
	Sex	0.65480	0.60690	0.70279
	Age & Sex	0.66480	0.61399	0.71563
OPT-MPI				
	Age	0.64490	0.59307	0.69679
	Sex	0.64930	0.59828	0.70025
	Age & Sex	0.66410	0.61160	0.71657

Abbreviations: AUC: Area under the curve; LCI: Lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OPT-MPI: Optimised-Multidimensional Prognostic Index; UCI: Upper confidence interval.

8.3.3 Secondary outcomes

8.3.3.1 All-cause mortality

8.3.3.1.1 3-month mortality

Separate univariate and multivariate logistic regression analyses for the MPI with either the ARS score or RUDAS score or the OPT-MPI for 3-month mortality can be

found in Appendix H - Table 11.6, Table 11.7, and Table 11.8.

In univariate analysis, the MPI with ARS (OR 2.94, 95% CI 1.93 to 4.45) or MPI with RUDAS (OR 2.35, 95% CI 1.70 to 3.26) or OPT-MPI (OR 2.93, 95% CI 1.93 to 4.45) as a continuous variable were associated with 3-month mortality. The MPI with ARS, MPI with RUDAS score and OPT-MPI as a continuous variable were similar to the original MPI (Table 8.4).

The MPI with ARS (Mild: OR reference group; moderate: OR 3.13, 95% CI 1.73 to 5.65; severe: OR 8.25, 95% CI 3.33 to 20.44), MPI with RUDAS (Mild: OR reference group; moderate: OR 4.34, 95% CI 1.69 to 11.15; severe: OR 15.06, 95% CI 5.38 to 42.15), and OPT-MPI (Mild: OR reference group; moderate: OR 2.96, 95% CI 1.57 to 5.55; severe: OR 8.55, 95% CI 3.65 to 19.99) as a categorical variable were also associated with 3-month mortality. Refer to Appendix H - Table 11.6, Table 11.7, and Table 11.8 for all optimised versions of the MPI univariate logistic regression analyses for 3-month mortality. The MPI with RUDAS score as a categorical variable was similar to the original MPI (Table 8.4).

Separate unadjusted 3-month mortality ROC curves for the MPI with either the ARS score or RUDAS score or the OPT-MPI can be found in Appendix H (Figure 11.7, Figure 11.8, and Figure 11.9). In terms of discrimination, the area under the ROC curve for 3-month mortality was 0.67 (95% CI: 0.60 to 0.73) for the MPI with the ARS (Figure 11.7), 0.68 (95% CI: 0.63 to 0.74) for the MPI with the RUDAS (Figure 11.8), and 0.67 (95% CI: 0.60 to 0.73) for the OPT-MPI (Figure 11.9). These figures are similar to the original MPI (Figure 8.3).

In multivariate analysis, the MPI with ARS score and OPT-MPI as a continuous variable showed age was a significant predictor for 3-month mortality (MPI-ARS: *p*

value = 0.039; OPT-MPI: *p* value = 0.047) MPI with RUDAS score showed age was not a significant predictor for 3-month mortality (*p* value = 0.229). This is similar to the original MPI (Table 8.4). As for sex, this was a significant predictor for 3-month mortality for all optimised versions of the MPI (MPI-ARS: *p* value = 0.027; MPI-RUDAS: *p* value = 0.029; OPT-MPI: *p* value = 0.034). This was comparable to the original MPI (Table 8.4). Refer to Appendix H - Table 11.6, Table 11.7, and Table 11.8 for all optimised versions of the MPI multivariate logistic regression results and 3-month mortality.

Separate adjusted 3-month mortality ROC curves for the MPI with ARS score, MPI with RUDAS score, and OPT-MPI adjusted for age or sex or both can be found in Appendix H - Figure 11.9, Figure 11.10, and Figure 11.11. For assessing discrimination, the area under the ROC curve for each optimised version of the MPI is summarised in Table 8.19. The predictive performance for optimised versions of the MPI did not substantially differ when compared the original MPI for 3-month mortality (Figure 8.4).

Table 8.19 Summary of AUC for MPI with ARS, MPI with RUDAS and OPT-MPI for 3-month mortality.

3-month mortality	Adjusted	AUC	LCI	UCI
MPI-ARS				
	Age	0.69890	0.63310	0.76470
	Sex	0.68260	0.60843	0.75680
	Age & Sex	0.69670	0.62342	0.76999
MPI-RUDAS				
	Age	0.70610	0.63970	0.77246
	Sex	0.70030	0.63641	0.76412
	Age & Sex	0.71080	0.64323	0.77841
OPT-MPI				
	Age	0.69670	0.62958	0.76376
	Sex	0.68430	0.61255	0.75608
	Age & Sex	0.69830	0.62565	0.77096

Abbreviations: AUC: Area under the curve; LCI: Lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OPT-MPI: Optimised-Multidimensional Prognostic Index; UCI: Upper confidence interval.

8.3.3.1.2 1-month mortality

Separate univariate and multivariate logistic regression analyses for the MPI with either the ARS score or RUDAS score or the OPT-MPI for 1-month mortality can be found in Appendix H - Table 11.9, Table 11.10, and Table 11.11.

In univariate analysis, the MPI with ARS (OR 3.56, 95% CI 2.05 to 6.17) or MPI with RUDAS (OR 4.73, 95% CI 2.58 to 8.65) or OPT-MPI (OR 3.77, 95% CI 2.16 to 5.57) as a continuous variable were associated with 1-month mortality. The MPI with ARS, MPI with RUDAS score and OPT-MPI as a continuous variable were similar to the original MPI (Table 8.5).

The MPI with ARS (Mild: OR reference group; moderate: OR 2.59, 95% CI 1.15 to 5.85; severe: OR 13.58, 95% CI 4.83 to 38.23), MPI with RUDAS (Mild: OR reference group; moderate: OR 5.11, 95% CI 1.18 to 22.05; severe: OR 23.51, 95% CI 5.16 to 107.05), and OPT-MPI (Mild: OR reference group; moderate: OR 3.41, 95% CI 1.35 to 6.57; severe: OR 14.04, 95% CI 4.73 to 41.71) as a categorical variable were also associated with 1-month mortality. Refer to Appendix H - Table 11.9, Table 11.10, and Table 11.11 for all optimised versions of the MPI univariate logistic regression analyses for 1-month mortality. The MPI with RUDAS score as a categorical variable was similar to the original MPI (Table 8.5).

Separate unadjusted 1-month mortality ROC curves for the MPI with either the ARS score or RUDAS score or the OPT-MPI can be found in Appendix H - Figure 11.13, Figure 11.14, and Figure 11.15. In terms of discrimination, the area under the ROC curve for 1-month mortality was 0.68 (95% CI: 0.59 to 0.77) for the MPI with the ARS (Figure 11.13), 0.71 (95% CI: 0.64 to 0.79) for the MPI with the RUDAS (Figure 11.14), and 0.70 (95% CI: 0.62 to 0.78) for the OPT-MPI (Figure 11.15).

These figures are similar to the original MPI (Figure 8.5).

In multivariate analysis, the MPI with ARS score, MPI with RUDAS score, and OPT-MPI as a continuous variable showed age was not a significant predictor for 1-month mortality (MPI-ARS: *p* value = 0.165; MPI-RUDAS: p value = 0.514; OPT-MPI: *p* value = 0.202). This is similar to the original MPI (Table 8.5). Additionally, sex was not a significant predictor for 1-month mortality for all optimised versions of the MPI (MPI-ARS: *p* value = 0.062; MPI-RUDAS: *p* value = 0.069; OPT-MPI: *p* value = 0.073). This differed from the original MPI (Table 8.5) where sex was significant. Refer to Appendix H - Table 11.9, Table 11.10, and Table 11.11 for all optimised versions of the MPI multivariate logistic regression results and 1-month mortality.

Separate adjusted 1-month mortality ROC curves for the MPI with ARS score, MPI with RUDAS score, and OPT-MPI adjusted for age or sex or both can be found in Appendix H - Figure 11.16, Figure 11.17, and Figure 11.18). For assessing discrimination, the area under the ROC curve for each optimised version of the MPI is summarised in Table 8.20. The predictive performance for optimised versions of the MPI did not substantially differ when compared the original MPI for 1-month mortality (Figure 8.6).

Table 8.20 Summary of AUC for MPI with ARS, MPI with RUDAS and OPT-MPI for 1-month mortality.

1-month mortality	Adjusted	AUC	LCI	UCI
MPI-ARS				
	Age	0.7084	0.62155	0.79530
	Sex	0.6979	0.59602	0.79983
	Age & Sex	0.7100	0.61286	0.80708
MPI-RUDAS				
	Age	0.7205	0.63356	0.80739
	Sex	0.7310	0.64948	0.81247
	Age & Sex	0.7368	0.65543	0.81807
OPT-MPI				
	Age	0.7181	0.63177	0.80437
	Sex	0.7172	0.62579	0.80861
	Age & Sex	0.7261	0.63623	0.81591

Abbreviations: AUC: Area under the curve; LCI: Lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OPT-MPI: Optimised-Multidimensional Prognostic Index; UCI: Upper confidence interval.

8.3.3.2 In-hospital Outcomes

8.3.3.2.1 In-hospital all-cause mortality

Separate univariate and multivariate logistic regression analyses for the MPI with either the ARS score or RUDAS score or the OPT-MPI for in-hospital mortality can be found in Appendix H - Table 11.12, Table 11.13, and Table 11.14.

In univariate analysis, the MPI with ARS (OR 3.35, 95% CI 1.77 to 6.32) or MPI with RUDAS (OR 4.63, 95% CI 2.30 to 9.33) or OPT-MPI (OR 4.01, 95% CI 2.10 to 7.65) as a continuous variable were associated with in-hospital mortality. The MPI with RUDAS score as a continuous variable were similar to the original MPI (Table 8.6).

The MPI with ARS (Mild: OR reference group; moderate: OR 3.01, 95% CI 1.77 to 6.32; severe: OR 11.46, 95% CI 3.29 to 39.88) and OPT-MPI (Mild: OR reference group; moderate: OR 5.45, 95% CI 1.57 to 18.86; severe: OR 17.44, 95% CI 4.19 to 72.49) as a categorical variable were also associated with in-hospital mortality. These figures are lower than the original MPI (Table 8.6). As for the MPI with RUDAS, the severe risk group was associated with in-hospital mortality, however

the moderate risk group was not (Mild: OR reference group; moderate: OR 7.61, 95% CI 1.00 to 57.95; severe: OR 30.66, 95% CI 3.81 to 246.54). Refer to Appendix H - Table 11.12, Table 11.13, and Table 11.14 for all optimised versions of the MPI univariate logistic regression analyses for in-hospital mortality.

Separate unadjusted in-hospital mortality ROC curves for the MPI with either the ARS score or RUDAS score or the OPT-MPI can be found in Appendix H - Figure 11.19, Figure 11.20, and Figure 11.21. In terms of discrimination, the area under the ROC curve for in-hospital mortality was 0.68 (95% CI: 0.58 to 0.78) for the MPI with the ARS (Figure 11.19), 0.72 (95% CI: 0.63 to 0.80) for the MPI with the RUDAS (Figure 11.20), and 0.72 (95% CI: 0.63 to 0.80) for the OPT-MPI (Figure 11.21). These figures are similar to the original MPI (Figure 8.7).

In multivariate analysis, the MPI with ARS score, MPI with RUDAS score, and OPT-MPI as a continuous variable showed age was not a significant predictor for in-hospital mortality (MPI-ARS: *p* value = 0.154; MPI-RUDAS: *p* value = 0.429; OPT-MPI: *p* value = 0.216). Additionally, sex was not a significant predictor for in-hospital mortality for all optimised versions of the MPI (MPI-ARS: *p* value = 0.123; MPI-RUDAS: *p* value = 0.129; OPT-MPI: *p* value = 0.130). This is similar to the original MPI (Table 8.6). Refer to Appendix H - Table 11.12, Table 11.13, and Table 11.14 for all optimised versions of the MPI multivariate logistic regression results and in-hospital mortality.

Separate adjusted in-hospital mortality ROC curves for the MPI with ARS score, MPI with RUDAS score, and OPT-MPI adjusted for age or sex or both can be found in Appendix H - Figure 11.22, Figure 11.23, and Figure 11.24). For assessing discrimination, the area under the ROC curve for each optimised version of the MPI

is summarised in Table 8.21. The predictive performance for MPI with RUDAS score and OPT-MPI did not substantially differ when compared the original MPI for in-hospital mortality (Figure 8.8).

Table 8.21 Summary of AUC for MPI with ARS, MPI with RUDAS and OPT-MPI for in-hospital mortality.

In-hospital mortality	Adjusted	AUC	LCI	UCI
MPI-ARS				
	Age	0.7054	0.60226	0.80858
	Sex	0.7060	0.59116	0.82080
	Age & Sex	0.7096	0.59627	0.82295
MPI-RUDAS				
	Age	0.7262	0.62354	0.82881
	Sex	0.7366	0.64503	0.82811
	Age & Sex	0.7424	0.64410	0.84078
OPT-MPI				
	Age	0.7319	0.63235	0.83142
	Sex	0.7433	0.65057	0.83595
	Age & Sex	0.7439	0.64334	0.84442

Abbreviations: AUC: Area under the curve; LCI: Lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OPT-MPI: Optimised-Multidimensional Prognostic Index; UCI: Upper confidence interval.

8.3.3.2.2 Falls

Separate univariate and multivariate logistic regression analyses for the MPI with either the ARS score or RUDAS score or the OPT-MPI for in-hospital falls can be found in Appendix H - Table 11.15, Table 11.16, and Table 11.17.

In univariate analysis, the MPI with ARS (OR 1.54, 95% CI 0.76 to 3.12) or MPI with RUDAS (OR 2.02, 95% CI 0.98 to 4.18) or OPT-MPI (OR 1.77, 95% CI 0.89 to 3.52) as a continuous variable were not associated with in-hospital falls. This differed slightly to the original MPI where MPI as a continuous variable was associated with in-hospital falls (Table 8.7).

The MPI with ARS (Mild: OR reference group; moderate: OR 1.91, 95% CI 0.77 to 4.73; severe: OR 1.50, 95% CI 0.18 to 12.34) and OPT-MPI (Mild: OR reference group; moderate: OR 1.56, 95% CI 0.60 to 4.08; severe: OR 3.43, 95% CI 0.85 to

13.77) as a continuous variable were not associated with in-hospital falls. As for the MPI with RUDAS the severe risk category was associated with in-hospital falls, however the moderate risk group was not (Mild: OR reference group; moderate: OR 1.49, 95% CI 0.47 to 4.67; severe: OR 3.95, 95% CI 1.03 to 15.14). Results from the MPI with RUDAS are similar to the original MPI (Table 8.7). Refer to Appendix H - Table 11.15, Table 11.16, and Table 11.17 for all optimised versions of the MPI univariate logistic regression analyses for in-hospital falls.

Separate unadjusted in-hospital falls ROC curves for the MPI with either the ARS score or RUDAS score or the OPT-MPI can be found in Appendix H - Figure 11.25, Figure 11.26, and Figure 11.27. In terms of discrimination, the area under the ROC curve for in-hospital falls was 0.57 (95% CI: 0.46 to 0.68) for the MPI with the ARS (Figure 11.25), 0.60 (95% CI: 0.48 to 0.72) for the MPI with the RUDAS (Figure 11.26), and 0.59 (95% CI: 0.47 to 0.70) for the OPT-MPI (Figure 62). These figures are similar to the original MPI (Figure 8.9).

In multivariate analysis, the MPI with ARS score, MPI with RUDAS, and OPT-MPI as a categorical variable showed age was not a significant predictor for in-hospital falls (MPI-ARS: *p* value = 0.130; MPI-RUDAS: *p* value = 0.246; OPT-MPI: *p* value = 0.161). Additionally, sex was not a significant predictor for in-hospital falls for all optimised versions of the MPI (MPI-ARS: *p* value = 0.674; MPI-RUDAS: *p* value = 0.633; OPT-MPI: *p* value = 0.653). This is similar to the original MPI (Table 8.7). Refer to Appendix H - Table 11.15, Table 11.16, and Table 11.17 for all optimised versions of the MPI multivariate logistic regression results and in-hospital falls.

Separate adjusted in-hospital falls ROC curves for the MPI with ARS score, MPI with RUDAS score, and OPT-MPI adjusted for age or sex or both can be found in

Appendix H - Figure 11.28, Figure 11.29, and Figure 11.30. For assessing discrimination, the area under the ROC curve for each optimised version of the MPI is summarised in Table 8.22. The predictive performance of the optimised versions of the MPI for in-hospital falls did not substantially differ from that of the original MPI (Figure 8.10).

Table 8.22 Summary of AUC for MPI with ARS, MPI with RUDAS and OPT-MPI for in-hospital falls.

In-hospital falls	Adjusted	AUC	LCI	UCI
MPI-ARS				
	Age	0.6302	0.50905	0.75139
	Sex	0.5810	0.46271	0.69923
	Age & Sex	0.6200	0.49217	0.74779
MPI-RUDAS				
	Age	0.6395	0.51370	0.76530
	Sex	0.5869	0.46078	0.71307
	Age & Sex	0.6305	0.50017	0.76074
OPT-MPI				
	Age	0.6331	0.50704	0.75919
	Sex	0.5903	0.47085	0.70779
	Age & Sex	0.6254	0.49606	0.75467

Abbreviations: AUC: Area under the curve; LCI: Lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OPT-MPI: Optimised-Multidimensional Prognostic Index; UCI: Upper confidence interval.

Separate Poisson regression analyses for the MPI with either the ARS score or RUDAS score or the OPT-MPI for number of in-hospital falls can be found in Appendix H - Table 11.18, Table 11.19, and Table 11.20.

In Poisson regression analysis, the Incidence-Rate Ratio (IRR) for the MPI with ARS (IRR 1.07, 95% CI 0.53 to 2.19), MPI with RUDAS (IRR 1.27, 95% CI 0.62 to 2.62), and OPT-MPI (IRR 1.33, 95% CI 0.67 to 2.61) as a continuous variable were not associated with number of in-hospital falls. The MPI with ARS (Mild: IRR reference group; moderate: IRR 1.17, 95% CI 0.48 to 2.82; severe: IRR 0.92, 95% CI 0.12 to 2.82), MPI with RUDAS (Mild: IRR reference group; moderate: IRR 1.11, 95% CI 0.36 to 3.40; severe: IRR 1.62, 95% CI 0.40 to 6.46), and OPT-MPI (Mild: IRR reference group; moderate: IRR 1.14, 95% CI 0.44 to 2.93; severe: IRR

1.94, 95% CI 0.50 to 7.49) as a categorical variable were not associated with number of in-hospital falls. Additionally, in a multivariate analysis, both age (MPI-ARS: *p* value = 0.258; MPI-RUDAS: *p* value = 0.314; OPT-MPI: *p* value = 0.306) and sex (MPI-ARS: *p* value = 0.885; MPI-RUDAS: *p* value = 0.871; OPT-MPI: *p* value = 0.879) was not a predictor for number of in-hospital falls and all optimised versions of the MPI. Both univariate and multivariate analyses are similar to the original MPI (Table 8.8). Refer to Appendix H - Table 11.18, Table 11.19, and Table 11.20 for all optimised versions of the MPI univariate and multivariate Poisson regression results and number of in-hospital falls.

8.3.3.2.3 Delirium

Separate univariate and multivariate logistic regression analyses for the MPI with either the ARS score or RUDAS score or the OPT-MPI for in-hospital delirium can be found in Appendix H - Table 11.21, Table 11.22, and Table 11.23.

In univariate analysis, the MPI with ARS (OR 2.29, 95% CI 1.54 to 3.42), MPI with RUDAS (OR 3.08, 95% CI 2.00 to 4.74), and the OPT-MPI (OR 3.12, 95% CI 2.08 to 4.69) as a continuous variable were associated with in-hospital delirium. Results are similar to the original MPI (Table 8.9).

The OPT-MPI (Mild: OR reference group; moderate: OR 2.08, 95% CI 1.16 to 3.73; severe: OR 10.96, 95% CI 5.09 to 23.61) as a categorical variable was associated with in-hospital delirium. As for the MPI with ARS (Mild: OR reference group; moderate: OR 1.54, 95% CI 0.90 to 2.62; severe: OR 7.70, 95% CI 3.43 to 17.31) and MPI with RUDAS (Mild: OR reference group; moderate: OR 1.52, 95% CI 0.77 to 2.98; severe: OR 7.94, 95% CI 3.70 to 17.02), the severe risk category was associated with in-hospital delirium, however the moderate risk group was not.

These results are similar to the original MPI (Table 8.9).

Separate unadjusted in-hospital delirium ROC curves for the MPI with either the ARS score or RUDAS score or the OPT-MPI can be found in Appendix H - Figure 11.31, Figure 11.32, and Figure 11.33. In terms of discrimination, the area under the ROC curve for in-hospital delirium was 0.61 (95% CI: 0.54 to 0.68) for the MPI with the ARS (Figure 11.31), 0.65 (95% CI: 0.59 to 0.72) for the MPI with the RUDAS (Figure 11.32), and 0.66 (95% CI: 0.60 to 0.73) for the OPT-MPI (Figure 11.33). These figures are similar to the original MPI (Figure 8.11).

In multivariate analysis, the MPI with ARS score, MPI with RUDAS, and OPT-MPI as a continuous variable showed age (MPI-ARS: *p* value <0.0001; MPI-RUDAS: *p* value = 0.004; OPT-MPI: *p* value = 0.001) and sex (MPI-ARS: *p* value = 0.023; MPI-RUDAS: *p* value = 0.021; OPT-MPI: *p* value = 0.017) were significant predictors for in-hospital delirium. This is similar to the original MPI (Table 8.9). Refer to Appendix H - Table 11.21, Table 11.22, and Table 11.23 for all optimised versions of the MPI multivariate logistic regression results and in-hospital delirium.

Separate adjusted in-hospital delirium ROC curves for the MPI with ARS score, MPI with RUDAS score, and OPT-MPI adjusted for age or sex or both can be found in Appendix H - Figure 11.34, Figure 11.35, and Figure 11.36. For assessing discrimination, the area under the ROC curve for each optimised version of the MPI is summarised in Table 8.23. The predictive performance for optimised versions of the MPI did not substantially differ when compared to the original MPI for in-hospital delirium (Figure 8.12).

Table 8.23 Summary of AUC for MPI with ARS, MPI with RUDAS and OPT-MPI for in-hospital delirium.

In-hospital delirium	Adjusted	AUC	LCI	UCI
MPI-ARS				
	Age	0.6948	0.63075	0.75894
	Sex	0.6350	0.56883	0.70116
	Age & Sex	0.7035	0.63894	0.76797
MPI-RUDAS				
	Age	0.7053	0.63655	0.77414
	Sex	0.6740	0.60628	0.74179
	Age & Sex	0.7118	0.64417	0.77942
OPT-MPI				
	Age	0.7194	0.65216	0.78668
	Sex	0.6869	0.62322	0.75064
	Age & Sex	0.7272	0.66300	0.79134

Abbreviations: AUC: Area under the curve; LCI: Lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OPT-MPI: Optimised-Multidimensional Prognostic Index; UCI: Upper confidence interval.

8.3.3.2.4 Length of stay

Separate mean LOS for the MPI with ARS score, MPI with RUDAS score, OPT-MPI can be found in Appendix H - Figure 11.37, Figure 11.38, and Figure 11.39. Mean LOS for the MPI with ARS score (Mild: 8.21, SD 10.70; Moderate: 10.73, SD 10.39; Severe: 11.73, SD 8.37), MPI with RUDAS score (Mild: 6.99, SD 9.30; Moderate: 10.07, SD 11.03; Severe: 12.97, SD 9.51), and OPT-MPI (Mild: 7.79, SD 10.21; Moderate: 10.58, SD 10.67; Severe: 13.13, SD 10.15) were similar to the original MPI (Figure 8.13).

Separate Cox univariate and multivariate proportional hazards analyses considering time-varying changes in the MPI with ARS score, MPI with RUDAS score, and OPT-MPI for LOS can be found in Appendix H - Table 11.24, Table 11.25, and Table 11.26. Mild and moderate risk groups of the MPI with ARS (Mild: HR 0.9992, 95% CI 0.9988 to 0.9997; Moderate: HR 0.7235, 95% CI 0.6133 to 0.8534) and OPT-MPI (Mild: HR 0.9993, 95% CI 0.9989 to 0.9998; Moderate: HR 0.7439, 95% CI 0.6328 to 0.8745) were associated with LOS in days, however not for the severe risk group (MPI-ARS: HR 0.9997, 95% CI 0.9986 to 1.0009; OPT-MPI: HR 0.9996,

95% CI 0.9990 to 1.0003). As for the MPI with RUDAS score, all three risk categories were associated with LOS (Mild: HR 5.81, 95% CI 2.62 to 12.86; Moderate: HR 4.19, 95% CI 1.90 to 9.25; Severe: HR 1.75, 95% CI 1.25 to 2.45). These results of the MPI with RUDAS score were similar to the original MPI (Table 8.10). Survival curves for the three optimised versions of the MPI are shown in Appendix H - Figure 11.40, Figure 11.41, and Figure 11.42.

For the MPI with ARS score and OPT-MPI, age was a significant predictor for LOS (MPI-ARS: *p* value = 0.002; OPT-MPI: *p* value = 0.002), however was not significant for the MPI with RUDAS score (*p* value = 0.087). Sex was not a significant predictor for LOS for all three optimised versions of the MPI (MPI-ARS: *p* value = 0.364; MPI-RUDAS: *p* value = 0.344; OPT-MPI: *p* value = 0.476). This was similar to the original MPI (Table 8.10). Refer to Appendix H - Table 11.24, Table 11.25, and Table 11.26 for multivariate Cox proportional hazards analyses.

8.3.3.3 Re-admission

8.3.3.3.1 30-day re-admission rate

Separate univariate and multivariate competing risk analyses for the MPI with either the ARS score, MPI with RUDAS score, OPT-MPI for 30-day re-admission rate can be found in Appendix H - Table 11.27, Table 11.28, and Table 11.29.

In a competing risk analysis, the sub-hazard ratio for the three versions of the MPI as a continuous variable were not significant for 30-day re-admission rate (MPI-ARS: SHR 0.78, 95% CI 0.57 to 1.07; MPI-RUDAS: SHR 1.05, 95% CI 0.78 to 1.42; OPT-MPI: SHR 0.89, 95% CI 0.65 to 1.21). The sub-hazard ratio for the MPI with ARS, MPI with RUDAS, and OPT-MPI as a categorical variable were not significant for 30-day re-admission rate for moderate risk group (Mild risk: reference group;

MPI-ARS: SHR 0.89, 95% CI 0.61 to 1.29; MPI-RUDAS: SHR 1.29, 95% CI 0.83 to 2.00; OPT-MPI: SHR 0.97, 95% CI 0.66 to 1.41) and severe risk group (Mild risk: reference group; MPI-ARS: SHR 0.23, 95% CI 0.03 to 1.57; MPI-RUDAS: SHR 0.84, 95% CI 0.36 to 1.96; OPT-MPI: SHR 0.56, 95% CI 0.18 to 1.70). The MPI with RUDAS score as either continuous or categorical variable was similar to the original MPI (Table 8.11).

Neither age (MPI-ARS: *p* value = 0.439; MPI-RUDAS: *p* value = 0.656; OPT-MPI: *p* value = 0.508) or sex (MPI-ARS: *p* value = 0.866; MPI-RUDAS: *p* value = 0.619; OPT-MPI: *p* value = 0.744) were predictors for 30-day re-admission rate. These results were similar to the original MPI (Table 8.11). Refer to Appendix H - Table 11.27, Table 11.28, and Table 11.29 for optimised versions of the MPI univariate and multivariate competing risk regression analyses for 30-day re-admission rate.

8.3.3.3.2 3-month re-admission

Separate univariate and multivariate competing risk analyses for the MPI with either the ARS score, MPI with RUDAS score, OPT-MPI for 3-month re-admission rate can be found in Appendix H - Table 11.30, Table 11.31, and Table 11.32.

In a competing risk analysis, the sub-hazard ratio for the three versions of the MPI as a continuous variable were not significant for 3-month re-admission rate (MPI-ARS: SHR 0.96, 95% CI 0.78 to 1.18; MPI-RUDAS: SHR 1.19, 95% CI 0.97 to 1.46; OPT-MPI: SHR 1.11, 95% CI 0.91 to 1.36). The sub-hazard ratio for the MPI with ARS, MPI with RUDAS, and OPT-MPI as a categorical variable were not significant for 3-month re-admission rate for moderate risk group (Mild risk: reference group; MPI-ARS: SHR 0.99, 95% CI 0.77 to 1.27; MPI-RUDAS: SHR 1.34, 95% CI 1.00 to 1.79; OPT-MPI: SHR 1.17, 95% CI 0.91 to 1.51) and severe risk group (Mild risk:

reference group; MPI-ARS: SHR 0.82, 95% CI 0.42 to 1.61; MPI-RUDAS: SHR 1.29, 95% CI 0.80 to 2.07; OPT-MPI: SHR 1.11, 95% CI 0.65 to 1.88). The MPI with RUDAS score as either continuous or categorical variable was similar to the original MPI (Table 8.12).

Neither age (MPI-ARS: *p* value = 0.075; MPI-RUDAS: *p* value = 0.224; OPT-MPI: *p* value = 0.128) or sex (MPI-ARS: *p* value = 0.540; MPI-RUDAS: *p* value = 0.350; OPT-MPI: *p* value = 0.383) were predictors for 3-month re-admission rate. These results were similar to the original MPI (Table 8.12). Refer to Appendix H - Table 11.30, Table 11.31, and Table 11.32 for optimised versions of the MPI univariate and multivariate competing risk regression analyses for 3-month re-admission rate.

Separate Poisson regression analyses for the MPI with either the ARS score or RUDAS score or the OPT-MPI for age or sex or both for number of re-admissions within 3 months can be found in Appendix H - Table 11.33, Table 11.34, Table 11.35. In Poisson regression analysis, the Incidence-Rate Ratio (IRR) for the MPI with ARS (IRR 0.87, 95% CI 0.72 to 1.06), MPI with RUDAS (IRR 1.14, 95% CI 0.95 to 1.37), and OPT-MPI (IRR 0.99, 95% CI 0.83 to 1.19) as a continuous variable were not associated with number of re-admissions within 3 months. Results were similar to the original MPI (Table 8.13). The MPI with ARS score was significant for the severe risk group (IRR 0.46, 95% CI 0.22 to 0.98), however the moderate risk group was not significant (IRR 0.97, 95% CI 0.77 to 1.20). The MPI with RUDAS score was significant for the moderate risk group (IRR 1.51, 95% CI 1.16 to 1.96), however not for the severe risk category (IRR 1.01, 95% CI 0.64 to 1.59). Results from the MPI with RUDAS score were similar to the original MPI (Table 8.13). As for the OPT-MPI as a categorical variable was not significant (Mild:

IRR reference group; moderate: IRR 1.06, 95% CI 0.85 to 1.33; severe: IRR 0.819, 95% CI 0.49 to 1.37).

In a multivariate Poisson regression analysis, both age (MPI-ARS: *p* value = 0.977; MPI-RUDAS: *p* value = 0.462; OPT-MPI: *p* value = 0.845) and sex (MPI-ARS: *p* value = 0.387; MPI-RUDAS: *p* value = 0.202; OPT-MPI: *p* value = 0.287) was not a predictor for number of re-admissions within 3 months and all optimised versions of the MPI. Multivariate analyses of the MPI with RUDAS score are similar to the original MPI (Table 8.13). Refer to Appendix H - Table 11.33, Table 11.34, and Table 11.35 for all optimised versions of the MPI univariate and multivariate Poisson regression results and number of re-admissions within 3 months.

8.3.3.3.3 6-month re-admission

Separate univariate and multivariate competing risk analyses for the MPI with either the ARS score, MPI with RUDAS score, OPT-MPI for 6-month re-admission rate can be found in Appendix H - Table 11.36, Table 11.37, and Table 11.38.

In a competing risk analysis, the sub-hazard ratio for the MPI with ARS score and OPT-MPI as a continuous variable were not significant for 6-month re-admission rate (MPI-ARS: SHR 0.96, 95% CI 0.80 to 1.16; OPT-MPI: SHR 1.05, 95% CI 0.88 to 1.26). This is similar to the original MPI (Table 8.14). The MPI with RUDAS score as a continuous variable was significant for 6-month re-admission rate (SHR 1.17, 95% CI 1.02 to 1.34). The sub-hazard ratio for the MPI with ARS and OPT-MPI as a categorical variable were also not significant for 6-month re-admission rate for moderate risk group (Mild risk: reference group; MPI-ARS: SHR 1.00, 95% CI 0.81 to 1.24; OPT-MPI: SHR 1.12, 95% CI 0.89 to 1.38) and severe risk group (Mild risk: reference group; MPI-ARS: SHR 0.78, 95% CI 0.41 to 1.48; OPT-MPI: SHR

0.96, 95% CI 0.58 to 1.60). These figures are similar to the original MPI (Table 8.14). As for the categorical variable MPI with RUDAS score, the moderate risk group (SHR 1.59, 95% CI 1.30 to 1.94) was significant for 6-month re-admission rate; however the severe risk group was not (SHR 1.06, 95% CI 0.75 to 1.49).

In multivariate analysis, the MPI with ARS score and OPT-MPI as a categorical variable showed age (MPI-ARS: *p* value = 0.778; OPT-MPI: *p* value = 0.903) was not a significant predictor for 6-month re-admission rate, however was significant for the MPI with RUDAS score (*p* value = 0.042). Sex was not a significant predictor for 6-month re-admission rate for all three optimised versions of the MPI (MPI-ARS: *p* value = 0.553; MPI-RUDAS: *p* value = 0.169; OPT-MPI: *p* value = 0.645). This is similar to the original MPI (Table 8.14). Refer to Appendix H - Table 11.36, Table 11.37, and Table 11.38 for all optimised versions of the MPI multivariate logistic regression results and 6-month re-admission rate.

Separate Poisson regression analyses for the MPI with either the ARS score or RUDAS score or the OPT-MPI for age or sex or both for number of re-admissions within 6 months can be found in Appendix H - Table 11.39, Table 11.40, Table 11.41. In Poisson regression analysis, the Incidence-Rate Ratio (IRR) for the MPI with ARS (IRR 1.00, 95% CI 0.87 to 1.15) and MPI with RUDAS (IRR 1.07, 95% CI 0.89 to 1.29), and OPT-MPI (IRR 1.09, 95% CI 0.95 to 1.24) as a continuous variable were not associated with number of re-admissions within 6 months. These results differed from the original MPI (Table 8.15) with results significant for number of re-admissions within 6 months. The MPI with ARS score and MPI with RUDAS score were not significant for the moderate risk group (MPI-ARS: IRR 1.09, 95% CI 0.93 to 1.29; MPI-RUDAS: IRR 1.17, 95% CI 0.91 to 1.51) and severe

risk group (MPI-ARS: IRR 0.72, 95% CI 0.45 to 1.16; MPI-RUDAS: IRR 1.05, 95% CI 0.68 to 1.62). As for the OPT-MPI, the moderate risk group was significant for number of re-admissions within 6 months (IRR 1.23, 95% CI 1.04 to 1.46); however not for the severe risk group (IRR 0.88, 95% CI 0.60 to 1.30). These results differed from the original MPI (Table 8.15).

In a multivariate Poisson regression analysis, sex (MPI-ARS: *p* value = 0.283; MPI-RUDAS: *p* value = 0.169; OPT-MPI: *p* value = 0.216) were not a predictor for number of re-admissions within 6 months and all optimised versions of the MPI. Age was a predictor for number of re-admissions within 6 months for the MPI-RUDAS (*p* value = 0.042); however not for both MPI-ARS and OPT-MPI (MPI-ARS: *p* value = 0.237; OPT-MPI: *p* value = 0.150). Multivariate analyses of the MPI with RUDAS score are similar to the original MPI (Table 8.15). Appendix H - Table 11.39, Table 11.40, Table 11.41 for all optimised versions of the MPI univariate and multivariate Poisson regression results and number of re-admissions within 6 months.

8.4 MPI Factor analysis

8.4.1 6-month mortality

8.4.1.1 Confirmatory factor analysis

Assessment of the eight items (cohabitation status, number of medications, ADL, IADL, SMPSQ, ESS, CIRS, and MNA) of the MPI as a single construct through a confirmatory factor analysis is shown in Figure 8.15. Refer to Table 8.24 for standardised individual coefficients of each eight MPI items.

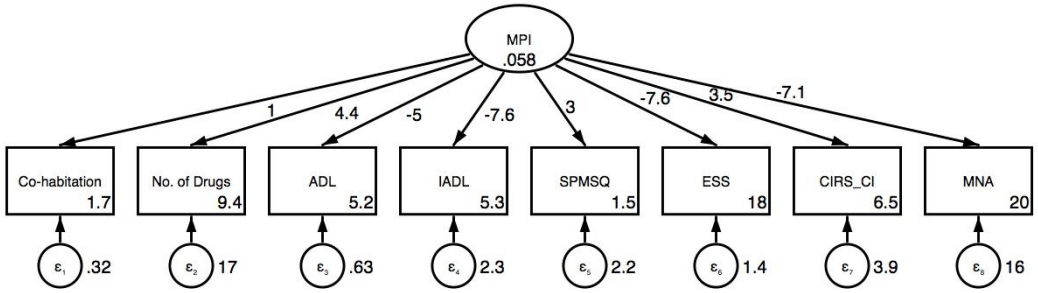


Figure 8.15 Structural equation model for the eight MPI items with error variance and standardised coefficients. Note: Ɛ: error variance. Abbreviations: ADL: Activity of daily living; CIRS-CI: Cumulative illness rating scale-illness severity score; ESS: Exton-Smith scale; IADL: Instrumental activities of daily living; MNA: Mini nutritional assessment; MPI: Multidimensional prognostic index; SPMSQ: Short portable mental status questionnaire.

Table 8.24 Structural equation model estimation for the eight MPI items.

Factor variable	Standardised Measurement	Coefficient	Standard error	*p* value	LCI	UCI
MPI						
	Cohabitation status	-0.02027	0.03977	*0.610*	-0.0982	0.0577
	Number of regular drugs	-0.24805	0.03745	*<0.0001*	-0.0321	-0.1746
	ADLscore	0.82193	0.01647	*<0.0001*	0.7896	0.8542
	IADLscore	0.74797	0.02046	*<0.0001*	0.7008	0.7881
	SPMSQscore	-0.43664	0.03260	*<0.0001*	-0.5005	-0.3727
	ESSscore	0.85713	0.01563	*<0.0001*	0.8265	0.8878
	CIRS CI	-0.39460	0.03405	*<0.0001*	-0.4613	-0.3279
	MNAscore	0.41143	0.03340	*<0.0001*	0.3460	0.4769
Variance error						
	Cohabitation status	0.99959	0.00161		0.9964	1.0028
	Number of regular drugs	0.93847	0.01858		0.9028	0.9756
	ADLscore	0.32444	0.02708		0.2755	0.3821
	IADLscore	0.44055	0.03060		0.3845	0.5048
	SPMSQscore	0.80935	0.02847		0.7554	0.8671
	ESSscore	0.26532	0.02679		0.2177	0.3234
	CIRS CI	0.84429	0.02687		0.7932	0.8986
	MNAscore	0.83072	0.02748		0.7786	0.8864
	Total MPI	1	-		-	-

Abbreviations: ADL: Activity of daily living; CIRS-CI: Cumulative illness rating scale-illness severity score; ESS: Exton-Smith scale; IADL: Instrumental activities of daily living; LCI: lower confidence interval MNA: Mini nutritional assessment; MPI: Multidimensional prognostic index; SPMSQ: Short portable mental status questionnaire; UCI: upper confidence interval.

For the MPI structure (Figure 11.3.1), goodness of fit test was statistically significant for the chi-square (χ^2) test (χ^2 (20) = 289.27; *p* value <0.0001). The root mean squared error of approximation (RMSEA) was 0.135, the Akaike's information criterion (AIC = 23,679.007) and Bayesian information criterion (BIC = 23,789.469)

were large. Other goodness of fit test for the Comparative fit index (CFI) was 0.845, the Tucker-Lewis index (TLI) was 0.783, and Standardized root mean squared residual (SRMR) of 0.079. These goodness of fit tests indicate poor model fit for the single factor eight item MPI.

8.4.1.2 Exploratory factor analysis

In an exploratory factor analysis using the eight items of the MPI with between 2 and 4 factors, a two factor model was identified: one factor related to physical function (ADL, IADL and ESS) and the other factor to comorbidities (number of drugs and CIRS-CI). Refer to Table 8.25 for individual factor loadings and Table 8.26 for standardised individual coefficients of the five MPI items.

Table 8.25 Exploratory factor analysis loadings for the eight MPI.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Uniqueness
Cohabitation status	-0.3745	0.0418	0.3772	-0.0054	0.7158
Number of regular drugs	-0.1335	**0.5755**	-0.0108	-0.0084	0.6508
ADLscore	**0.8032**	-0.0782	-0.0834	0.0247	0.3412
IADLscore	**0.7435**	-0.1882	-0.181	-0.0189	0.3787
SPMSQscore	-0.4583	-0.0600	0.0015	0.1096	0.7744
ESSscore	**0.8074**	-0.1612	0.1085	-0.0207	0.3099
CIRS CI	-0.2849	**0.5829**	0.0221	0.0021	0.5785
MNAscore	0.3815	-0.1569	0.2185	0.0372	0.7807

Abbreviations: ADL: Activity of daily living; CIRS-CI: Cumulative illness rating scale-illness severity score; ESS: Exton-Smith scale; IADL: Instrumental activities of daily living; MNA: Mini nutritional assessment; SPMSQ: Short portable mental status questionnaire.

Table 8.26 Structural equation model estimation for the two factor variables containing five MPI items.

Factor variable	Standardised Measurement	Coefficient	Standard error	p value	LCI	UCI
Comorbidities						
	Number of regular drugs	0.52937	0.04775	<0.0001	0.4358	0.6230
	CIRS CI	0.90837	0.06846	<0.0001	0.7742	1.0425
Physical function						
	ADL score	0.84767	0.01669	<0.0001	0.8150	0.8804
	IADL score	0.74420	0.02054	<0.0001	0.7039	0.7845
	ESS score	0.83909	0.01704	<0.0001	0.8057	0.8725
Variance error						
	Number of regular drugs	0.71977	0.05056		0.6272	0.8260
	CIRS CI	0.17487	0.12437		0.0434	0.7048
	ADLscore	0.28145	0.02829		0.2311	0.3427
	IADLscore	0.44617	0.03057		0.3901	0.5103
	ESS score	0.29593	0.02859		0.2449	0.3576
	Comorbidities	1	-		-	-
	Physical function	1	-		-	-

Abbreviations: ADL: Activity of daily living; CIRS-CI: Cumulative illness rating scale-illness severity score; ESS: Exton-Smith scale; IADL: Instrumental activities of daily living; LCI: lower confidence interval MNA: Mini nutritional assessment; MPI: Multidimensional prognostic index; SPMSQ: Short portable mental status questionnaire; UCI: upper confidence interval.

For the two factor MPI structure (Figure 8.16), for the goodness of fit test the χ^2 was lower than seen in the confirmatory factor analysis ($\chi^2(4) = 20.90$; p value = 0.0003). The RMSEA was within the 0.08 cut-off for good model fit (RMSEA = 0.076) and the AIC (15,438.769) and BIC (15,512.410) figures were lower than the confirmatory factor analysis. Other goodness of fit tests was 0.987 for the CFI, the TLI was 0.967, and the SRMR was 0.027. The goodness of fit tests indicates good model fit for the two factor solution.

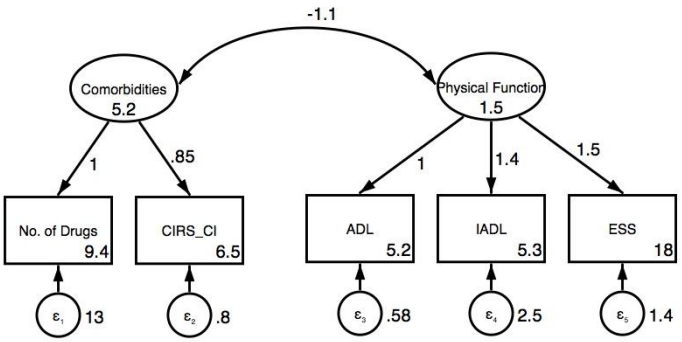


Figure 8.16 Structural equation model using two factors with error variance and standardised coefficients. Note: Ɛ: error variance. Abbreviations: ADL: Activity of daily living; CIRS-CI: Cumulative illness rating scale-illness severity score; ESS: Exton-Smith scale; IADL: Instrumental activities of daily living; MPI: Multidimensional prognostic index.

9 PART B - DISCUSSION

This study demonstrated that the validation of the MPI in a geographically different patient population showed inferior discrimination to that of the derivation and validation study for 6-month mortality (Pilotto et al. 2008). A relatively low discrimination was also observed with secondary outcomes (3-, 1-month mortality, in-hospital mortality, falls, and delirium). MPI associations with re-admission rate for 30 days, 3-, and 6-months, number of in-hospital falls, and number of re-admissions within 3- and 6-months were insignificant. Additional analyses using factor analysis showed that the assumption of equal weighting given to the eight domains of the original MPI is not appropriate. In addition, the MPI really consists of more than one underlying construct. There are 2 distinct constructs that can be derived using just 5 of the original 8 items. The other items should be considered as separate items to these 2 constructs.

For the primary outcome, when compared to the mild risk group (Mild: OR reference group), there was a three-fold increased odds of 6-month mortality for the moderate risk group (OR 2.98, 95% CI 1.82 to 4.87) and a five-fold increased odds for the severe risk group (OR 5.06, 95% CI 2.53 to 10.09). The area under the ROC curve was lower (AUC 0.63, 95% CI 0.58 to 0.67) when compared to the derivation study cohorts, (AUC 0.75, 95% CI 0.70 to 0.80 (Pilotto et al. 2008)). Four studies investigating the performance of the MPI for predicting 6-month mortality reported AUC figures between 0.79-0.81 (Giantin et al. 2013, Pilotto et al. 2009b, Pilotto et al. 2009c, Sancarlo et al. 2012), similar to the derivation study (Pilotto et al. 2008). However, three of the studies had a small sample size, between 134-262 patients (Giantin et al. 2013, Pilotto et al. 2009b, Pilotto et al. 2009c), and all studies were

conducted in patient populations with specific medical conditions (CAP (Pilotto et al. 2009b), dementia (Pilotto et al. 2009c), TIA (Sancarlo et al. 2012), and oncology patients (Giantin et al. 2013) with higher overall mortality risk.

For secondary mortality outcomes, the MPI was associated with 3- and 1-month mortality. The odds of 3-month mortality was slightly less than a four-fold increase for the moderate risk group (OR 3.80, 95% CI 1.68 to 8.59) and a twelve-fold increase for the severe risk group (OR 12.34, 95% CI 4.81 to 31.71) when compared to the mild risk group (Mild: OR reference group). As for 1-month mortality, a four-fold increase in odds was observed for the moderate risk group (OR 4.06, 95% CI 1.19 to 13.79) and a twenty-fold increase for the severe risk group (OR 20.16, 95% CI 5.49 to 74.11) when compared to the mild risk group (Mild: OR reference group). Discrimination of the MPI in the FMC study cohort, when assessed for 3-month mortality, was slightly higher (AUC 0.68, 95% CI 0.62 to 0.74) than that observed for the primary outcome (AUC 0.63, 6-month mortality). As for 1-month mortality, the MPI performed slightly worse (AUC 0.71, 95% CI 0.64 to 0.79) when compared to other similar patient population validation studies with AUC ranging from 0.76 to 0.77 (Fontana et al. 2013, Pilotto et al. 2012b, Sancarlo et al. 2011). Four other studies investigating the performance of the MPI for predicting 1-month mortality reported AUC figures between 0.79-0.80 (Pilotto et al. 2009a, Pilotto et al. 2009b, Pilotto et al. 2009c, Sancarlo et al. 2012). However, three of the studies had small sample size, between 134-262 patients (Pilotto et al. 2009a, Pilotto et al. 2009b, Pilotto et al. 2009c), and all studies were conducted in patient populations with specific medical conditions (GI bleed (Pilotto et al. 2009a), CAP (Pilotto et al. 2009b), dementia (Pilotto et al. 2009c), and TIA patients (Sancarlo et al. 2012)).

For secondary in-hospital outcomes, the MPI was associated with in-hospital mortality, and the MPI severe risk category was associated with in-hospital falls and delirium. The odds of in-hospital mortality were a nine-fold increase for the moderate risk group (OR 9.72, 95% CI 1.28 to 73.72) and a thirty-seven-fold increase for the severe risk group (OR 37.59, 95% CI 4.60 to 306.90) when compared to the mild risk group (Mild: OR reference group). For in-hospital falls and delirium, a four-fold (OR 4.38, 95% CI 1.22 to 15.63) and seven-fold (OR 7.64, 95% CI 3.62 to 16.13) increase in odds was observed for the severe risk group when compared to the mild risk group (Mild: OR reference group), respectively. No association of the MPI was observed for the moderate risk group for in-hospital falls (*p* value = 0.632) and delirium (*p* value = 0.246). No association was observed for the number of in-hospital falls for the MPI moderate risk group (*p* value = 0.792) and severe risk group (*p* value = 0.338). Discrimination of the MPI in the FMC study cohort, when assessed for in-hospital mortality, was similar (AUC 0.72, 95% CI 0.65 to 0.80) to other validation studies with AUC ranging between 0.76-0.85 (Pilotto et al. 2016a, Volpato et al. 2015). The AUC for the MPI performed poorly in the FMC study cohort for in-hospital falls (AUC 0.60, 95% CI 0.48 to 0.72) and delirium (AUC 0.64, 95% CI 0.49 to 0.77). When adjusted for age and sex, the AUC for delirium improved (AUC 0.71, 95% CI 0.63 to 0.78). At present, no study has assessed the performance of the MPI for predicting in-hospital falls and delirium. These outcomes were part of an exploratory analysis to gain further insight on the MPI and possible associations with different outcomes as the study was not powered for detecting the size of effect for in-hospital falls and delirium. The MPI was associated with LOS (in days) where patients in the mild, moderate, and severe risk group had five times (HR 5.12, 95% CI 2.22 to 11.85), four times (HR 3.90, 95% CI

1.69 to 9.00), and two times (HR 1.72, 95% CI 1.20 to 2.45) increased risk of earlier discharge, respectively. Mean LOS for the FMC study (Mild: 7.43 days, SD: 9.66, Moderate: 10.14 days, SD: 10.95, Severe days: 12.79 SD: 9.73) was shorter to other validation studies, with LOS ranging between 9.7-10.1 days for the mild risk group, 11.9-12.5 days for the moderate risk group, and 12.0-13.4 for the severe risk group (Pilotto et al. 2016a, Volpato et al. 2015). One of these studies assessed the MPI performance LOS with an AUC 0.74 (95% CI 0.71 to 0.77), however this study excluded patients who died within hospital and assessed LOS as a binary outcome (≤10 days versus >10 days) using logistic regression (Pilotto et al. 2016a).

For secondary re-admission outcomes, the MPI moderate risk category was associated with 3-month re-admission rate, number of re-admissions within 3 months, and 6-month re-admission rate. The moderate risk group had a 1.37-fold increase in the cumulative incidence amongst those who did not die within 3 months. As for the number of re-admissions within 3 months, the MPI moderate risk group had 1.53 (95% CI 1.19 to 1.97) times the rate of re-admission than those in the mild risk group. For the number of re-admissions within 6 months, the MPI moderate risk group had 1.64 (95% CI 1.36 to 1.99) times the rate of re-admission than those in the mild risk group. No associations were observed with the MPI for 30-day re-admission rate (Moderate: *p* value = 0.174; Severe: *p* value = 0.404), 3-month re-admission rate for the MPI severe risk group (*p* value = 0.649), the number of re-admissions within 3 months for the MPI severe risk group (*p* value = 0.730), 6-month re-admission rate for the MPI (Moderate: *p* value = 0.563; Severe: *p* value = 0.943), and the number of re-admission within 6 months for the MPI severe risk group (*p* value = 0.694). At present, there are no studies that assess the performance of the MPI for predicting re-admission rate for 30 days, 3- and 6-months. These

outcomes were part of an exploratory analysis to gain further insight on the MPI and possible associations with different outcomes as the study was not powered for detecting the size of effect for re-admission data.

An arising concern in geriatric patients is the increasing evidence that certain medications, in particular anticholinergics, with specific pharmacological effects might independently predict physical and cognitive decline and mortality in older adults and not the total number of drugs (Bostock et al. 2010, Ruxton et al. 2015). The ARS score is calculated by the sum of the ARS rankings assigned to each drug with anticholinergic effects based on their anticholinergic potency. Therefore, the MPI was optimised by substituting the number of drugs with the ARS score (Rudolph et al. 2008). In addition, the cognitive screen test (SPMSQ) in the MPI was substituted with the RUDAS which is a frontal lobe assessment and is suitable for a multicultural population (Storey et al. 2004). Separate analyses for the MPI with ARS score or RUDAS score will not be further discussed as results did not substantially differ from the optimised-MPI (with ARS and RUDAS scores). Optimising the MPI with the ARS and RUDAS scores was associated, for the primary outcome of 6-month mortality, with a two-fold odds of mortality for the moderate risk group (OR 2.43, 95% CI 1.61 to 3.68) and a four-fold odds for the severe risk group (OR 3.90, 95% CI 1.93 to 7.88) when compared to the mild risk group (Mild: OR reference group). The area under the ROC curve of the optimised MPI performed similar (AUC 0.62, 95% CI 0.57 to 0.67) to the MPI in this FMC study population. Adjusting for age and sex resulted in a slight improvement of the AUC, 0.66 (95% CI 0.61 to 0.72), however performance was still lower than what was observed in the MPI derivation study (Pilotto et al. 2008).

The optimised MPI for secondary outcomes was associated with 3-, and 1-month mortality, in-hospital mortality, in-hospital delirium, LOS for mild and moderate risk groups, and number of re-admissions within 6 months for the moderate risk group. The odds of 3-month mortality was a three-fold increase for the moderate risk group (OR 2.96, 95% CI 1.57 to 5.55) and an eight-fold increase for the severe risk group (OR 8.55, 95% CI 3.65 to 19.99) when compared to the mild risk group (Mild: OR reference group). As for 1-month mortality, a three-fold increase in odds was observed for the moderate risk group (OR 3.41, 95% CI 1.35 to 8.61) and a fourteen-fold increase for the severe risk group (OR 14.04, 95% CI 4.73 to 41.71) when compared to the mild risk group (Mild: OR reference group). In terms of discrimination, the optimised MPI showed similar AUC for 3- (AUC 0.67, 95% CI 0.60 to 0.73) and 1-month (AUC 0.70, 95% CI 0.62 to 0.78) mortality. Even with the MPI being optimised with the ARS and RUDAS scores the original MPI showed only slightly better associations for 3- and 1-month mortality and slightly better predictive performance.

Of the in-hospital outcomes, the optimised MPI was associated with in-hospital mortality and delirium. The odds of in-hospital mortality were a five-fold increase for the moderate risk group (OR 5.45, 95% CI 1.57 to 18.86) and a seventeen-fold increase for the severe risk group (OR 17.44, 95% CI 4.19 to 72.49) when compared to the mild risk group (Mild: OR reference group). As for delirium, a two-fold (OR 4.38, 95% CI 1.22 to 15.63) and eleven-fold (OR 7.64, 95% CI 3.62 to 16.13) increase in odds was observed for the moderate and severe risk groups when compared to the mild risk group (Mild: OR reference group), respectively. In terms of discrimination, the optimised MPI showed similar AUC for in-hospital mortality (AUC 0.72, 95% CI 0.63 to 0.80) and delirium (AUC 0.66, 95% CI 0.60 to 0.73).

Even with the MPI being optimised with the ARS and RUDAS scores the original MPI showed slightly better associations for in-hospital mortality and delirium and slightly better predictive performance. The optimised MPI was associated with LOS for patients in the mild and moderate risk group with a 1% increase risk of earlier discharge for the mild risk group (HR 0.9993, 95% CI 0.9989 to 0.9998) and a 26% increase risk of earlier discharge for the moderate risk group (HR 0.7439, 95% CI 0.6328 to 0.8745). The optimised MPI for the severe risk group was not significant (p = 0.286). Mean LOS for the optimised MPI (Mild: 7.79, SD: 10.21, Moderate: 10.58, SD: 10.67, Severe: 13.13 SD: 10.15) was similar to the MPI in this FMC study cohort.

For secondary re-admission outcomes, the optimised MPI was only associated with the moderate risk group for the number re-admissions with 6 months. The optimised MPI moderate risk group had 1.23 (95% CI 1.04 to 1.46) times the rate of re-admission than those in the mild risk group. Even with the MPI being optimised with the ARS and RUDAS scores the original MPI showed slightly better associations for re-admission rates (30-day, 3-, and 6-months) and number of re-admissions (3-, and 6-months).

In the derivation study, the eight items of the MPI had equal weighting indicating that the MPI formed a single construct (Pilotto et al. 2008). Using a confirmatory factor analysis, this indicated that the eight items of the MPI had poor goodness of fit test scores together indicating that the MPI does not consist of a single underlying construct. Therefore, an exploratory factor analysis was conducted to identify any strong correlations among the eight MPI items. In the FMC study cohort, two factors were identified: factor 1 (ADL IADL and ESS), and factor 2 (Number of drugs, and

CIRS_CI). Goodness of fit test for the simplified MPI showed good model fit. This study shows that the MPI can be simplified with fewer items, and assuming the presence of 2 underlying constructs. This simplification of the MPI was not validated in the FMC study cohort as the study sample size would not be sufficient. Therefore, the simplified MPI needs to be validated in a separate patient cohort to assess the predictive performance for the primary outcome.

This study has some limitations. The MPI in the derivation study was primarily constructed and validated for 12-month mortality (Pilotto et al. 2008). Due to time constraints, 12-month mortality was not assessed for the MPI in the FMC study cohort. Even though the derivation study assessed the MPI for 6-month mortality, performance in the FMC study cohort was significantly lower than the derivation study (Pilotto et al. 2008). Additionally, patient outcomes may have not been captured as health outcomes for patients are not on a national-wide database. Therefore, if patients moved outside of South Australia (SA) or were admitted to a private hospital within SA or interstate this would have been missed and may result in lower prevalence of outcomes. An additional limitation is that our findings represent current practices at a single centre and may not be a true representation of other populations. In particular, admission thresholds could differ from the derivation study (Pilotto et al. 2008) to the FMC study cohort with FMC admitting more severely ill patients into hospital. This could account for more patients being assigned into the moderate risk group of the MPI.

This study highlights concerns of the predictive performance of the MPI for use in different geographical and hospital patient populations. The performance of the MPI for 6-month mortality was less discriminative than previously reported. In addition,

optimising the MPI with the ARS and RUDAS score did not substantially improve the performance when compared to the original MPI. Future research should assess the applicability of the MPI by validation studies conducted in different geographical regions to that of the original MPI derivation population. Furthermore, exploratory analyses on in-hospital falls, delirium, and re-admission data show other possible outcomes that the MPI could be used for in future studies within larger patient populations. Overall, larger prospective multicentre studies of the performance of the MPI as well as simplified MPI scores are needed to confirm these findings before their application in routine clinical practice.

Part C

CONCLUDING REMARKS ON

CLINICAL PREDICTION RULES

10 PART C - CONCLUDING REMARKS

In the current era, the use of CPRs has become an increasingly popular EBM approach with the ultimate goal of improving health outcomes (Ebell 2001, Steyerberg 2008). In this study, two types of CPRs were assessed for their predictive performance at FMC. The first, Wells and revised Geneva scores, are currently used in clinical practice at FMC (Wells et al. 2000, Le Gal et al. 2006b). The second, MPI, has not been used in Australia (Pilotto et al. 2008). This study showed that the use of such tools in either a heterogeneous patient population (Wells and revised Geneva scores) and/or a different geographical population (MPI) can result in a substantially lower predictive performance. Importantly, validation of such CPRs in the target patient population is a crucial step before their introduction in routine clinical practice.

Many CPR models are developed for various clinical outcomes to enhance decision making (Vogenberg 2009, Traeger et al. 2017, Vickers and Elkin 2006, Wyatt and Altman 1995). Even though many CPRs are being developed yearly, there are relatively few studies of validation when compared to model development (Vogenberg 2009, Traeger et al. 2017, Vickers and Elkin 2006, Wyatt and Altman 1995). Importantly, internal validation of CPRs that show good predictive performance does not necessarily translate into automatic use in patient populations that are different from those originally investigated.

Validating CPRs in a different geographical region to that of the derivation study provides a more robust assessment of the tool's predictive performance (Steyerberg 2008). It is expected that the predictive performance of CPRs externally validated will tend to produce less favourable results than in the derivation study's internal

validation. The FMC study assessing the PE CPRs, Wells (Wells et al. 2000) and revised Geneva scores (Le Gal et al. 2006b), and the geriatric CPR, MPI (Pilotto et al. 2008), showed that the predictive performance was substantially lower to that of the derivation studies. Such differences in the performance figures may have arisen through external investigators using different definitions of predictors, outcomes, and patient selection (Steyerberg 2008). Another issue is that the case mix of patients varies from geographical regions with variances in admission thresholds under different health care institutes. Higher admission thresholds at an institute, i.e. more severely ill patients in hospital, may result in vast differences in the predictive performance of CPRs to the derivation studies. However, validating CPRs in a different geographical region provides important information regarding the applicability of such tools and future directions of poor CPRs by either adjusting predictor weightings or adding or removing predictor variables from the model (Steyerberg 2008, van Houwelingen 2000, Toll et al. 2008).

Another important factor to consider is the generalisability of CPRs (Wyatt and Altman 1995). Derivation studies usually apply exclusion criteria, as seen in the derivations studies of the Wells and revised Geneva scores (Wells et al. 2000, Le Gal et al. 2006b). In addition, other validation studies tend to follow the same exclusion criteria as to what was applied in derivation studies (Moons et al. 2009). Therefore, it is important to see if CPRs can be applied to an all-inclusive patient population with co-morbidities or other patient characteristics that would represent exclusion criteria in the development of the original scoring systems (Steyerberg 2008, Altman et al. 2009, Moons et al. 2009, Riley et al. 2016). At FMC, the Wells and revised Geneva scores are already implemented into clinical practice with no exclusions applied. The FMC study showed that the predictive performance of both PE scores were

substantially lower than the derivation studies (Wells et al. 2000, Le Gal et al. 2006b). Even applying similar exclusion criteria to that of the derivation studies, this did not change the predictive performance of both scores. A reason for such differences could be due to the PE CPRs primarily developed in ED/outpatients. In the FMC study, patients assessed with 24 hours (ED/outpatients) compared to those assessed post 24 hours (inpatients) had slightly higher predictive performance for both PE scores. However, this slight improvement in ED/outpatients was still lower than expected. Thus, it should not be assumed that CPRs can simply be generalised from one patient population to another and also limiting the number of exclusions of the study population would give a more realistic overall predictive performance of a CPR in an all-inclusive patient setting (Moons et al. 2009).

This study highlights several concerns regarding the routine use of original CPRs in different geographical patient populations or use in an all-inclusive patient population which the derivation studies did not assess. This highlights the importance and potential future research directions of validating CPRs in large prospective multicentre studies with patient populations representative of those for which the tools will be used as well as applicability of CPRs in different geographical healthcare populations.

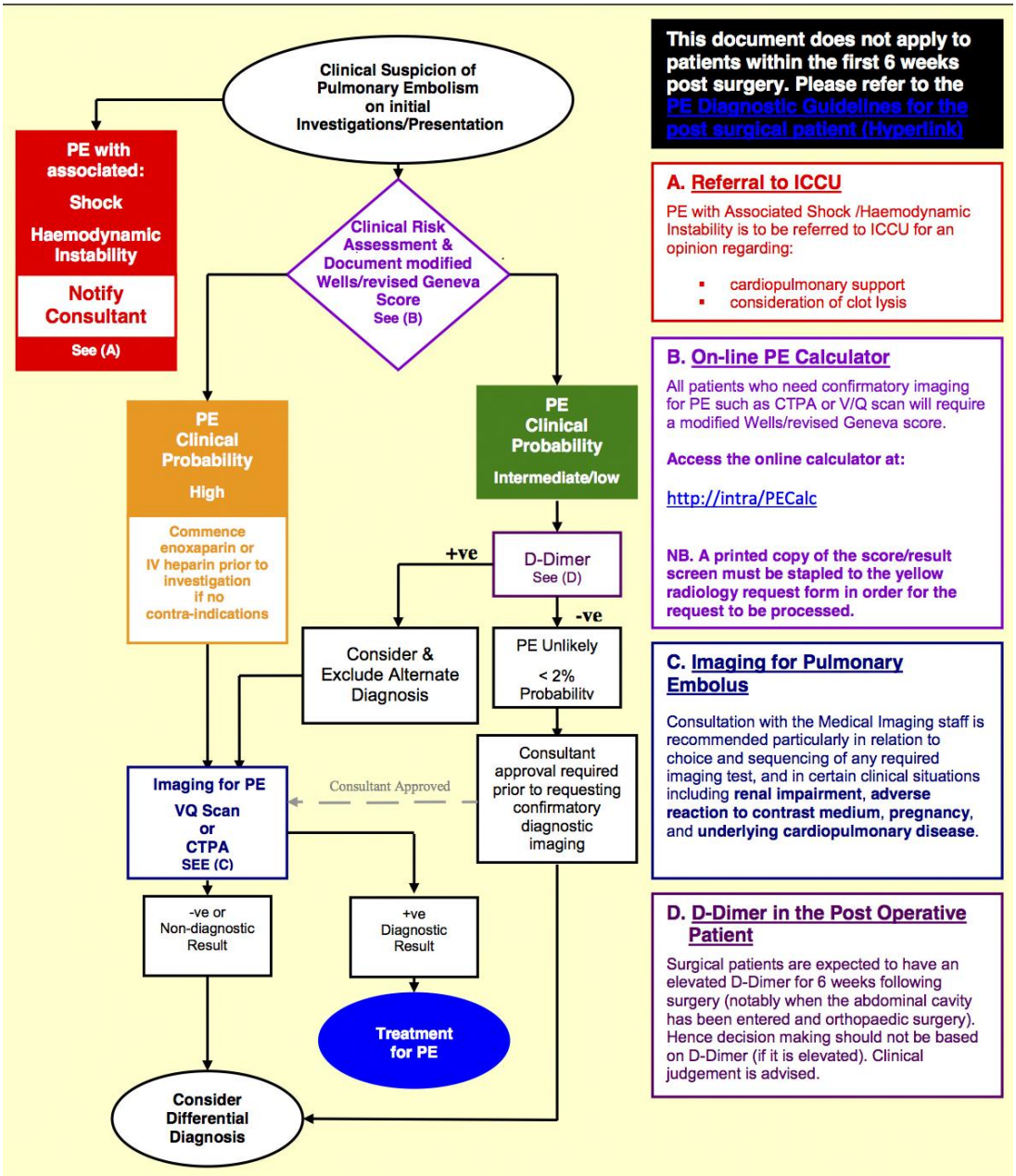
11 APPENDICES

APPENDIX A: FMC general patient algorithm for PE assessment

Government of South Australia
SA Health

Pulmonary Embolism (PE) Diagnostic Guidelines
For Patients Presenting with a Suspected Pulmonary Embolism

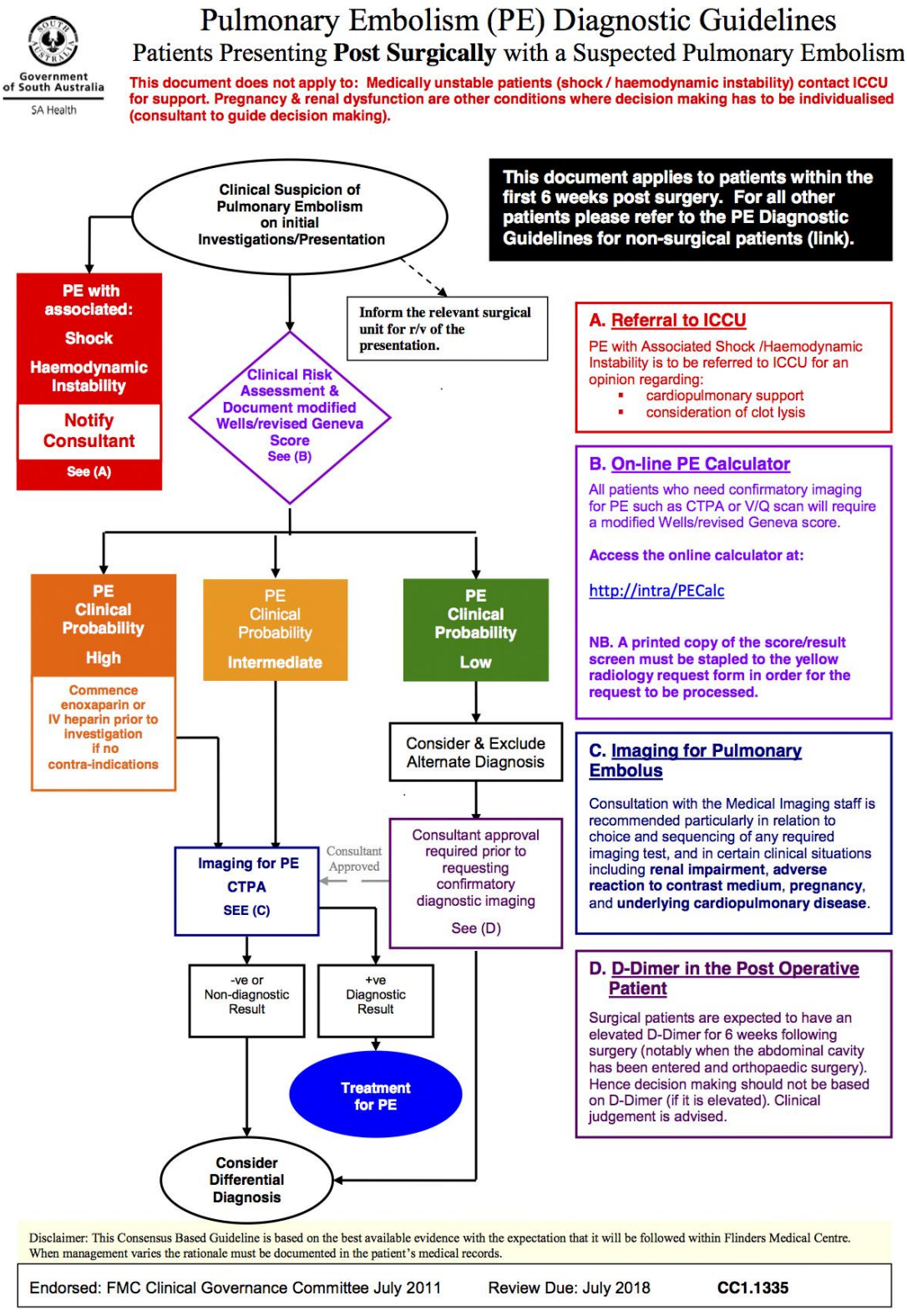
This document does not apply to: Medically unstable patients (shock / haemodynamic instability) contact ICCU for support. Pregnancy & renal dysfunction are other conditions where decision making has to be individualised (consultant to guide decision making).



Disclaimer: This Consensus Based Guideline is based on the best available evidence with the expectation that it will be followed within Flinders Medical Centre. When management varies the rationale must be documented in the patient's medical records.

Endorsed: FMC Clinical Governance Committee July 2011 Review Due: July 2018 **CC1.1334**

APPENDIX B: FMC post-surgical patient algorithm for PE assessment



APPENDIX C: FMC ethics approval letter for PE study

Southern Adelaide Clinical Human Research Ethics Committee

Government of South Australia
Southern Adelaide Health Service

02 April 2014

Dear Dr Rose

This is a formal correspondence from the Southern Adelaide Clinical Human Research Ethics Committee. Whilst this official title of the committee has changed the committee is still properly constituted under AHEC requirements with the registration number EC00188. This committee operates in accordance with the "National Statement on Ethical Conduct in Human Research (2007)." This department only uses email correspondence for all documents unless prior arrangements have been made with the manager. No hard copy correspondence will be issued.

Application Number: 287.10

Title: Implementing a clinical pathway in the evaluation of suspected pulmonary embolism, and a comparison of two clinical risk assessment tools

Chief Investigator: Dr Anand Rose

The Issue: The Southern Adelaide Health Service / Flinders University Human Research Ethics Committee (SAFUHREC) have approved the above project amendment. Your project may now incorporate these amendments into your research. The approval extends to the following documents/changes:

- Cover letter dated 27 March 2014
- SAC HREC General research application dated 27 March 2014
- SAC HREC annual review form for 2011
- SAC HREC annual review form for 2012
- SAC HRC annual review form for 2013
- Request for ethics approval extension for two years

Approval period: **02 April 2014 – 02 April 2016**

Please read the terms and conditions of ethical approval below, as researchers have a significant responsibility to comply with reporting requirements and the other stated conditions.

For example, the implications of not providing annual reports and requesting an extension for research prior to approval expiring could lead to the suspension of the research, and has further serious consequences.

Please retain a copy of this approval for your records.

Flinders Medical Centre

The Flats G5 – Rooms 3 and 4

Flinders Drive, Bedford Park SA 5042

T: 08 8204 6453

E:Research.ethics @health.sa.gov.au

APPENDIX D: FMC ethics approval letter for MPI study

FLINDERS MEDICAL CENTRE

Government of South Australia
Southern Adelaide Health Service

19 August 2015

Professor Arduino Mangoni
Department of Clinical Pharmacology
Flinders Medical Centre
BEDFORD PARK SA 5042

Dear Professor Mangoni

HREC reference number:	HREC/15/SAC/140 (170.15)
SSA reference number:	SSA/15/SAC/275
Project title:	Assessment and validation of a Multidimensional Prognostic Index in older inpatients
Ethics approval:	29 June 2015 – 29 June 2018
Site:	Flinders Medical Centre
Subject:	Site Specific Assessment Review

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to commence.

- SAC HREC approval letter dated 29 June 2015
- Site Specific Assessment form
- CV for Professor Arduino Mangoni
- Deed poll by Kimberley Ruxton dated 17 July 2015
- Flinders University indemnity approval dated 08 April 2015
- SA Health indemnity approval dated 30 April 2015
- Participant information sheet and consent form v2 dated 16 June 2015
- Participant information sheet and consent form – person responsible v2 dated 16 June
- 2015
- The Rowland Universal Dementia Assessment Scale: a multicultural cognitive
- assessment scale (RUDAS) –no date
- Multidimensional Prognostic Index (MPI) – no date
- Abbreviated Mental test Score – no date

HREC reviewed documents listed on the approval letter dated 29 June 2015 from the SAC HREC are accepted as part of the site authorisation.

Should you have any queries about the consideration of your Site Specific Assessment form, please contact Timothy Jones on 8204 4507.

The SSA reference number should be quoted in any correspondence about this matter.

If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.

Yours sincerely

Timothy Jones
Acting Research Governance Officer, Southern Adelaide Local Health Network

Flinders Medical Centre
The Flats G5 – Rooms 3 and 4
Flinders Drive, Bedford Park SA 5042
T: 08 8204 6453
F: 08 8204 4586
E:Research.ethics @health.sa.gov.au

APPENDIX E: AMT score paper

Abbreviated Mental Test Score

Patient's details: **Date of test:**		
Scoring *Each correctly answered question scores 1 point.*		
Interpretation *Scores ≤ 7 is indicative of likely cognitive impairment.*		
Comment on alertness level: Alert/normal Vigilant Lethargic Stupor Coma Uncertain		
Instrument		
1. Age	0	1
2. Time (to nearest hour)	0	1
3. Address (for recall at end of test) Say to patient: I am going to say an address: '42 West Street' Can you say that address please? I am going to ask you to repeat it for me in a few minutes.	0	1
4. Year	0	1
5. Name your home address	0	1
6. Recognition of two persons/objects	0	1
7. Date of birth	0	1
8. Year of First/Second World War	0	1
9. Name of current Taoiseach	0	1
10. Count backwards 20-1	0	1
TOTAL SCORE		
Signature of Examiner_____ Source: Commonwealth Dept. Health & Human Services (1996) Dementia Kit. Canberra AGPS		

APPENDIX F: RUDAS score paper

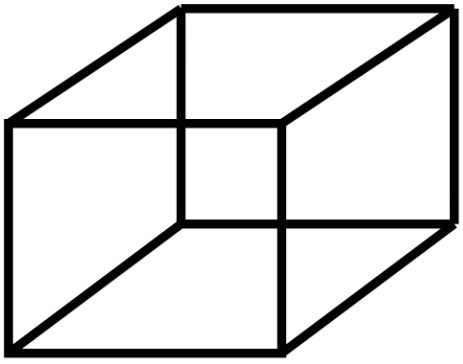
R U D A S

The Rowland Universal Dementia Assessment Scale: A Multicultural Cognitive Assessment Scale.
(Storey, Rowland, Basic, Conforti & Dickson, 2004). International Psychogeriatrics, 16 (1), 13-31

Date: ____/____/____ Patient **Name:** _____

Item		Max Score
Memory 1. (Instructions) I want you to imagine that we are going shopping. Here is a list of grocery items. I would like you to remember the following items which we need to get from the shop. When we get to the shop in about 5 mins. time I will ask you what it is that we have to buy. You must remember the list for me. **Tea, Cooking Oil, Eggs, Soap** Please repeat this list for me (ask person to repeat the list 3 times)**.** (If person did not repeat all four words, repeat the list until the person has learned them and can repeat them, or, up to a maximum of five times.)		
Visuospatial Orientation 2. I am going to ask you to identify/show me different parts of the body. *(Correct = 1)*. Once the person correctly answers 5 parts of this question, do not continue as the maximum score is 5.		
(1) show me your right foot	1	
(2) show me your left hand	1	
(3) with your right hand touch your left shoulder	1	
(4) with your left hand touch your right ear	1	
(5) which is (indicate/point to) my left knee	1	
(6) which is (indicate/point to) my right elbow	1	
(7) with your right hand indicate/point to my left eye	1	
(8) with your left hand indicate/point to my left foot	1	
		..../5
Praxis 3. I am going to show you an action/exercise with my hands. I want you to watch me and copy what I do. Copy me when I do this . . . (One hand in fist, the other palm down on table - alternate simultaneously.) Now do it with me: Now I would like you to keep doing this action at this pace until I tell you to stop - approximately 10 seconds. (Demonstrate at moderate walking pace). Score as: *Normal* = 2 *(very few if any errors; self-corrected, progressively better; good maintenance; only very slight lack of synchrony between hands)* *Partially Adequate* = 1 *(noticeable errors with some attempt to self-correct; some attempt at maintenance; poor synchrony)* *Failed* = 0 *(cannot do the task; no maintenance; no attempt whatsoever)*		
		..../2
Visuoconstructional Drawing 4. Please draw this picture exactly as it looks to you (Show cube on back of page). *(Yes = 1)* Score as:		
(1) Has person drawn a picture based on a square?	1	
(2) Do all internal lines appear in person's drawing?	1	
		
(3) Do all external lines appear in person's drawing?	1	
		
		..../3
Judgment 5. You are standing on the side of a busy street. There is no pedestrian crossing and no traffic lights. Tell me what you would do to get across to the other side of the road **safely**. (If person gives incomplete response that does not address both parts of answer, use prompt: "Is there anything else you would do?") Record exactly what patient says and circle all parts of response which were prompted.		
Score as: Did person indicate that they would look for traffic? *(YES = 2;YES PROMPTED = 1; NO = 0)* Did person make any additional safety proposals? *(YES = 2;YES PROMPTED = 1; NO = 0)*	.....2 2	
		..../4

Memory Recall 1. (Recall) We have just arrived at the shop. Can you remember the list of groceries we need to buy? (Prompt: If person cannot recall any of the list, say "The first one was 'tea'." *(Score 2 points each for any item recalled which was not prompted – use only 'tea' as a prompt.)* *Tea* .....2 *Cooking Oil* .....2 *Eggs* .....2 *Soap* .....2 **..../8** **Language** 6. I am going to time you for one minute. In that one minute, I would like you to tell me the names of as many different animals as you can. We'll see how many different animals you can name in one minute. (Repeat instructions if necessary). Maximum score for this item is 8. If person names 8 new animals in less than one minute there is no need to continue. 1. ..... 5. ..... 2. ..... 6. ..... 3. ..... 7. ..... 4. ..... 8. ..... **..../8**		
TOTAL SCORE =		**/30**



APPENDIX G: MPI score paper

REGIONE DEL VENETO
AZIENDA ULSS 16 PADOVA

OSPEDALE S. ANTONIO
Unità Operativa Complessa di GERIATRIA

MULTIDIMENSIONAL PROGNOSTIC INDEX (MPI) *

CO-HABITATION STATUS

Does the patient live:	
Alone	
With family/other	
In institution	

MEDICATION USE

Number of drugs used	

** Pilotto A, Ferrucci L, Franceschi M et al. Development and validation of a Multidimensional Prognostic Index for 1-Year Mortality from a Comprehensive Geriatric Assessment in Hospitalized Older Patients. Rejuvenation Res 2008;11:151-161.*

ACTIVITIES OF DAILY LIVING (ADL) *

A) **BATHING** (either sponge bath, tub bath, or shower)	
- Receives no assistance (gets in and out of tub by self if tub is usual means of bathing)	1
- Receives assistance in bathing only one part of the body (such as back or a leg)	1
- Receives assistance in bathing more than one part of the body (or not bathed)	0
B) **DRESSING** (gets clothes from closets and drawers – including underclothes, outer garments, and using fasteners including braces, if worn)	
- Gets clothes and gets completely dressed without assistance	1
- Gets clothes and gets dressed without assistance except for assistance in tying shoes	1
- Receives assistance in getting clothes or in getting dressed, or stays partly or completely undressed	0
C) **TOILETING** (going to the "toilet room" for bowel and urine elimination, cleaning self after elimination, and arranging clothes)	
- Goes to "toilet room," cleans self, and arranges clothes without assistance (may use object for support such as cane, walker, or wheelchair and may manage night bedpan or commode, emptying same in morning)	1
- Receives assistance in going to "toilet room" or in cleaning self or in arranging clothes after elimination or in use of night bedpan or commode	0
- Doesn't go to room termed "toilet" for the elimination process	0
D) **TRANSFER**	
- Moves in and out of bed as well as in and out of chair without assistance (may be using object for support such as cane or walker)	1
- Moves in and out of bed or chair with assistance	0
- Doesn't get out of bed	0
E) **CONTINENCE**	
- Controls urination and bowel movement completely by self	1
- Has occasional "accidents"	0
- Supervision helps keep urine or bowel control, catheter is used, or is incontinent	0
F) **FEEDING**	
- Feeds self without assistance	1
- Feeds self except for getting assistance in cutting meat or buttering bread	1
- Receives assistance in feeding or is fed partly or completely by using tubes or intravenous fluids	0

TOTAL _____

** Katz S, Ford AB, Moskowitz RW et al. Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychological function. JAMA 1963; 185: 914-19.*

INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (IADL)*

A) **ABILITY TO USE TELEPHONE**	
- Operates telephone on own initiative: looks up and dials numbers, etc.	1
- Dials a few well-known numbers	1
- Answers telephone but does not dial	1
- Does not use telephone at all	0
B) **SHOPPING**	
- Takes care of all shopping needs independently	1
- Shops independently for small purchases	0
- Needs to be accompanied on any shopping trip	0
- Completely unable to shop	0
C) **FOOD PREPARATION**	
- Plans, prepares and serves adequate meals independently	1
- Prepares adequate meals if supplied with ingredients	0
- Heats, serves and prepares meals or prepares meals but does not maintain adequate diet	0
- Needs to have meals prepared and served	0
D) **HOUSEKEEPING**	
- Maintains house alone or with occasional assistance (e.g. "heavy work domestic help")	1
- Performs light daily tasks such as dishwashing, bed making, etc.	1
- Performs light daily tasks but cannot maintain acceptable level of cleanliness	1
- Needs help with all home maintenance tasks	0
- Does not participate in any housekeeping tasks	0
E) **LAUNDRY**	
- Does personal laundry completely	1
- Launders small items; rinses stockings, etc.	1
- All laundry must be done by others	0
F) **MODE OF TRANSPORTATION**	
- Travels independently on public transportation or drives own car	1
- Arranges own travel via taxi, but does not otherwise use public transportation	1
- Travels on public transportation when accompanied by another	1
- Travel limited to taxi or automobile with assistance of another	0
- Does not travel at all	0
G) **RESPOSIBILITY FOR OWN MEDICTIONS**	
- Is responsible for taking medication in correct dosages at correct time	1
- Takes responsibility if medication is prepared in advance in separate dosage	0
- Is not capable of dispensing own medication	0
H) **ABILITY TO HANDLE FINANCES**	
- Manages financial matters independently (budgets, writes checks, pays rent, bills goes to bank), collects and keeps track of income	1
- Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
- Incapable if handling money	0

TOTAL _____

***** *Lawton MP, Brody EM. Assessment of older people:self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-86.*

SHORT PORTABLE MENTAL STATUS QUESTIONNAIRE (SPMSQ) *

(Record the errors)

What is the date today? (Correct only when the month, date, and year are all correct)	1
What day of the week is it?	1
What is the name of this place? (Correct if any of the description of the location is given)	1
What is your street address?	1
How old are you?	1
When were you born?	1
Who is the Prime Minister now? (Requires only the correct last name)	1
Who was the Prime Minister before?	1
What was your mother's maiden name?	1
Subtract 3 from 20 and keep subtracting 3 from each new number at least for 3 times (The entire series must be performed correctly to be scored as correct)	1

TOTAL _____

** Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. J Am Geriatr Soc. 1975; 23:433-441.*

EXTON-SMITH SCALE (ESS) *

(evaluation of pressure sores risk)

General Condition		**Incontinence**	
Bad	1	Doubly incontinent	1
Poor	2	Usually of urine	2
Fair	3	Occasional	3
Good	4	Not	4
Mental State		**Mobility in Bed**	
Stuporosous	1	Immobile	1
Confused	2	Very limited	2
Apathetic	3	Slightly limited	3
Alert	4	Full	4
Activity			
In bed all day	1	**TOTAL _____**	
Chairfast	2		
Walks with help	3	*Score 16-20: minimum risk*	
Ambulant	4	*Score 10-15: medium risk*	
		Score 5-9: high risk	

** Bliss MR., McLaren R., Exton-Smith AN. Mattresses for preventing pressure sores in geriatric patients. Mon Bull Minist Health Public Health Lab Serv 1966*

CUMULATIVE ILLNESS RATING SCALE (C.I.R.S.) *

	NONE	MILD	MODERATE	SEVERE	EXTREMELY SEVERE
1. Cardiac (heart only)	1	2	3	4	5
2. Hypertension (rating is based on severity)	1	2	3	4	5
3. Vascular (arteries, veins, lymphatics)	1	2	3	4	5
4. Respiratory (lungs, bronchi, trachea)	1	2	3	4	5
5. EENT (eye, ear, nose, throat, larynx)	1	2	3	4	5
6. Upper GI (esophagus, stomach, duodenum, biliary and pancreatic trees)	1	2	3	4	5
7. Lower GI (intestines, hernias)	1	2	3	4	5
8. Hepatic (liver only)	1	2	3	4	5
9. Renal (kidneys only)	1	2	3	4	5
10. Other GU (ureters, bladder, urethra, prostate, genitals)	1	2	3	4	5
11. Musculo-skeletal-integumentary (muscles, bone, skin)	1	2	3	4	5
12. Neurological (brain, spinal cord, nerves)	1	2	3	4	5
13. Endocrine-metabolic (including diabetes, hyperlipidemia, infections, toxicity)	1	2	3	4	5
14. Psychiatric (dementia, depression, anxiety, agitation, psychosis)	1	2	3	4	5

ILLNESS SEVERITY SCORE (CIRS-IS) mean of all single item (excluded the psychiatric item)	**COMORBIDITY INDEX (CIRS-CI)** number of items with a score of 3 or greater (excluded the psychiatric item)
_____	_____

***** *Conwell Y, Forbes NT, Cox C, Caine ED. Validation of a measure of physical illness burden at autopsy: the Cumulative Illness Rating Scale. J Am Geriatr Soc 1993; 41: 38-41.*

MINI NUTRITIONAL ASSESSMENT (MNA) *

A) Anthropometric Assessment

1) Body Mass Index (BMI) Weight:_____kg Height:_____cm	0 BMI <19	1 BMI = 19-20	2 BMI = 21-22	3 BMI ≥ 23
2) Mid-arm circumference (MAC) in cm_____	0 MAC<21	0.5 MAC ≤ 22	1 MAC > 22	
3) Calf circumference (CC) in cm_____	0 CC < 31	1 CC ≥ 31		
4) Weight loss (last three months)	0 loss > 3Kg	1 does not know	2 loss between 1-3Kg	3 no weight loss

B) General Assessment

5) Lives independently (not in a nursing home or hospital)			0 no	1 yes
6) Takes more than 3 prescription drugs per day			0 yes	1 no
7) Has suffered psychological stress or acute disease in the past 3 months			0 yes	2 no
8) Mobility	0 bed or chair bound	1 able to get out of bed/chair but does not go out	2 goes out	
9) Neuropsychological problems	0 severe dementia or depression	1 mild dementia	2 no psychological problems	
10) Pressure sores or skin ulcers			0 yes	1 no

C) Dietary Assessment

11) How many full meals does the patient eat daily?	0 1 meal	1 2 meals	2 3 meals
12) Consumes: Points if: 1 yes 0 2 yes 0.5 3 yes 1	at least 1 serving of dairy products (milk, cheese, yogurt) per day yes no	2 or more servings of legumes or eggs per week yes no	meat, fisk or poultry every day yes no
13) Consumes 2 or more servings of fruits or vegetables per day?	0 no	1 yes	
14) Has food intake declined over the past 3 months due to loss of appetite?	0 severe loss of appetite	1 moderate loss of appetite	2 no loss of appetite
15) How much fluidi s consumed per day?	0 less than 5 glasses	0.5 5 to 9 glasses	1 more than 9 glasses
16) Mode of feeding	0 with assistance	1 self-feed with some difficulty	2 self-feed without any problem

D) Self Assessment

17) Do they view themselves a s having nutritional problems?	0 major malnutrition	1 does not know	2 no nutritional problems	
18) In comparison with other people of same age, how they consider their health status?	0 not as good	0.5 does not know	1 as good	2 better
			TOTALE (max 30 punti)_____	
MALNUTRITION INDICATOR SCORE: ≥ 24 = well-nourished, 17-23.5 = at risk of malnutrition, < 17 = malnourished				

** Vellas B et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999; 15: 116-22.*

Normogram for the calculation of knee height

HEIGHT (m)	Men (18-59 years)	1.94	1.93	1.92	1.91	1.90	1.89	1.88	1.87	1.865	1.86	1.85	1.84	1.83	1.82	1.81
	Men (60-90 years)	1.94	1.93	1.92	1.91	1.90	1.89	1.88	1.87	1.86	1.85	1.84	1.83	1.82	1.81	1.80
	Knee height (cm)	6 5	64.5	64	63.5	63	62.5	62	61.5	61	60.5	60	59.5	59	58.5	58
HEIGHT (m)	Women (18-59 years)	1.89	1.88	1.875	1.87	1.86	1.85	1.84	1.83	1.82	1.81	1.80	1.79	1.78	1.77	1.76
	Women (60-90 years)	1.86	1.85	1.84	1.835	1.83	1.82	1.81	1.80	1.79	1.78	1.77	1.76	1.75	1.74	1.73
HEIGHT (m)	Men (18-59 years)	1.80	1.79	1.78	1.77	1.76	1.75	1.74	1.73	1.72	1.71	1.705	1.70	1.69	1.68	1.67
	Men (60-90 years)	1.79	1.78	1.77	1.76	1.74	1.73	1.72	1.71	1.70	1.69	1.68	1.67	1.66	1.65	1.64
	Knee height (cm)	57.5	57	56.5	56	55.5	55	54.5	54	53.5	53	52.5	52	51.5	51	50.5
HEIGHT (m)	Women (18-59 years)	1.75	1.74	1.735	1.73	1.72	1.71	1.70	1.69	1.68	1.67	1.66	1.65	1.64	1.63	1.62
	Women (60-90 years)	1.72	1.71	1.70	1.69	1.68	1.67	1.66	1.65	1.64	1.63	1.625	1.62	1.61	1.60	1.59
HEIGHT (m)	Men (18-59 years)	1.66	1.65	1.64	1.63	1.62	1.61	1.60	1.59	1.58	1.57	1.56	1.555	1.55	1.54	1.53
	Men (60-90 years)	1.63	1.62	1.61	1.60	1.59	1.58	1.57	1.56	1.55	1.54	1.53	1.52	1.51	1.49	1.48
	Knee height (cm)	5 0	49.5	49	48.5	48	47.5	47	46.5	46	45.5	45	44.5	44	43.5	43
HEIGHT (m)	Women (18-59 years)	1.61	1.60	1.59	1.585	1.58	1.57	1.56	1.55	1.54	1.53	1.52	1.51	1.50	1.49	1.48
	Women (60-90 years)	1.58	1.57	1.56	1.55	1.54	1.53	1.52	1.51	1.50	1.49	1.48	1.47	1.46	1.45	1.44

MPI - Multidimensional Prognostic Index

	Score given to each domain		
	Low (Value = 0)	**Middle (Value = 0.5)**	**High (Value = 1)**
SPMSQ [a]	0-3	4-7	8-10
ESS [b]	16-20	10-15	5-9
ADL [c]	6-5	4-3	2-0
IADL [c]	8-6	5-4	3-0
CIRS [d]	0	1-2	≥ 3
MNA [e]	≥ 24	17 to 23.5	<17
Number of drugs	0-3	4-6	≥ 7
Social status	Lives with family	Institutionalized	Living alone
Add up the scores assigned to each domain, and then divide the sum by 8		**TOTAL SCORE**	

Legend:

RISK	**Mild (MPI 1)**	**Moderate (MPI 2)**	**Severe (MPI 3)**
RANGE	**0.00 - 0.33**	**0.34-0.66**	**0.67-1.0**

[to] Number of errors
[b] Exton Smith Scale Score: 16-20, minimum risk, 10-15, moderate risk; 5-9, high risk of developing
[c] Number of active functional activities
[d] Number of pathological (score> 3)
[e] ≥ 24: satisfactory; 17-23.5: at risk of malnutrition; <17: Malnutrition

APPENDIX H: Optimised MPI results

11.1 Study patient characteristics

11.1.1 MPI with ARS score

In terms of patient allocation into the MPI scores categories with the ARS score (Table 11.1), most patients were in the mild risk category (53.1%) followed closely by the mild risk category (42.5%) and only a few in the severe risk category (4.5%). Higher MPI with ARS scores were significantly associated with older age (*p* value = 0.0001), female sex (*p* value = 0.0001), delirium (*p* value = 0.0001), in-hospital mortality (*p* value = 0.0001), longer LOS (*p* value = 0.0001), and higher mortality after 1-month, 3-, and 6-months mortality (*p* value = 0.0001). Re-admission rates for 30 days (*p* value = 0.1924), 3-month re-admission rate (*p* value = 0.5739), 6-month re-admission rate (*p* value = 0.1471), and falls (*p* value = 0.3664) did not significantly differ between MPI with ARS risk groups.

Table 11.1 Characteristics FMC patient cohort by MPI-ARS category.

Characteristics	Mild risk 0.0-0.33	Moderate risk 0.34-0.66	Severe risk 0.67-1.0
Patients, n (%)	391 (53.1)	313 (42.5)	33 (4.5)
Women, n (%) *	166 (42.5)	185 (59.1)	19 (57.6)
Men	225 (57.5)	128 (40.9)	14 (42.4)
Prognostic index score			
Range	0.06-0.31	0.38-0.63	0.69-0.88
Mean ± SD*	0.24 ± 0.06	0.46 ± 0.08	0.72 ± 0.05
Age			
Range	65-96	65-101	73-102
Mean ± SD*	78.6 ± 7.9	80.2 ± 8.8	86.3 ± 7.2
Mortality, n (%)			
In-hospital*	6 (1.5)	14 (4.5)	5 (15.2)
1 month*	9 (2.3)	18 (5.8)	8 (24.2)
3 month*	17 (4.4)	39 (12.5)	9 (27.3)
6 month*	45 (11.5)	80 (25.6)	12 (36.4)
Fall, n (%)	8 (2.1)	12 (3.8)	1 (3.0)
Delirium, n (%)*	27 (6.9)	36 (8.5)	12 (36.4)
Re-admission rate, %			
30 days	14.3	13.4	3.6
3-month	28.6	31.1	25.0
6-month	39.0	46.2	35.7
LOS, in days*	8.2 ± 10.7	10.7 ± 10.4	11.7 ± 8.4

Note: * p value = 0.0001. Abbreviations: ARS: anticholinergic risk score; LOS: length of stay; MPI: Multidimensional prognostic index; n: number; SD: Standard deviation.

11.1.2 MPI with RUDAS score

In terms of patient allocation into the MPI scores categories with the RUDAS score (Table 11.2); most patients were in the moderate risk category (60.4%) with just under a third in the mild risk category (29.7%) and only a few in the severe risk category (9.9%). Higher MPI with RUDAS scores were significantly associated with older age (*p* value = 0.0001), female sex (*p* value = 0.0003), delirium (*p* value = 0.0001), in-hospital mortality (*p* value = 0.0001), longer LOS (*p* value = 0.0001), and higher mortality after 1-month, 3-, and 6-months mortality (*p* value = 0.0001). Re-admission rate for 3-month (*p* value = 0.0358) and 6-month (*p* value = 0.0093) were significant for the MPI with RUDAS score risk groups. Re-admission rates for 30 days (*p* value = 0.2773) and falls (*p* value = 0.0709) did not significantly differ between MPI with RUDAS risk groups.

Table 11.2 Characteristics FMC patient cohort by MPI-RUDAS category.

Characteristics	Mild risk 0.0-0.33	Moderate risk 0.34-0.66	Severe risk 0.67-1.0
Patients, n (%)	219 (29.7)	445 (60.4)	73 (9.9)
Women, n (%)***	85 (38.8)	243 (54.6)	42 (57.5)
Men	134 (61.2)	202 (45.4)	31 (42.5)
Prognostic index score			
Range	0.06-0.31	0.38-0.63	0.69-0.88
Mean ± SD*	0.26 ± 0.06	0.48 ± 0.08	0.75 ± 0.06
Age			
Range	65-96	65-101	66-102
Mean ± SD*	76.0 ± 7.7	80.4 ± 8.1	85.5 ± 7.8
Mortality, n (%)			
In-hospital*	1 (0.5)	15 (3.4)	9 (12.3)
1 month*	2 (0.9)	20 (4.5)	13 (17.8)
3 month*	5 (2.3)	41 (9.2)	19 (26.0)
6 month*	19 (8.7)	93 (20.9)	25 (34.3)
Fall, n (%)	4 (1.8)	12 (2.7)	5 (6.9)
Delirium, n (%)*	12 (5.5)	36 (8.1)	23 (31.5)
Re-admission rate, %			
30 days	11.0	15.1	10.9
3-month	22.0	32.6	34.4
6-month	32.6	46.3	43.8
LOS, in days*	7.0 ± 9.3	10.1 ± 11.0	13.0 ± 9.5

Note: * p value = 0.0001, *** p value = 0.0003. Abbreviations: LOS: length of stay; MPI: Multidimensional prognostic index; No. number; RUDAS: Rowland University dementia assessment scale; SD: Standard deviation.

11.2 Primary outcome

11.2.1 6-month all-cause mortality

11.2.1.1 Univariate and multivariate logistic regression analyses

Table 11.3 Six-month mortality univariate and multivariate logistic regression of MPI-ARS items, age, and sex.

		6-Month Mortality				
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI-ARS Continuous	0.2628	0.8474	2.3336	1.7057	3.1927	*<0.0001*
MPI-ARS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.2545	0.9708	2.6400	1.7675	3.9431	*<0.0001*
Severe	0.1624	1.4802	4.3937	2.0256	9.5300	*<0.0001*
Multivariate						
MPI-ARS Continuous	0.2410	0.7815	2.1848	1.5883	3.0052	*<0.0001*
Age	0.1081	0.0244	1.0247	1.0014	1.0485	*0.038*
MPI-ARS Continuous	0.2883	0.9458	2.5748	1.8659	3.5530	*<0.0001*
Sex	0.1828	0.6988	2.0114	1.3555	2.9850	*0.001*
MPI-ARS Continuous	0.2655	0.8773	2.4043	1.7348	3.3322	*<0.0001*
Age	0.1192	0.0274	1.0277	1.0040	1.0520	*0.022*
Sex	0.1900	0.7315	2.0781	1.3955	3.0947	*<0.0001*
MPI-ARS Categorical						
Moderate	0.2425	0.9309	2.5368	1.6940	3.7989	*<0.0001*
Severe	0.1407	1.2912	3.6372	1.6455	8.0395	*0.001*
Age	0.1137	0.0257	1.0261	1.0027	1.0500	*0.029*
MPI-ARS Categorical						
Moderate	0.2849	1.1071	3.0255	2.0016	4.5733	*<0.0001*
Severe	0.1743	1.6192	5.0490	2.2911	11.1268	*<0.0001*
Sex	0.1866	0.7167	2.0476	1.3789	3.0407	*<0.0001*
MPI-ARS Categorical						
Moderate	0.2730	1.0702	2.9159	1.9238	4.4197	*<0.0001*
Severe	0.1515	1.4195	4.1349	1.8497	9.2434	*<0.0001*
Age	0.1262	0.0292	1.0296	1.0058	1.0540	*0.084*
Sex	0.1948	0.7552	2.1280	1.4275	3.1722	*<0.0001*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.4 Six-month mortality univariate and multivariate logistic regression of MPI-RUDAS items, age, and sex.

	6-Month Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI-RUDAS Continuous	0.2714	0.8555	2.3527	1.6969	3.2617	*<0.0001*
MPI-RUDAS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.2642	1.0228	2.7811	1.6483	4.6923	*<0.0001*
Severe	0.2684	1.7016	5.4825	2.7926	10.7634	*<0.0001*
Multivariate						
MPI-RUDAS Continuous	0.2456	0.7762	2.1732	1.5403	3.0663	*<0.0001*
Age	0.0760	0.0171	1.0173	0.9932	1.0420	*0.162*
MPI-RUDAS Continuous	0.2916	0.9331	2.5424	1.8247	3.5425	*<0.0001*
Sex	0.0174	0.6647	1.9439	1.3148	2.8740	*0.001*
MPI-RUDAS Continuous	0.4409	0.8475	2.3338	1.6506	3.2997	*<0.0001*
Age	0.0880	0.0202	1.0204	0.9959	1.0454	*0.103*
Sex	0.1793	0.6889	1.9916	1.3434	2.9525	*0.001*
MPI-RUDAS Categorical						
Moderate	0.4988	0.9478	2.5799	1.5135	4.3977	*<0.0001*
Severe	0.8109	1.5408	4.6683	2.2964	9.4899	*<0.0001*
Age	0.0763	0.0173	1.0174	0.9933	1.0421	*0.158*
MPI-RUDAS Categorical						
Moderate	0.5915	1.1393	3.1246	1.8383	5.3109	*<0.0001*
Severe	0.9624	1.8536	6.3828	3.2084	12.6981	*<0.0001*
Sex	0.1751	0.6741	1.9623	1.3281	2.8994	*0.001*
MPI-RUDAS Categorical						
Moderate	0.7586	1.0619	2.8919	1.6867	4.9579	*<0.0001*
Severe	0.8678	1.6798	5.3644	2.6192	10.9869	*<0.0001*
Age	0.0888	0.0205	1.0207	0.9963	1.0457	*0.097*
Sex	0.1809	0.6997	2.0132	1.3587	2.9830	*<0.0001*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.5 Six-month mortality univariate and multivariate logistic regression of OPT-MPI items, age, and sex.

	6-Month Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
OPT-MPI Continuous	0.2436	0.7557	2.1290	1.5664	2.8938	*<0.0001*
OPT-MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.2366	0.8888	2.4322	1.6068	3.6817	*<0.0001*
Severe	0.1736	1.3603	3.8974	1.9281	7.8781	*<0.0001*
Multivariate						
OPT-MPI Continuous	0.2195	0.6847	1.9832	1.4496	2.7131	*<0.0001*
Age	0.1091	0.0244	1.0248	1.0014	1.0487	*0.038*
OPT-MPI Continuous	0.2646	0.8332	2.3007	1.6832	3.1448	*<0.0001*
Sex	0.1731	0.6568	1.9286	1.3050	2.8502	*0.001*
OPT-MPI Continuous	0.2393	0.7594	2.1369	1.5553	2.9360	*<0.0001*
Age	0.1204	0.0274	1.0278	1.0040	1.0522	*0.022*
Sex	0.1806	0.6904	1.9945	1.3445	2.9577	*0.001*
OPT-MPI Categorical						
Moderate	0.2214	0.8371	2.3097	1.5205	3.5085	*<0.0001*
Severe	0.1508	1.1891	3.2843	1.5958	6.7592	*0.001*
Age	0.1124	0.0253	1.0256	1.0022	1.0496	*0.032*
OPT-MPI Categorical						
Moderate	0.2636	1.0069	2.7370	1.7910	4.1828	*<0.0001*
Severe	0.1852	1.4753	4.3722	2.1369	8.9459	*<0.0001*
Sex	0.1769	0.6749	1.9638	1.3278	2.9043	*0.001*
OPT-MPI Categorical						
Moderate	0.2478	0.9544	2.5970	1.6935	3.9825	*<0.0001*
Severe	0.1618	1.2998	3.6686	1.7699	7.6043	*<0.0001*
Age	0.1241	0.0285	1.0289	1.0051	1.0533	*0.017*
Sex	0.1847	0.7106	2.0351	1.3714	3.0201	*<0.0001*

Abbreviations: β: beta; LCI: lower confidence interval; OPT-MPI: Optimised-Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

11.2.1.1.1 Univariate ROC curves

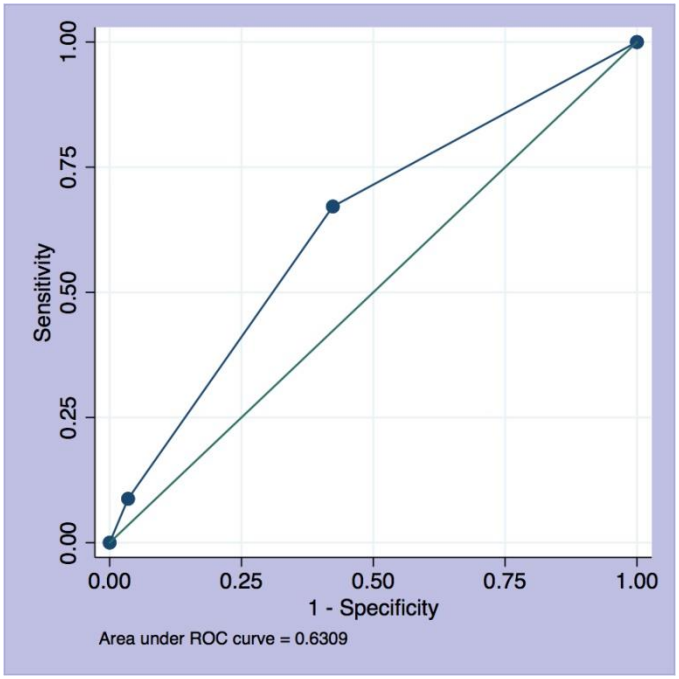


Figure 11.1 ROC curve for unadjusted MPI-ARS for 6-month mortality.

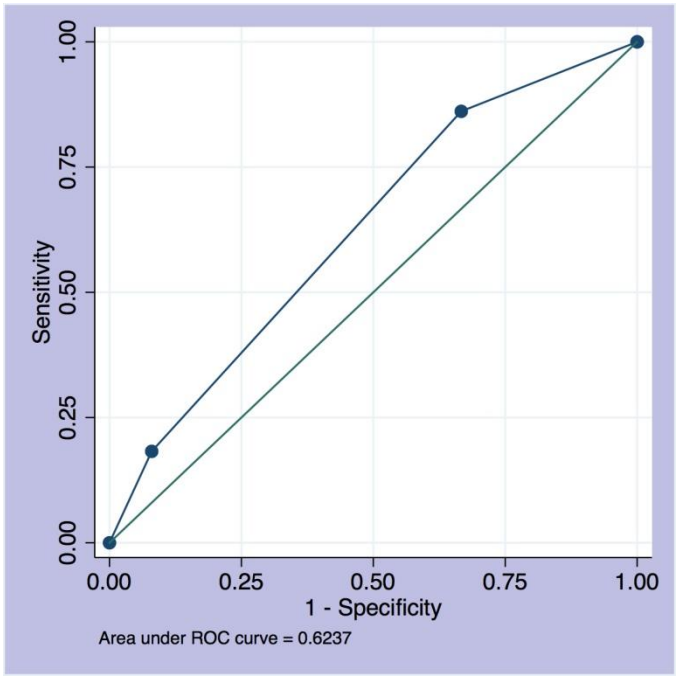


Figure 11.2 ROC curve for unadjusted MPI-RUDAS for 6-month mortality.

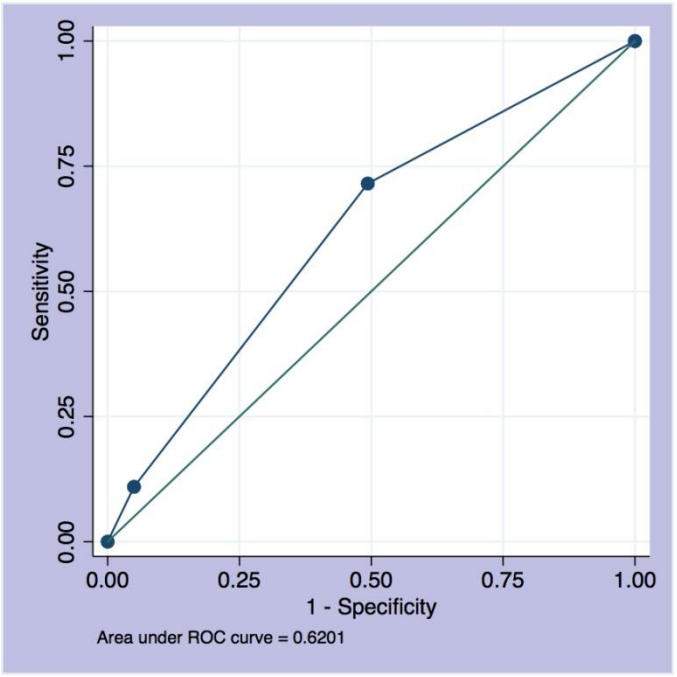


Figure 11.3 ROC curve for unadjusted OPT-MPI for 6-month mortality.

11.2.1.1.2 Multivariate ROC curve

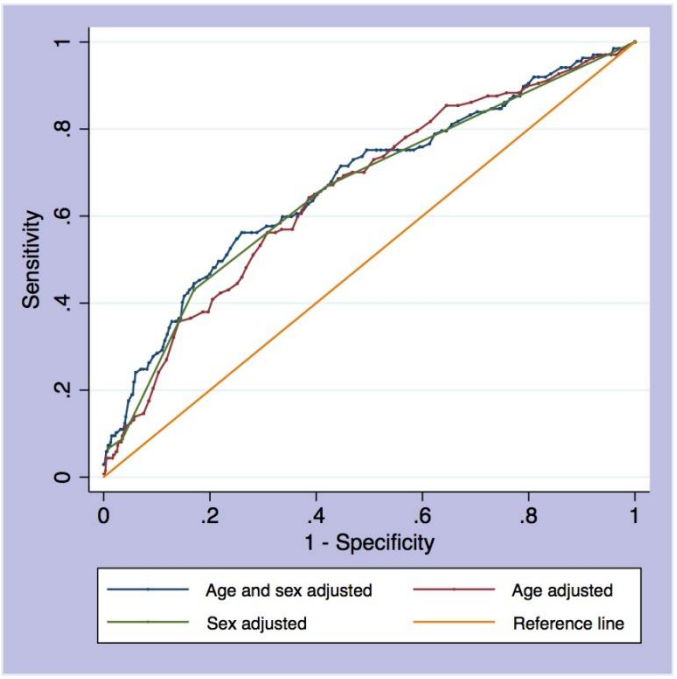


Figure 11.4 ROC curve for adjusted MPI-ARS for 6-month mortality.

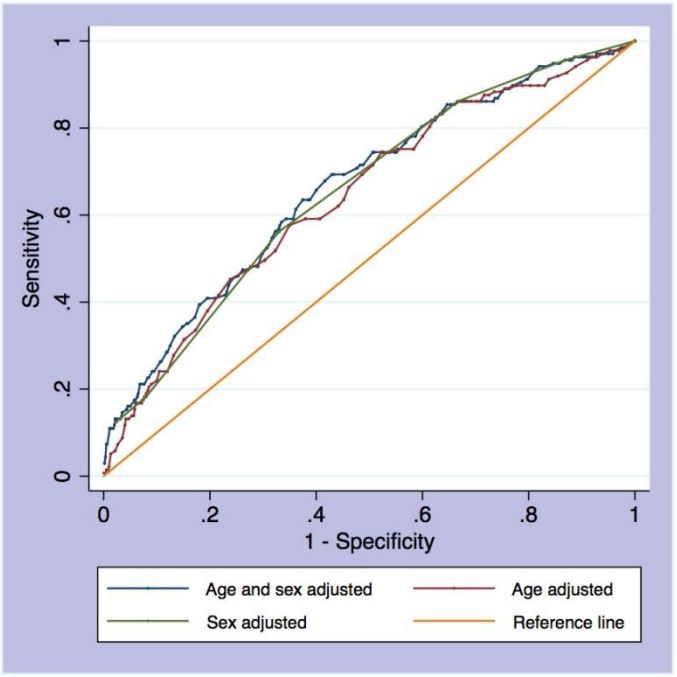


Figure 11.5 ROC curve for adjusted MPI-RUDAS for 6-month mortality.

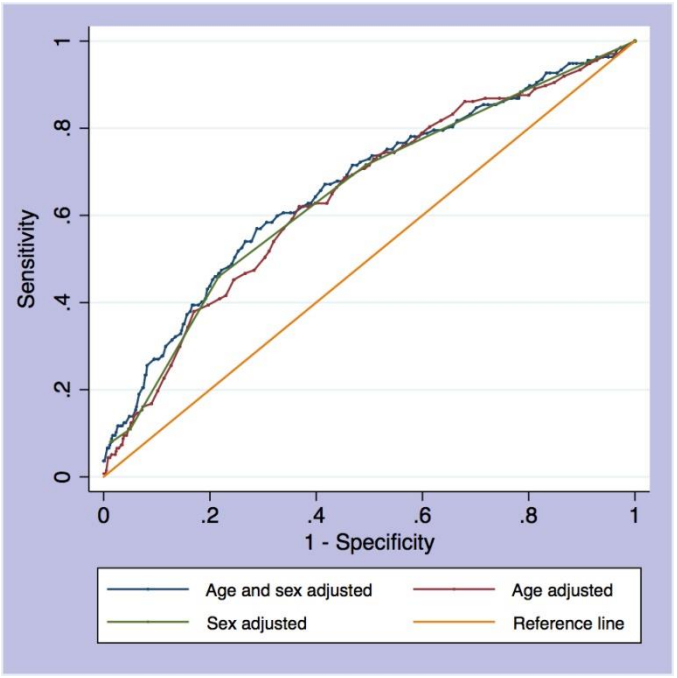


Figure 11.6 ROC curve for adjusted OPT-MPI for 6-month mortality.

11.2.2 Secondary outcomes

11.2.2.1 3-month all-cause mortality

11.2.2.1.1 Univariate and multivariate logistic regression analyses

Table 11.6 Three-month mortality univariate and multivariate logistic regression of MPI-ARS items, age, and sex.

	3-Month Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI-ARS Continuous	0.3275	1.0786	2.9405	1.9319	4.4757	*<0.0001*
MPI-ARS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.2932	1.1415	3.1314	1.7348	5.6521	*0.001*
Severe	0.2268	2.1102	8.2500	3.3299	20.4397	*<0.0001*
Multivariate						
MPI-ARS Continuous	0.2936	0.9752	2.6517	1.7295	4.0656	*<0.0001*
Age	0.1449	0.0334	1.0340	1.0017	1.0674	*0.039*
MPI-ARS Continuous	0.3448	1.1483	3.1527	2.0620	4.8204	*<0.0001*
Sex	0.1560	0.6054	1.8320	1.0730	3.1279	*0.027*
MPI-ARS Continuous	0.3104	1.0454	2.8445	1.8503	4.3729	*<0.0001*
Age	0.1564	0.0366	1.0373	1.0044	1.0712	*0.026*
Sex	0.1670	0.6550	1.9252	1.1205	3.3076	*0.018*
MPI-ARS Categorical						
Moderate	0.2753	1.0833	2.9545	1.6302	5.3545	*<0.0001*
Severe	0.1982	1.8638	6.4483	2.5302	16.4339	*<0.0001*
Age	0.1474	0.0342	1.0348	1.0024	1.0682	*0.035*
MPI-ARS Categorical						
Moderate	0.3169	1.2497	3.4894	1.9146	6.3594	*<0.0001*
Severe	0.2358	2.2230	9.2348	3.6770	23.1935	*<0.0001*
Sex	0.1576	0.6144	1.8486	1.0824	3.1571	*0.024*
MPI-ARS Categorical						
Moderate	0.2992	1.1963	3.3079	1.8077	6.0533	*<0.0001*
Severe	0.2068	1.9760	7.2140	2.8086	18.5296	*<0.0001*
Age	0.1595	0.0376	1.0383	1.0055	1.0722	*0.022*
Sex	0.1692	0.6688	1.9520	1.1363	3.3531	*0.015*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.7 Three-month mortality univariate and multivariate logistic regression of MPI-RUDAS items, age, and sex.

	3-Month Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI-RUDAS Continuous	0.0668	1.3188	3.7389	2.3674	5.9050	*<0.0001*
MPI-RUDAS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.3600	1.4687	4.3436	1.6915	11.1540	*0.002*
Severe	0.4060	2.7120	15.0593	5.3798	42.1546	*<0.0001*
Multivariate						
MPI-RUDAS Continuous	0.3683	1.2223	3.3951	2.0977	5.4950	*<0.0001*
Age	0.0867	0.0205	1.0207	0.9872	1.0554	*0.229*
MPI-RUDAS Continuous	0.4115	1.3743	3.9522	2.4948	6.2610	*<0.0001*
Sex	0.1494	0.5961	1.8150	1.0618	3.1024	*0.029*
MPI-RUDAS Continuous	0.3780	1.2704	3.5624	2.2049	5.7557	*<0.0001*
Age	0.1025	0.0245	1.0248	0.9908	1.0600	*0.154*
Sex	0.1586	0.6371	1.8911	1.1004	3.2498	*0.021*
MPI-RUDAS Categorical						
Moderate	0.3367	1.3783	3.9682	1.5278	10.3068	*0.005*
Severe	0.3761	2.5214	12.4459	4.2570	36.3873	*<0.0001*
Age	0.0861	0.0206	1.0208	0.9873	1.0554	*0.227*
MPI-RUDAS Categorical						
Moderate	0.3793	1.5657	4.7862	1.8545	12.3527	*0.001*
Severe	0.4206	2.8423	17.1547	6.0608	48.5553	*<0.0001*
Sex	0.1487	0.6006	1.8231	1.0678	3.1128	*0.028*
MPI-RUDAS Categorical						
Moderate	0.3543	1.4729	4.3621	1.6745	11.3634	*0.003*
Severe	0.3877	2.6389	13.9984	4.7741	41.0455	*<0.0001*
Age	0.1017	0.0247	1.0250	0.9910	1.0601	*0.151*
Sex	0.1579	0.6422	1.9006	1.1073	3.2621	*0.020*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.8 Three-month mortality univariate and multivariate logistic regression of OPT-MPI items, age, and sex.

	3-Month Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
OPT-MPI Continuous	0.3362	1.0742	2.9275	1.9267	4.4482	*<0.0001*
OPT-MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.2811	1.0840	2.9565	1.5745	5.5513	*0.001*
Severe	0.2668	2.1454	8.5455	3.6523	19.9945	*<0.0001*
Multivariate						
OPT-MPI Continuous	0.3016	0.9715	2.6419	1.7230	4.0509	*<0.0001*
Age	0.1400	0.0324	1.0329	1.0004	1.0666	*0.047*
OPT-MPI Continuous	0.3497	1.1278	3.0887	2.0286	4.7028	*<0.0001*
Sex	0.1479	0.5749	1.7769	1.0433	3.0263	*0.034*
OPT-MPI Continuous	0.3146	1.0267	2.7919	1.8208	4.2809	*<0.0001*
Age	0.1530	0.0359	1.0365	1.0034	1.0707	*0.030*
Sex	0.1601	0.6297	1.8771	1.0948	3.2182	*0.022*
OPT-MPI Categorical						
Moderate	0.2603	1.0139	2.7562	1.4606	5.2010	*0.002*
Severe	0.2375	1.9291	6.8830	2.8657	16.5317	*<0.0001*
Age	0.1404	0.0326	1.0331	1.0005	1.0668	*0.046*
OPT-MPI Categorical						
Moderate	0.3021	1.1784	3.2493	1.7173	6.1479	*<0.0001*
Severe	0.2755	2.2409	9.4020	3.9752	22.2375	*<0.0001*
Sex	0.1486	0.5788	1.7839	1.0466	3.0407	*0.033*
OPT-MPI Categorical						
Moderate	0.2804	1.1083	3.0292	1.5935	5.7584	*0.001*
Severe	0.2461	2.0284	7.6023	3.1498	18.3485	*<0.0001*
Age	0.1534	0.0361	1.0368	1.0037	1.0709	*0.029*
Sex	0.1609	0.6351	1.8872	1.1007	3.2357	*0.021*

Abbreviations: β: beta; LCI: lower confidence interval; OPT-MPI: Optimised-Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

11.2.2.1.2 Univariate ROC curves

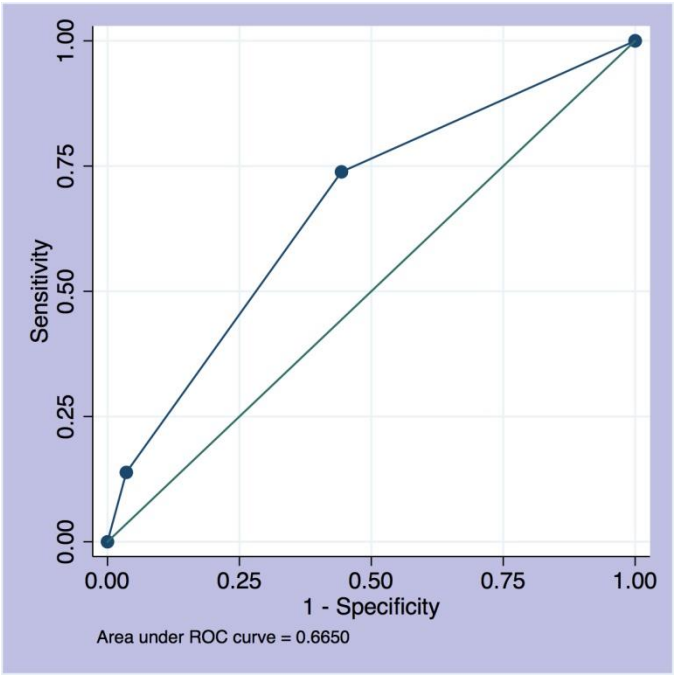


Figure 11.7 ROC curve for unadjusted MPI-ARS for 3-month mortality.

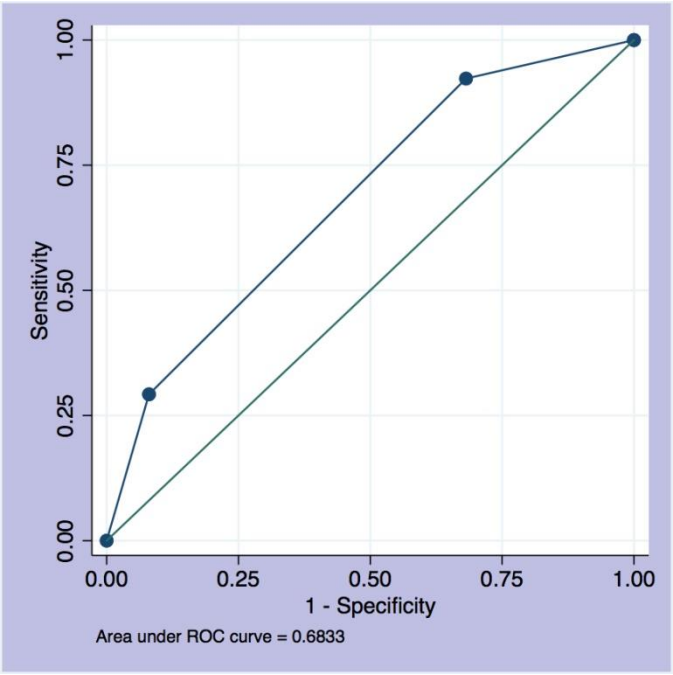


Figure 11.8 ROC curve for unadjusted MPI-RUDAS for 3-month mortality.

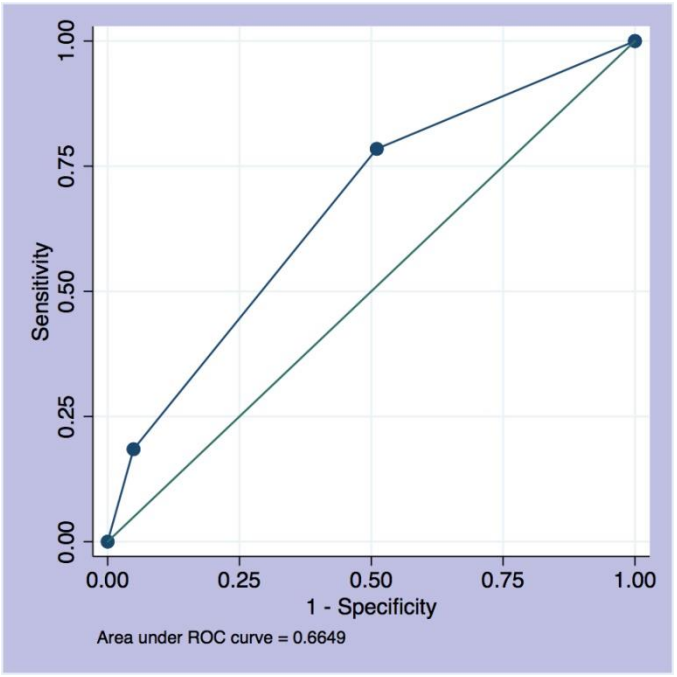


Figure 11.9 ROC curve for unadjusted OPT-MPI for 3-month mortality.

11.2.2.1.3 Multivariate ROC curve

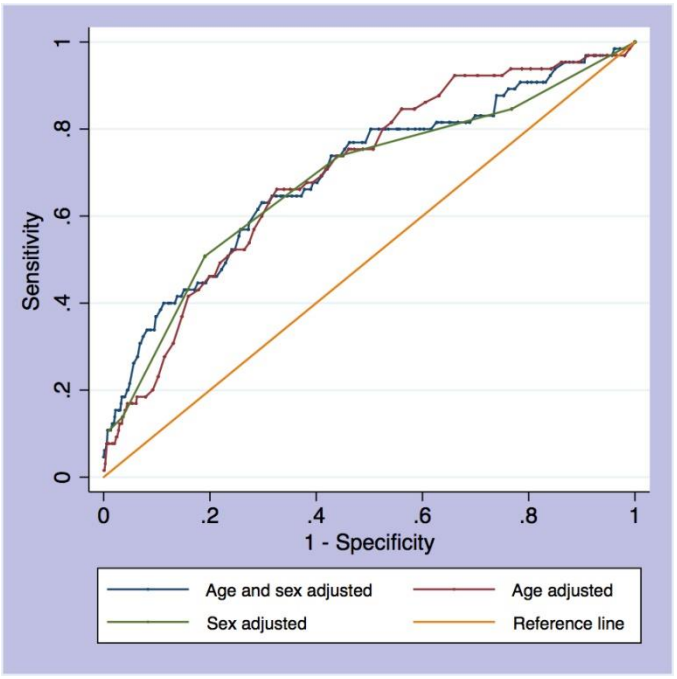


Figure 11.10 ROC curve for adjusted MPI-ARS for 3-month mortality.

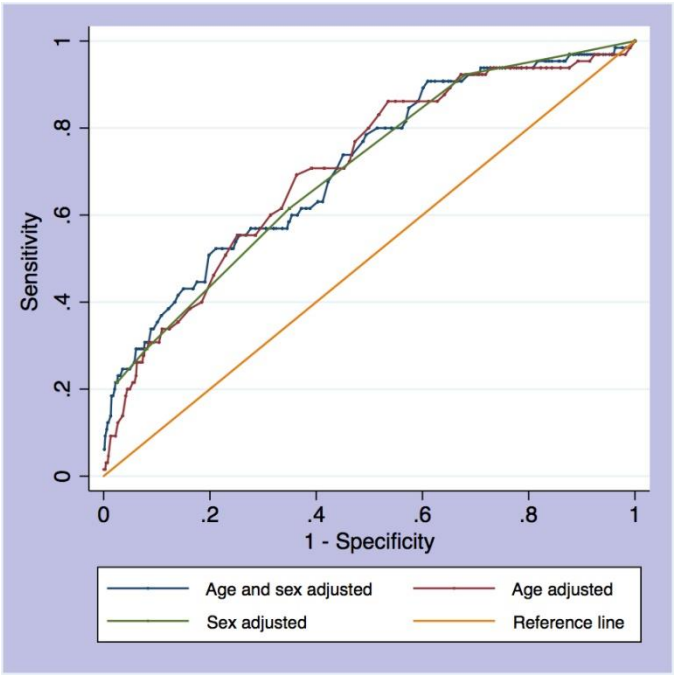


Figure 11.11 ROC curve for adjusted MPI-RUDAS for 3-month mortality.

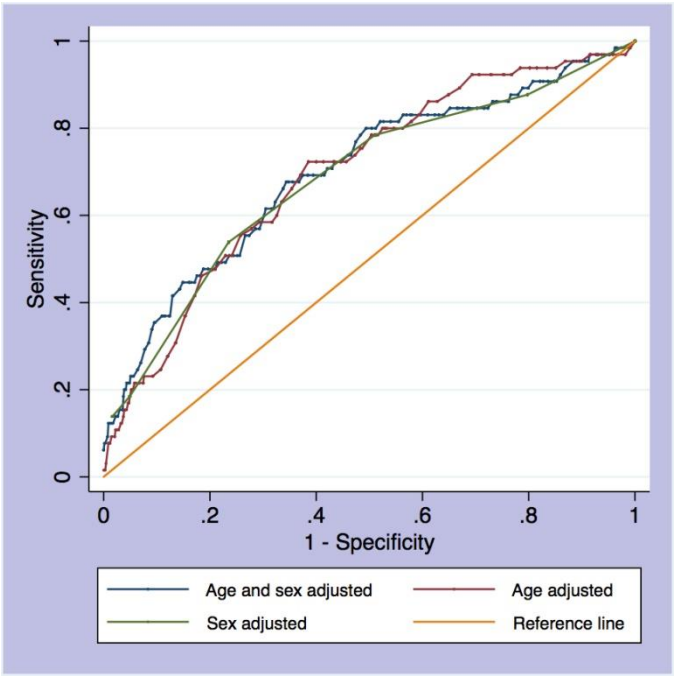


Figure 11.12 ROC curve for adjusted OPT-MPI for 3-month mortality.

11.2.2.2 1-month all-cause mortality

11.2.2.2.1 Univariate and multivariate logistic regression analyses

Table 11.9 One-month mortality univariate and multivariate logistic regression of MPI-ARS items, age, and sex.

Risk factors	Standardised β coefficient	1-Month Mortality Coefficient	OR	LCI	UCI	*p* value
Univariate						
MPI-ARS Continuous	0.3775	1.2685	3.5554	2.0491	6.1692	*<0.0001*
MPI-ARS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.2444	0.9516	2.5898	1.1470	5.8476	*0.022*
Severe	0.2804	2.6088	13.5822	4.8259	38.2262	*<0.0001*
Multivariate						
MPI-ARS Continuous	0.3450	1.1648	3.2054	1.8260	5.6268	*<0.0001*
Age	0.1272	0.0299	1.0303	0.9878	1.0747	*0.165*
MPI-ARS Continuous	0.3925	1.3348	3.7993	2.1863	6.6024	*<0.0001*
Sex	0.1714	0.6792	1.9724	0.9668	4.0237	*0.062*
MPI-ARS Continuous	0.3589	1.2306	3.4233	1.9539	5.9980	*<0.0001*
Age	0.1421	0.0339	1.0345	0.9911	1.0797	*0.121*
Sex	0.1831	0.7316	2.0784	1.0107	4.2738	*0.047*
MPI-ARS Categorical						
Moderate	0.2296	0.9006	2.4611	1.0846	5.5847	*0.031*
Severe	0.2530	2.4024	11.0501	3.7603	32.4720	*<0.0001*
Age	0.1220	0.0282	1.0286	0.9855	1.0736	*0.197*
MPI-ARS Categorical						
Moderate	0.2689	1.0625	2.8937	1.2689	6.5993	*0.012*
Severe	0.2891	2.7298	15.3298	5.3514	43.9146	*<0.0001*
Sex	0.1689	0.6598	1.9344	0.9424	3.9705	*0.072*
MPI-ARS Categorical						
Moderate	0.2536	1.0131	2.7542	1.2024	6.3088	*0.017*
Severe	0.2636	2.5169	12.3900	1.4803	36.7227	*<0.0001*
Age	0.1387	0.0327	1.0332	0.9894	1.0790	*0.140*
Sex	0.1814	0.7163	2.0468	0.9898	4.2323	*0.053*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.10 One-month mortality univariate and multivariate logistic regression of MPI-RUDAS items, age, and sex.

	1-Month Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI-RUDAS Continuous	0.4556	1.5529	4.7250	2.5818	8.6474	*<0.0001*
MPI-RUDAS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.3893	1.6304	5.1059	1.1826	22.0456	*0.029*
Severe	0.4605	3.1574	23.5083	5.1627	107.0456	*<0.0001*
Multivariate						
MPI-RUDAS Continuous	0.4341	1.4813	4.3987	2.3205	8.3382	*<0.0001*
Age	0.0609	0.0148	1.0149	0.9708	1.0610	*0.514*
MPI-RUDAS Continuous	0.4665	1.6054	4.9796	2.7150	9.1332	*<0.0001*
Sex	0.1613	0.6632	1.9409	0.9500	3.9655	*0.069*
MPI-RUDAS Continuous	0.4395	1.5196	4.5704	2.4251	8.6133	*<0.0001*
Age	0.0820	0.0202	1.0204	0.9756	1.0673	*0.378*
Sex	0.1703	0.7038	2.0214	0.9817	4.1622	*0.056*
MPI-RUDAS Categorical						
Moderate	0.3729	1.5645	4.7801	1.0924	20.9155	*0.038*
Severe	0.4394	3.0177	20.4448	4.2497	98.3566	*<0.0001*
Age	0.0606	0.0148	1.0149	0.9709	1.0610	*0.512*
MPI-RUDAS Categorical						
Moderate	0.4086	1.7339	5.6625	1.3054	24.5630	*0.021*
Severe	0.4743	3.2954	26.9889	5.8639	124.2183	*<0.0001*
Sex	0.1603	0.6653	1.9451	0.9525	3.9719	*0.068*
MPI-RUDAS Categorical						
Moderate	0.3886	1.6579	5.2483	1.1975	23.0010	*0.028*
Severe	0.4481	3.1299	22.8712	4.7622	109.8431	*<0.0001*
Age	0.0814	0.0203	1.0205	0.9757	1.0673	*0.376*
Sex	0.1692	0.7061	2.0261	0.9847	4.1690	*0.055*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.11 One-month mortality univariate and multivariate logistic regression of OPT-MPI items, age, and sex.

	1-Month Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
OPT-MPI Continuous	0.4036	1.3270	3.7697	2.1642	6.5664	*<0.0001*
OPT-MPI Categorical						
Mild	reference group	0.0000	1.00			-
Moderate	0.3115	1.2280	3.4144	1.3541	8.6095	*0.009*
Severe	0.3214	2.6420	14.0417	4.7274	41.7078	*<0.0001*
Multivariate						
OPT-MPI Continuous	0.3726	1.2307	3.4235	1.9376	6.0487	*<0.0001*
Age	0.1169	0.0278	1.0281	0.9853	1.0729	*0.202*
OPT-MPI Continuous	0.4142	1.3756	3.9574	2.2739	6.8876	*<0.0001*
Sex	0.1625	0.6719	1.9579	0.9406	3.9022	*0.073*
OPT-MPI Continuous	0.3200	1.2802	3.5974	2.0460	6.3251	*<0.0001*
Age	0.1353	0.0326	1.0331	0.9894	1.0788	*0.139*
Sex	0.1764	0.7122	2.0384	0.9912	4.1918	*0.053*
OPT-MPI Categorical						
Moderate	0.2940	1.1667	3.2115	1.2663	8.1443	*0.014*
Severe	0.2967	2.4553	11.6498	3.7827	35.8790	*<0.0001*
Age	0.1165	0.0275	1.0279	0.9849	1.0728	*0.206*
OPT-MPI Categorical						
Moderate	0.3329	1.3302	3.7816	1.4882	9.6096	*0.005*
Severe	0.3295	2.7458	15.5777	5.1811	46.8367	*<0.0001*
Sex	0.1622	0.6473	1.9105	0.9360	3.8992	*0.075*
OPT-MPI Categorical						
Moderate	0.3132	1.2654	3.5446	1.3879	9.0526	*0.008*
Severe	0.3037	2.5589	12.9217	4.1834	39.9127	*<0.0001*
Age	0.1353	0.0326	1.0331	0.9893	1.0788	*0.140*
Sex	0.1763	0.7115	2.0369	0.9894	4.1935	*0.053*

Abbreviations: β: beta; LCI: lower confidence interval; OPT-MPI: Optimised-Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

11.2.2.2.2 Univariate ROC curves

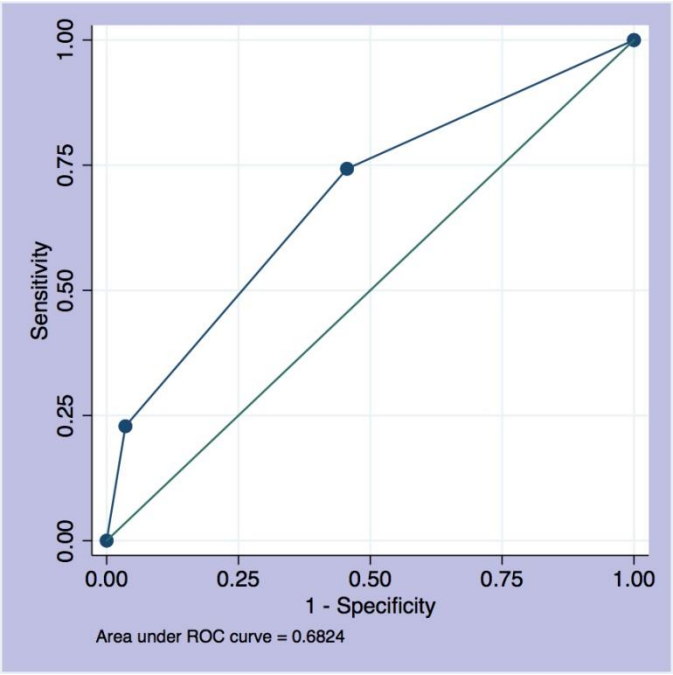


Figure 11.13 ROC curve for unadjusted MPI-ARS for 1-month mortality.

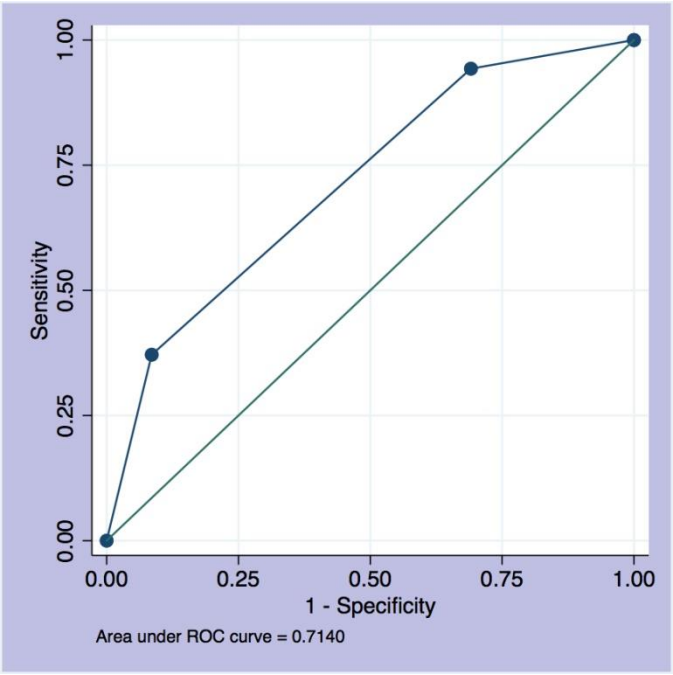


Figure 11.14 ROC curve for unadjusted MPI-RUDAS for 1-month mortality.

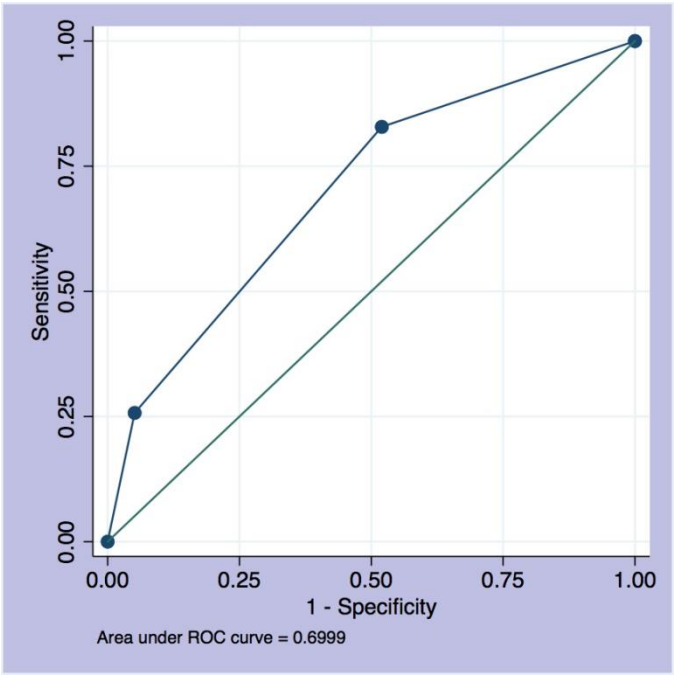


Figure 11.15 ROC curve for unadjusted OPT-MPI for 1-month mortality.

11.2.2.2.3 Multivariate ROC curve

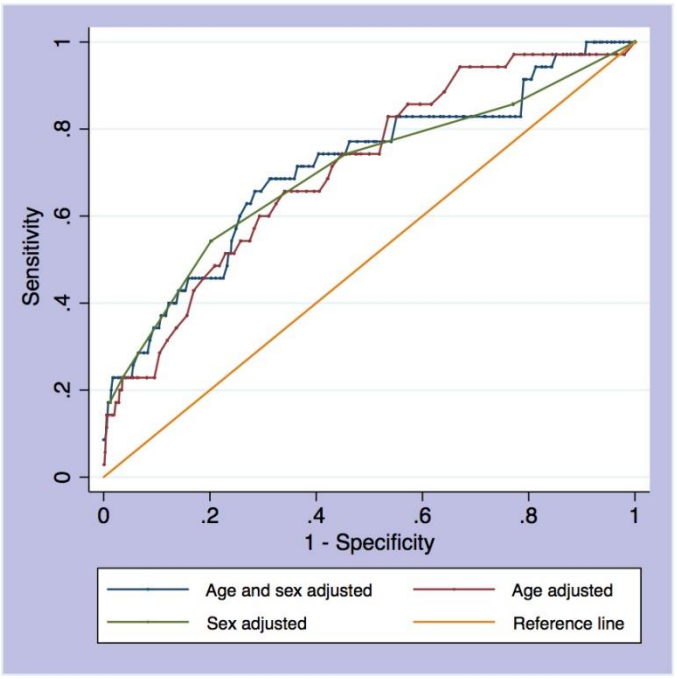


Figure 11.16 ROC curve for adjusted MPI-ARS for 1-month mortality.

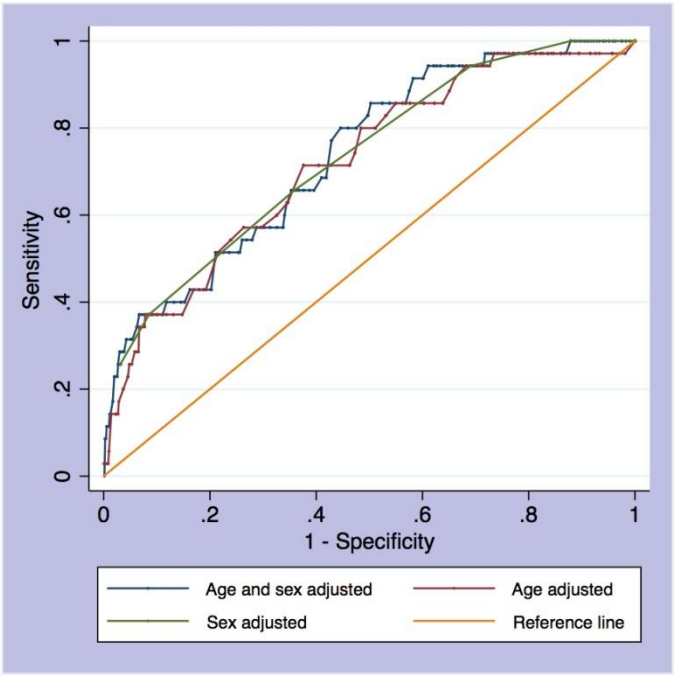


Figure 11.17 ROC curve for adjusted MPI-RUDAS for 1-month mortality.

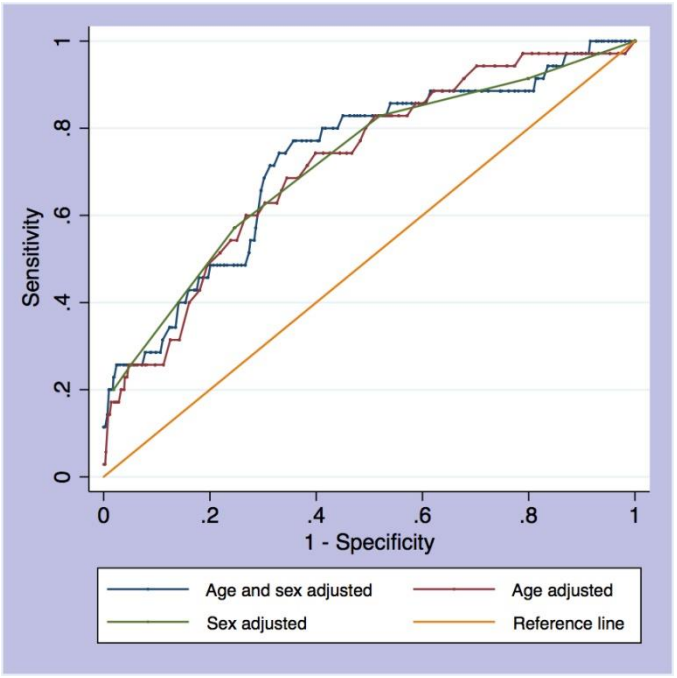


Figure 11.18 ROC curve for adjusted OPT-MPI for 1-month mortality.

11.2.2.3 In-hospital all-cause mortality

11.2.2.3.1 Univariate and multivariate logistic regression analyses

Table 11.12 In-hospital mortality univariate and multivariate logistic regression of MPI-ARS items, age, and sex.

	In-hospital Mortality					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI-ARS Continuous	0.3619	1.2078	3.3463	1.7706	6.3243	*<0.0001*
MPI-ARS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.2814	1.1001	3.0045	1.1410	7.9115	*0.026*
Severe	0.2610	2.4387	11.4583	3.2918	39.8848	*<0.0001*
Multivariate						
MPI-ARS Continuous	0.3215	1.0817	2.9497	1.5410	5.6461	*0.001*
Age	0.1545	0.0361	1.0368	0.9865	1.0896	*0.154*
MPI-ARS Continuous	0.3758	1.2683	3.5547	1.8824	6.7126	*<0.0001*
Sex	0.1665	0.6547	1.9245	0.8383	4.4182	*0.123*
MPI-ARS Continuous	0.3351	1.1449	3.1421	1.6488	5.9879	*0.001*
Age	0.1693	0.0402	1.0410	0.9899	1.0948	*0.118*
Sex	0.1803	0.7175	2.0494	0.8838	4.7518	*0.094*
MPI-ARS Categorical						
Moderate	0.2614	1.0335	2.8108	1.0607	7.4488	*0.038*
Severe	0.2302	2.1759	8.8097	2.4076	32.2355	*0.001*
Age	0.1537	0.0358	1.0365	0.9860	1.0896	*0.16*
MPI-ARS Categorical						
Moderate	0.3050	1.2087	3.3492	1.2844	8.9133	*0.016*
Severe	0.2690	2.5486	12.7890	3.6210	45.1691	*<0.0001*
Sex	0.1659	0.6499	1.9153	0.8318	4.4101	*0.127*
MPI-ARS Categorical						
Moderate	0.2845	1.1454	3.1437	1.1746	8.4141	*0.023*
Severe	0.2379	2.2897	9.8719	2.6867	36.2726	*0.001*
Age	0.1693	0.0402	1.0410	0.9898	1.0949	*0.119*
Sex	0.1803	0.7176	2.0495	0.8824	4.7602	*0.095*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.13 In-hospital mortality univariate and multivariate logistic regression of MPI-RUDAS items, age, and sex.

		In-hospital Mortality				
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI-RUDAS Continuous	0.4510	1.5329	4.6314	2.2982	9.3332	*<0.0001*
MPI-RUDAS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.4686	2.0288	7.6046	0.9980	57.9480	*0.050*
Severe	0.4828	3.4228	30.6562	3.8120	246.5393	*0.001*
Multivariate						
MPI-RUDAS Continuous	0.4198	1.4312	4.1839	1.9919	8.7879	*<0.0001*
Age	0.0868	0.0211	1.0213	0.9693	1.0761	*0.429*
MPI-RUDAS Continuous	0.4608	1.5800	4.8549	2.4080	9.7885	*<0.0001*
Sex	0.1574	0.6448	1.9057	0.8288	4.3817	*0.129*
MPI-RUDAS Continuous	0.4249	1.4681	4.3409	2.0853	9.0364	*<0.0001*
Age	0.1080	0.0266	1.0270	0.9741	1.0827	*0.324*
Sex	0.1694	0.6994	2.0125	0.8666	4.6737	*0.104*
MPI-RUDAS Categorical						
Moderate	0.4453	1.9344	6.9201	0.8961	53.4382	*0.064*
Severe	0.4532	3.2235	25.1151	2.9553	213.4385	*0.003*
Age	0.0837	0.0212	1.0214	0.9695	1.0761	*0.426*
MPI-RUDAS Categorical						
Moderate	0.4862	2.1297	8.4125	1.0994	64.3746	*0.040*
Severe	0.4953	3.5528	34.9109	4.3037	283.1890	*0.001*
Sex	0.1526	0.6539	1.9230	0.8382	4.4114	*0.123*
MPI-RUDAS Categorical						
Moderate	0.4595	2.0294	7.6093	0.9842	58.8339	*0.052*
Severe	0.4613	3.3355	28.0931	3.3181	237.8506	*0.002*
Age	0.1039	0.0268	1.0271	0.9744	1.0827	*0.319*
Sex	0.1640	0.7083	2.0306	0.8769	4.7018	*0.098*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.14 In-hospital mortality univariate and multivariate logistic regression of OPT-MPI items, age, and sex.

		In-hospital Mortality				
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
OPT-MPI Continuous	0.4188	1.3877	4.0054	2.0977	7.6481	*<0.0001*
OPT-MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.4134	1.6948	5.4454	1.5721	18.8615	*0.008*
Severe	0.3344	2.8585	17.4359	4.1936	72.4935	*<0.0001*
Multivariate						
OPT-MPI Continuous	0.3827	1.2750	3.5787	1.8424	6.9515	*<0.0001*
Age	0.1325	0.0317	1.0322	0.9817	1.0854	*0.216*
OPT-MPI Continuous	0.4279	1.4303	4.1800	2.1956	7.9579	*<0.0001*
Sex	0.1596	0.6426	1.9014	0.8276	4.3683	*0.130*
OPT-MPI Continuous	0.3909	1.3217	3.7498	1.9456	7.2273	*<0.0001*
Age	0.1526	0.0371	1.0378	0.9862	1.0921	*0.154*
Sex	0.1765	0.7190	2.0524	0.8820	4.7756	*0.095*
OPT-MPI Categorical						
Moderate	0.3922	1.6215	5.0604	1.4522	17.6334	*0.011*
Severe	0.3057	2.6355	13.9503	3.2274	60.2998	*<0.0001*
Age	0.1327	0.0327	1.0332	0.9828	1.0862	*0.200*
OPT-MPI Categorical						
Moderate	0.4332	1.7990	6.0437	1.7320	21.0886	*0.005*
Severe	0.3416	2.9587	19.2732	4.5897	80.9331	*<0.0001*
Sex	0.1601	0.6638	1.9423	0.8464	4.4568	*0.117*
OPT-MPI Categorical						
Moderate	0.4094	1.7227	5.5998	1.5964	19.6421	*0.007*
Severe	0.3128	2.7449	15.5630	3.6003	67.2741	*<0.0001*
Age	0.1505	0.0377	1.0384	0.9872	1.0923	*0.144*
Sex	0.1750	0.7354	2.0864	0.9006	4.8333	*0.086*

Abbreviations: β: beta; LCI: lower confidence interval; OPT-MPI: Optimised-Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

11.2.2.3.2 Univariate ROC curves

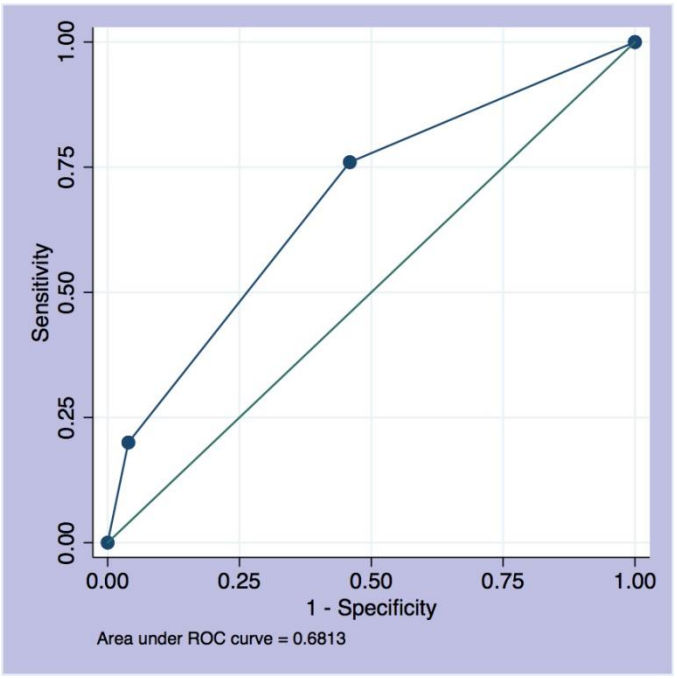


Figure 11.19 ROC curve for unadjusted MPI-ARS for in-hospital mortality.

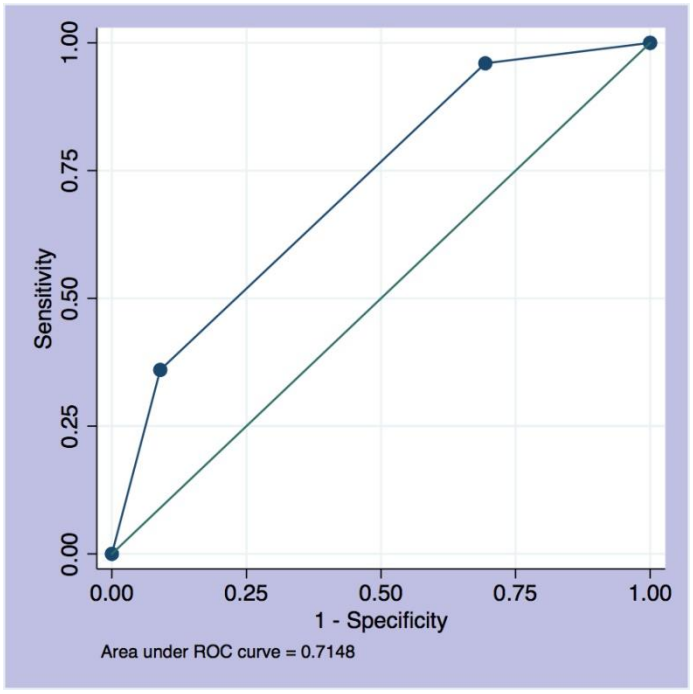


Figure 11.20 ROC curve for unadjusted MPI-RUDAS for in-hospital mortality.

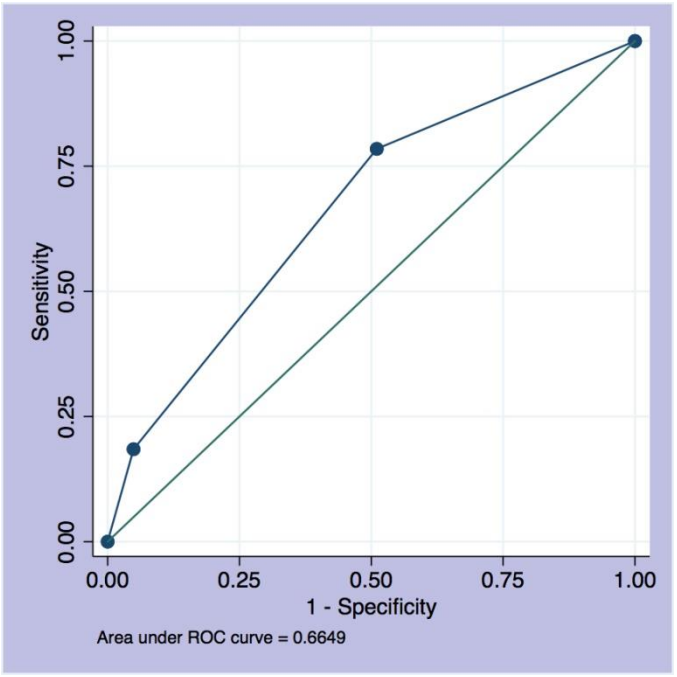


Figure 11.21 ROC curve for unadjusted OPT-MPI for in-hospital mortality.

11.2.2.3.3 Multivariate ROC curve

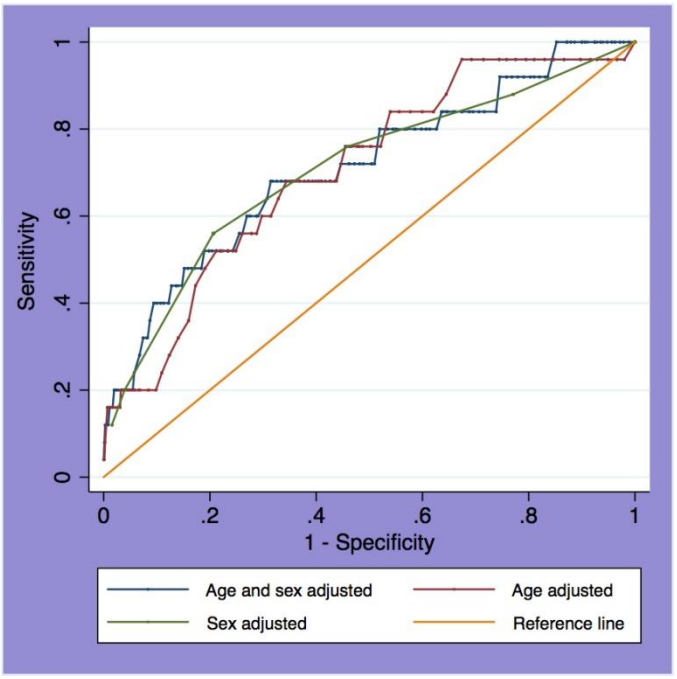


Figure 11.22 ROC curve for adjusted MPI-ARS for in-hospital mortality.

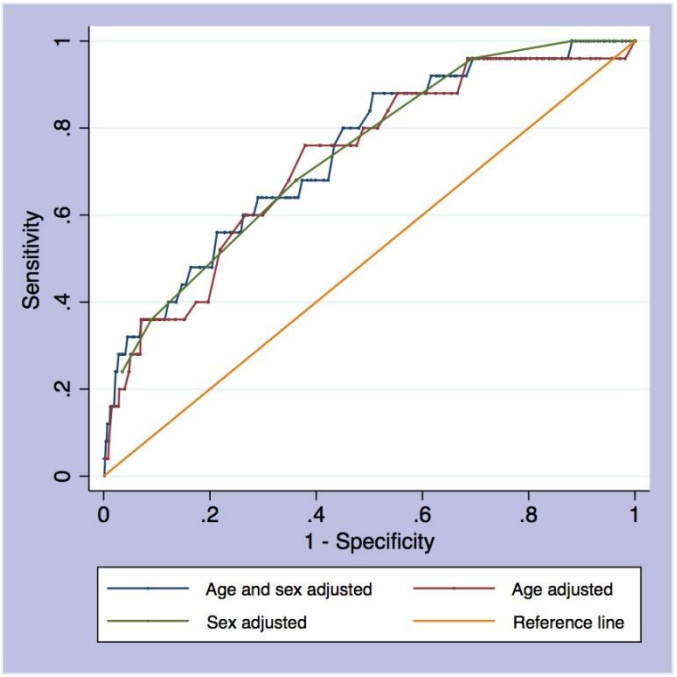


Figure 11.23 ROC curve for adjusted MPI-RUDAS for in-hospital mortality.

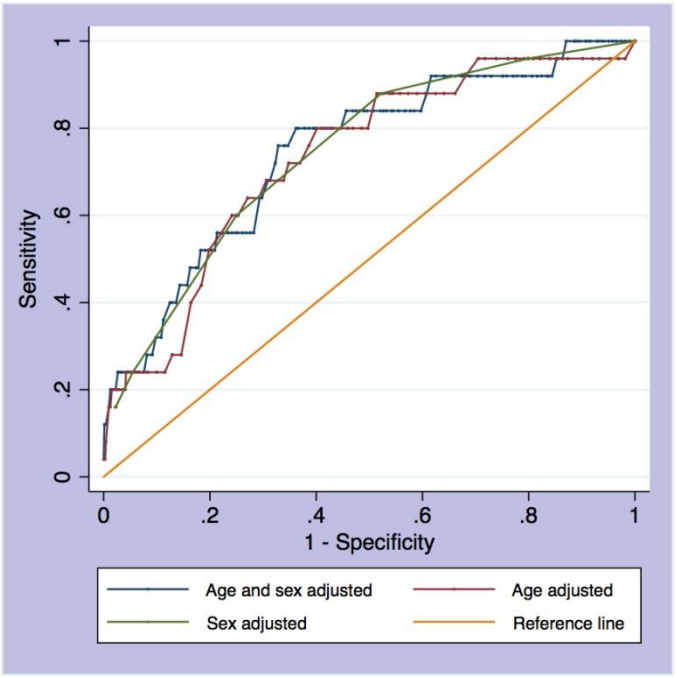


Figure 11.24 ROC curve for adjusted OPT-MPI for in-hospital mortality.

11.2.2.4 In-hospital falls

11.2.2.4.1 Univariate and multivariate logistic regression analyses

Table 11.15 In-hospital falls univariate and multivariate logistic regression of MPI-ARS items, age, and sex.

	In-hospital Falls					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI-ARS Continuous	0.1380	0.4336	1.5428	0.7639	3.1160	*0.227*
MPI-ARS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.1737	0.6464	1.9086	0.7704	4.7286	*0.163*
Severe	0.0453	0.4029	1.4961	0.1814	12.3390	*0.708*
Multivariate						
MPI-ARS Continuous	0.0971	0.3102	1.3638	0.6691	2.7798	*0.394*
Age	0.1877	0.0417	1.0426	0.9878	1.1003	*0.130*
MPI-ARS Continuous	0.1448	0.4556	1.5770	0.7769	3.2012	*0.207*
Sex	0.0514	0.1884	1.2074	0.5013	2.9079	*0.674*
MPI-ARS Continuous	0.1053	0.3370	1.4007	0.6843	2.8671	*0.357*
Age	0.1914	0.0426	1.0435	0.9885	1.1015	*0.123*
Sex	0.0623	0.2322	1.2613	0.5207	3.0554	*0.607*
MPI-ARS Categorical						
Moderate	0.1484	0.5624	1.7549	0.7020	4.3875	*0.229*
Severe	0.0084	0.0759	1.0788	0.1258	9.2492	*0.945*
Age	0.1945	0.0435	1.0444	0.9899	1.1020	*0.112*
MPI-ARS Categorical						
Moderate	0.1830	0.6824	1.9785	0.7890	4.9613	*0.146*
Severe	0.0489	0.4354	1.5456	0.1866	12.8050	*0.687*
Sex	0.0584	0.2152	1.2401	0.5135	2.9949	*0.632*
MPI-ARS Categorical						
Moderate	0.1590	0.6040	1.8295	0.7236	4.6257	*0.202*
Severe	0.0133	0.1204	1.1280	0.1312	9.6946	*0.913*
Age	0.1981	0.0444	1.0454	0.9906	1.1031	*0.106*
Sex	0.0689	0.2586	1.2951	0.5340	3.1411	*0.567*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.16 In-hospital falls univariate and multivariate logistic regression of MPI-RUDAS items, age, and sex.

Risk factors	In-hospital Falls					
	Standardised β coefficient	Coefficient	OR	LCI	UCI	*p* value
Univariate						
MPI-RUDAS Continuous	0.2261	0.7042	2.0222	0.9780	4.1812	*0.057*
MPI-RUDAS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.1053	0.3985	1.4896	0.4748	4.6732	*0.495*
Severe	0.2218	1.3743	3.9522	1.0320	15.1354	*0.045*
Multivariate						
MPI-RUDAS Continuous	0.1738	0.5466	1.7273	0.7991	3.7337	*0.165*
Age	0.1486	0.0333	1.0339	0.9773	1.0937	*0.246*
MPI-RUDAS Continuous	0.2320	0.7234	2.0614	0.9954	4.2689	*0.051*
Sex	0.0574	0.2138	1.2384	0.5155	2.9750	*0.633*
MPI-RUDAS Continuous	0.1807	0.5699	1.7680	0.8195	3.8142	*0.146*
Age	0.1532	0.0344	1.0350	0.9783	1.0950	*0.231*
Sex	0.0675	0.2543	1.2896	0.5335	3.1176	*0.572*
MPI-RUDAS Categorical						
Moderate	0.0654	0.2502	1.2842	0.3980	4.1444	*0.676*
Severe	0.1697	1.0622	2.8927	0.6843	12.2277	*0.149*
Age	0.1485	0.0331	1.0337	0.9770	1.0936	*0.250*
MPI-RUDAS Categorical						
Moderate	0.1133	0.4295	1.5365	0.4857	4.8604	*0.465*
Severe	0.2275	1.4115	4.1022	1.0599	15.8763	*0.041*
Sex	0.0533	0.1976	1.2184	0.5055	2.9369	*0.660*
MPI-RUDAS Categorical						
Moderate	0.0750	0.2875	1.3331	0.4104	4.3299	*0.632*
Severe	0.1765	1.1076	3.0270	0.7134	12.8432	*0.133*
Age	0.1530	0.0342	1.0348	0.9780	1.0949	*0.235*
Sex	0.0638	0.2391	1.2701	0.5234	3.0820	*0.597*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.17 In-hospital falls univariate and multivariate logistic regression of OPT-MPI items, age, and sex.

	In-hospital Falls					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
OPT-MPI Continuous	0.1869	0.5722	1.7722	0.8924	3.5195	*0.102*
OPT-MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.1210	0.4461	1.5621	0.5984	4.0781	*0.362*
Severe	0.1602	1.2321	3.4286	0.8540	13.7655	*0.082*
Multivariate						
OPT-MPI Continuous	0.1449	0.4499	1.5682	0.7783	3.1599	*0.208*
Age	0.1733	0.0387	1.0394	0.9847	1.0973	*0.161*
OPT-MPI Continuous	0.1927	0.5909	1.8056	0.9074	3.5928	*0.092*
Sex	0.0545	0.2013	1.2230	0.5090	2.9389	*0.653*
OPT-MPI Continuous	0.1522	0.4737	1.6059	0.7959	3.2404	*0.186*
Age	0.1779	0.0398	1.0406	0.9856	1.0987	*0.151*
Sex	0.0663	0.2485	1.2821	0.5300	3.1017	*0.581*
OPT-MPI Categorical						
Moderate	0.0955	0.3571	1.4292	0.5418	3.7703	*0.471*
Severe	0.1239	0.9664	2.6284	0.6225	11.0970	*0.189*
Age	0.1718	0.0383	1.0390	0.9841	1.0970	*0.167*
OPT-MPI Categorical						
Moderate	0.1288	0.4756	1.6090	0.6103	4.2421	*0.336*
Severe	0.1634	1.2581	3.5189	0.8715	14.2080	*0.077*
Sex	0.0514	0.1894	1.2085	0.5012	2.9137	*0.673*
OPT-MPI Categorical						
Moderate	0.1043	0.3911	1.4786	0.5559	3.9327	*0.433*
Severe	0.1284	1.0038	2.7286	0.6448	11.5476	*0.173*
Age	0.1768	0.0395	1.0403	0.9851	1.0986	*0.156*
Sex	0.0647	0.2424	1.2743	0.5256	3.0896	*0.592*

Abbreviations: β: beta; LCI: lower confidence interval; OPT-MPI: Optimised-Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

11.2.2.4.2 Univariate ROC curves

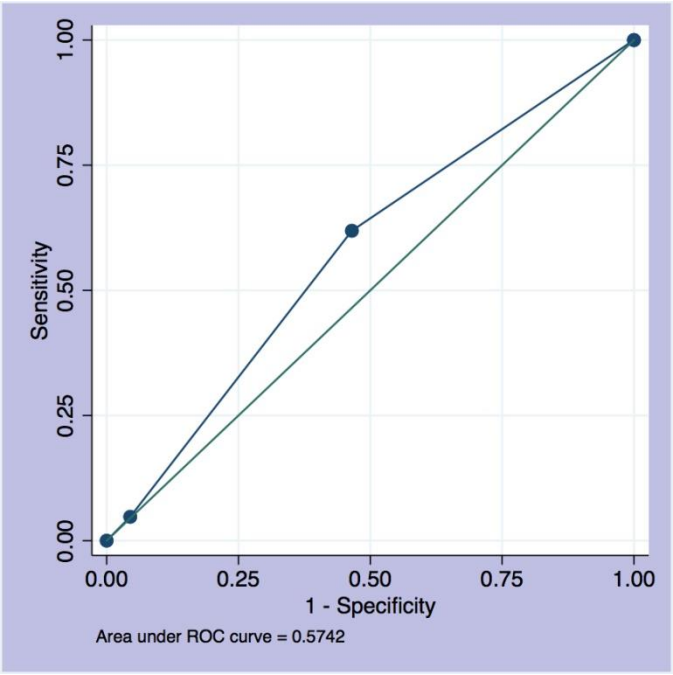


Figure 11.25 ROC curve for unadjusted MPI-ARS for in-hospital falls.

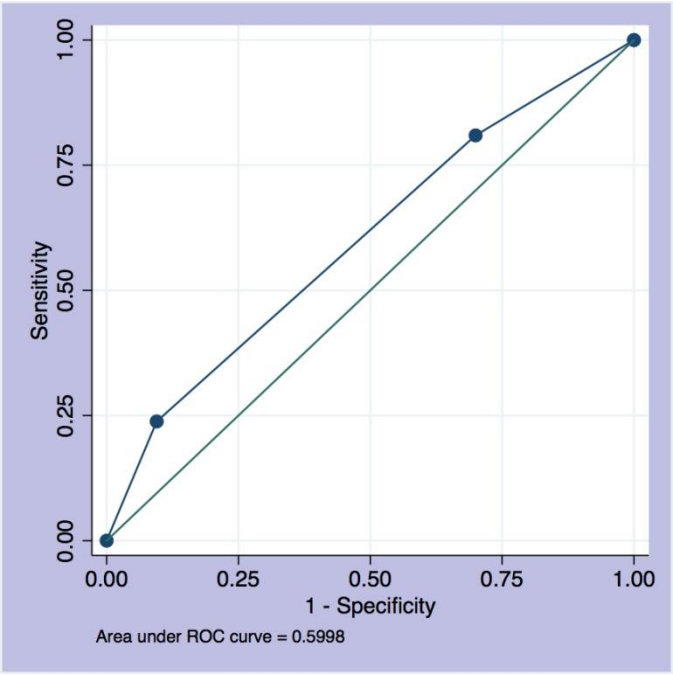


Figure 11.26 ROC curve for unadjusted MPI-RUDAS for in-hospital falls.

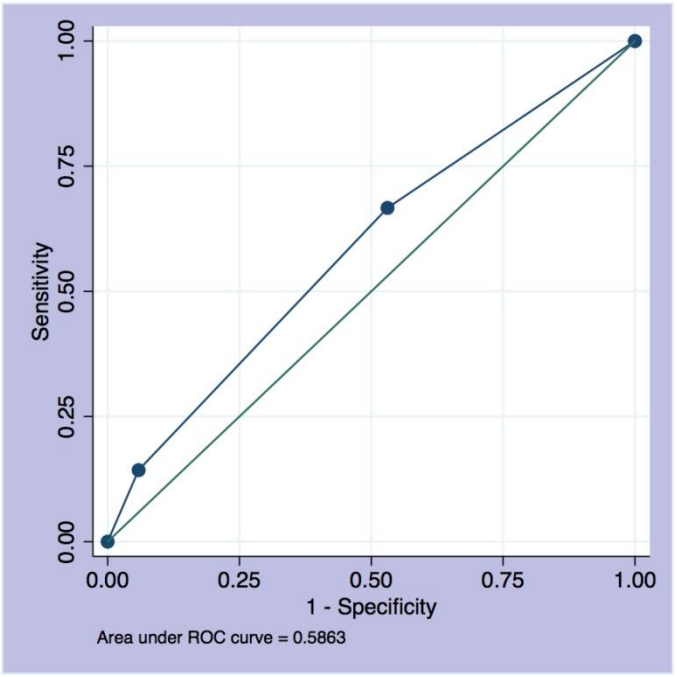


Figure 11.27 ROC curve for unadjusted OPT-MPI for in-hospital falls.

11.2.2.4.3 Multivariate ROC curve

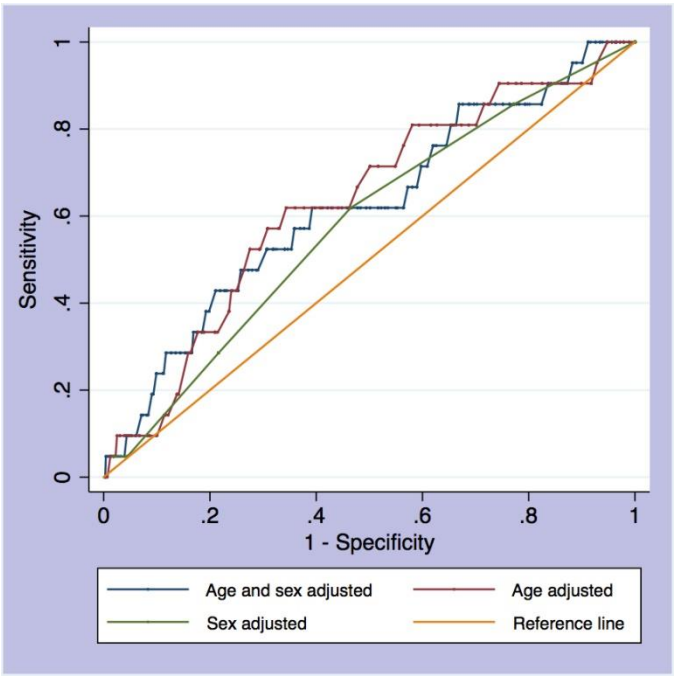


Figure 11.28 ROC curve for adjusted MPI-ARS for in-hospital falls.

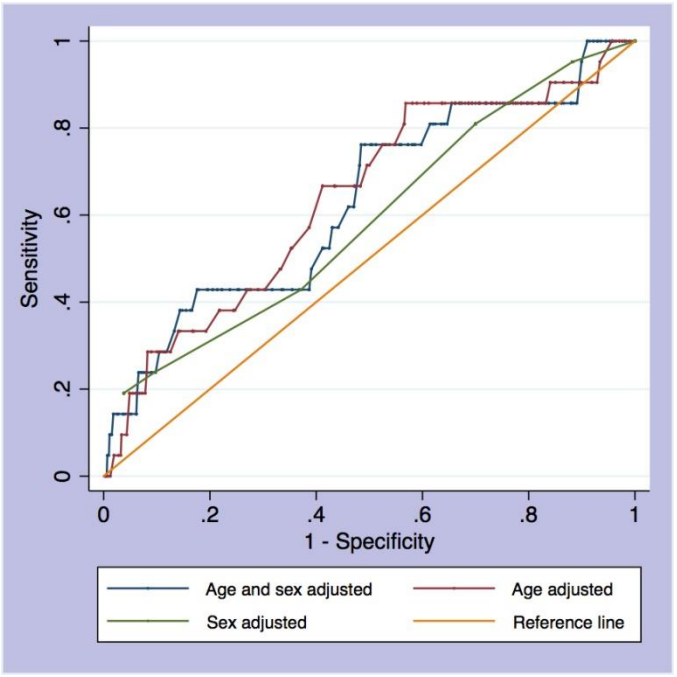


Figure 11.29 ROC curve for adjusted MPI-RUDAS for in-hospital falls.

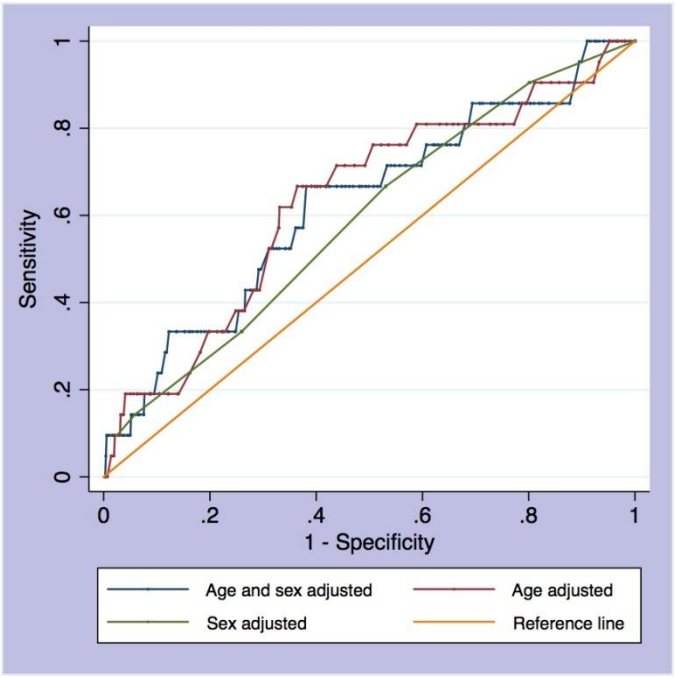


Figure 11.30 ROC curve for adjusted OPT-MPI for in-hospital falls.

11.2.2.4.4 Univariate and multivariate Poisson regression analyses

Table 11.18 Number of in-hospital falls univariate and multivariate Poisson regression of MPI-ARS items adjusted for age and sex.

Risk factors	IRR	Number of Falls Standard error	LCI	UCI	*p* value
Univariate					
MPI-ARS Continuous	1.0734	0.3911	0.5255	2.1924	*0.846*
MPI-ARS Categorical					
Mild	reference group	1.00	-	-	-
Moderate	1.1694	0.5256	0.4846	2.8220	*0.728*
Severe	0.9222	0.9721	0.1168	7.2789	*0.939*
Multivariate					
MPI-ARS Continuous	1.0023	0.3676	0.4884	2.0568	*0.995*
Age	1.0306	0.0275	0.9781	1.0860	*0.258*
MPI-ARS Continuous	1.0684	0.3910	0.5215	2.1890	*0.857*
Sex	0.9232	0.4043	0.3913	2.1782	*0.855*
MPI-ARS Continuous	0.9996	0.3682	0.4856	2.0575	*0.999*
Age	1.0304	0.0276	0.9777	1.0860	*0.263*
Sex	0.9587	0.4219	0.4047	2.2712	*0.924*
MPI-ARS Categorical					
Moderate	1.1089	0.5013	0.4572	2.6897	*0.819*
Severe	0.7744	0.8240	0.0962	6.2328	*0.810*
Age	1.0311	0.0275	0.9786	1.0864	*0.251*
MPI-ARS Categorical					
Moderate	1.1606	0.5247	0.4785	2.8154	*0.742*
Severe	0.9225	0.9724	0.1169	7.2812	*0.939*
Sex	0.9344	0.4108	0.3947	2.2120	*0.877*
MPI-ARS Categorical					
Moderate	1.1053	0.5031	0.4530	2.6972	*0.826*
Severe	0.7742	0.8239	0.0962	6.2332	*0.810*
Age	1.0310	0.0276	0.9783	1.0865	*0.254*
Sex	0.9732	0.4300	0.4094	2.3136	*0.951*

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; UCI: upper confidence interval.

Table 11.19 Number of in-hospital falls univariate and multivariate Poisson regression of MPI-RUDAS items adjusted for age and sex.

Risk factors	IRR	Number of Falls Standard error	LCI	UCI	*p* value
Univariate					
MPI-RUDAS Continuous	1.2711	0.4691	0.6166	2.6201	*0.516*
MPI-RUDAS Categorical					
Mild	reference group	1.00	-	-	-
Moderate	1.1102	0.6348	0.3620	3.4048	*0.855*
Severe	1.6156	1.1424	0.4041	6.4600	*0.497*
Multivariate					
MPI-RUDAS Continuous	1.1355	0.4409	0.5305	2.4305	*0.743*
Age	1.0280	0.0283	0.9741	1.0850	*0.314*
MPI-RUDAS Continuous	1.2676	0.4692	0.6137	2.6185	*0.522*
Sex	0.9317	0.4075	0.3953	2.1956	*0.871*
MPI-RUDAS Continuous	1.1339	0.4413	0.5288	2.4316	*0.747*
Age	1.0279	0.0283	0.9738	1.0850	*0.319*
Sex	0.9659	0.4245	0.4081	2.2858	*0.937*
MPI-RUDAS Categorical					
Moderate	0.9602	0.5657	0.3026	3.0468	*0.945*
Severe	1.2822	0.9494	0.3004	5.4726	*0.737*
Age	1.0288	0.0284	0.9745	1.0860	*0.305*
MPI-RUDAS Categorical					
Moderate	1.0995	0.6313	0.3568	3.3877	*0.869*
Severe	1.6056	1.1366	0.4009	6.4299	*0.504*
Sex	0.9218	0.4045	0.3901	2.1784	*0.853*
MPI-RUDAS Categorical					
Moderate	0.9553	0.5650	0.2997	3.0450	*0.938*
Severe	1.2772	0.9478	0.2983	5.4688	*0.742*
Age	1.0285	0.0285	0.9742	1.0860	*0.310*
Sex	0.9552	0.4210	0.4026	2.2661	*0.917*

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; UCI: upper confidence interval.

Table 11.20 Number of in-hospital falls univariate and multivariate Poisson regression of OPT-MPI items, age, and sex.

		Number of Falls			
Risk factors	**IRR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
OPT-MPI Continuous	1.3229	0.4594	0.6699	2.6128	*0.420*
OPT-MPI Categorical					
Mild	reference group		-	-	
Moderate	1.1362	0.5494	0.4405	2.9310	*0.792*
Severe	1.9369	1.3366	0.5009	7.4902	*0.338*
Multivariate					
OPT-MPI Continuous	1.2390	0.4370	0.6207	2.4733	*0.543*
Age	1.0277	0.0274	0.9753	1.0830	*0.306*
OPT-MPI Continuous	1.3199	0.4599	0.6668	2.6128	*0.426*
Sex	0.9357	0.4092	0.3971	2.2051	*0.879*
OPT-MPI Continuous	1.2378	0.4374	0.6192	2.4744	*0.546*
Age	1.0276	0.0275	0.9750	1.0830	*0.31*
Sex	0.9725	0.4274	0.4109	2.3015	*0.949*
OPT-MPI Categorical					
Moderate	1.0659	0.5197	0.4099	2.7719	*0.896*
Severe	1.6969	1.1903	0.4291	6.7100	*0.451*
Age	1.0277	0.0275	0.9752	1.0831	*0.307*
OPT-MPI Categorical					
Moderate	1.1225	0.5466	0.4322	2.9155	*0.812*
Severe	1.9378	1.3372	0.5011	7.4935	*0.338*
Sex	0.9120	0.4021	0.3844	2.1640	*0.835*
OPT-MPI Categorical					
Moderate	1.0597	0.5168	0.4053	2.7709	*0.906*
Severe	1.6963	1.1905	0.4287	6.7125	*0.451*
Age	1.0274	0.0276	0.9747	1.0830	*0.314*
Sex	0.9521	0.4212	0.4000	2.2661	*0.912*

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; OPT-MPI: Optimised-Multidimensional Prognostic Index; UCI: upper confidence interval.

11.2.2.5 In-hospital delirium

11.2.2.5.1 Univariate and multivariate logistic regression analyses

Table 11.21 In-hospital delirium univariate and multivariate logistic regression of MPI-ARS items, age, and sex.

		In-hospital Delirium				
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI-ARS Continuous	0.2576	0.8294	2.2919	1.5373	3.4169	*<0.0001*
MPI-ARS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.1137	0.4287	1.5353	0.8988	2.6222	*0.116*
Severe	0.2265	2.0417	7.7037	3.4275	17.3148	*<0.0001*
Multivariate						
MPI-ARS Continuous	0.1994	0.6622	1.9390	1.2914	2.9115	*0.001*
Age	0.2534	0.0585	1.0602	1.0272	1.0943	*<0.0001*
MPI-ARS Continuous	0.2763	0.8986	2.4561	1.6426	3.6829	*<0.0001*
Sex	0.1561	0.5923	1.8081	1.0847	3.0139	*0.023*
MPI-ARS Continuous	0.2195	0.7407	2.0973	1.3923	3.1593	*<0.0001*
Age	0.2642	0.0619	1.0639	1.0304	1.0985	*<0.0001*
Sex	0.1723	0.6776	1.9691	1.1681	3.3194	*0.011*
MPI-ARS Categorical						
Moderate	0.0824	0.3207	1.3781	0.7998	2.3745	*0.248*
Severe	0.1786	1.6620	5.2700	2.2709	12.2299	*<0.0001*
Age	0.2480	0.0569	1.0586	1.0251	1.0931	*0.001*
MPI-ARS Categorical						
Moderate	0.1373	0.5236	1.6882	0.9799	2.9084	*0.059*
Severe	0.2357	2.1486	8.5729	3.7590	19.5515	*<0.0001*
Sex	0.1487	0.5608	1.7521	1.0444	2.9393	*0.034*
MPI-ARS Categorical						
Moderate	0.1074	0.4250	1.5296	0.8797	2.6596	*0.132*
Severe	0.1878	1.7759	5.9055	2.5236	13.8192	*<0.0001*
Age	0.2597	0.0606	1.0625	1.0285	1.0975	*<0.0001*
Sex	0.1669	0.6527	1.9207	1.1334	3.2546	*0.015*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.22 In-hospital delirium univariate and multivariate logistic regression of MPI-RUDAS items, age, and sex.

	In-hospital Delirium					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
MPI-RUDAS Continuous	0.3475	1.1242	3.0778	1.9984	4.7400	*<0.0001*
MPI-RUDAS Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.1076	0.4176	1.5183	0.7736	2.9802	*0.225*
Severe	0.3258	2.0713	7.9350	3.6989	17.0222	*<0.0001*
Multivariate						
MPI-RUDAS Continuous	0.2752	0.9085	2.4806	1.5739	3.9096	*<0.0001*
Age	0.2047	0.0481	1.0493	1.0153	1.0845	*0.004*
MPI-RUDAS Continuous	0.3617	1.1829	3.2638	2.1133	5.0407	*<0.0001*
Sex	0.1551	0.6060	1.8331	1.0974	3.0620	*0.021*
MPI-RUDAS Continuous	0.2902	0.9748	2.6506	1.6840	4.1721	*<0.0001*
Age	0.2185	0.0523	1.0537	1.0192	1.0894	*0.002*
Sex	0.1718	0.6896	1.9929	1.1812	3.3623	*0.010*
MPI-RUDAS Categorical						
Moderate	0.0512	0.2030	1.2250	0.6129	2.4487	*0.566*
Severe	0.2531	1.6440	5.1760	2.2922	11.6880	*<0.0001*
Age	0.2096	0.0485	1.0497	1.0154	1.0853	*0.004*
MPI-RUDAS Categorical						
Moderate	0.1295	0.5093	1.6641	0.8427	3.2861	*0.142*
Severe	0.3419	2.2008	9.0323	4.1481	19.6674	*<0.0001*
Sex	0.1526	0.5869	1.7985	1.0676	3.0296	*0.027*
MPI-RUDAS Categorical						
Moderate	0.0762	0.3081	1.3608	0.6774	2.7336	*0.387*
Severe	0.2703	1.7887	5.9819	2.6285	13.6138	*<0.0001*
Age	0.2224	0.0525	1.0539	1.0190	1.0898	*0.002*
Sex	0.1695	0.6701	1.9545	1.1478	3.3282	*0.014*

Abbreviations: β: beta; LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; OR: odds ratio; UCI: upper confidence interval.

Table 11.23 In-hospital delirium univariate and multivariate logistic regression of OPT-MPI items, age, and sex.

	In-hospital Delirium					
Risk factors	**Standardised β coefficient**	**Coefficient**	**OR**	**LCI**	**UCI**	***p* value**
Univariate						
OPT-MPI Continuous	0.3541	1.1391	3.1240	2.0797	4.6927	*<0.0001*
OPT-MPI Categorical						
Mild	reference group	0.0000	1.00	-	-	-
Moderate	0.1911	0.7308	2.0767	1.1550	3.7340	*0.015*
Severe	0.3003	2.3945	10.9623	5.0906	23.6068	*<0.0001*
Multivariate						
OPT-MPI Continuous	0.2980	0.9812	2.6677	1.7610	4.0412	*<0.0001*
Age	0.2227	0.0527	1.0541	1.0210	1.0882	*0.001*
OPT-MPI Continuous	0.3686	1.1994	3.3181	2.2025	4.9989	*<0.0001*
Sex	0.1598	0.6266	1.8712	1.1171	3.1344	*0.017*
OPT-MPI Continuous	0.3132	1.0498	2.8571	1.8840	4.3329	*<0.0001*
Age	0.2370	0.0571	1.0588	1.0250	1.0936	*0.001*
Sex	0.1786	0.7213	2.0570	1.2133	3.4876	*0.007*
OPT-MPI Categorical						
Moderate	0.1570	0.6161	1.8517	1.0218	3.3554	*0.042*
Severe	0.2540	2.0787	7.9943	3.6140	17.6838	*<0.0001*
Age	0.2222	0.0519	1.0533	1.0199	1.0878	*0.002*
OPT-MPI Categorical						
Moderate	0.2136	0.8275	2.2875	1.2625	4.1446	*0.006*
Severe	0.3099	2.5038	12.2293	5.5971	26.7204	*<0.0001*
Sex	0.1557	0.6025	1.8267	1.0833	3.0804	*0.024*
OPT-MPI Categorical						
Moderate	0.1790	0.7162	2.0467	1.1206	3.7382	*0.020*
Severe	0.2635	2.1988	9.0142	4.0415	20.1055	*<0.0001*
Age	0.2377	0.0566	1.0583	1.0242	1.0935	*0.001*
Sex	0.1766	0.7056	2.0251	1.1872	3.4542	*0.010*

Abbreviations: β: beta; LCI: lower confidence interval; OPT-MPI: Optimised-Multidimensional Prognostic Index; OR: odds ratio; UCI: upper confidence interval.

11.2.2.5.2 Univariate ROC curves

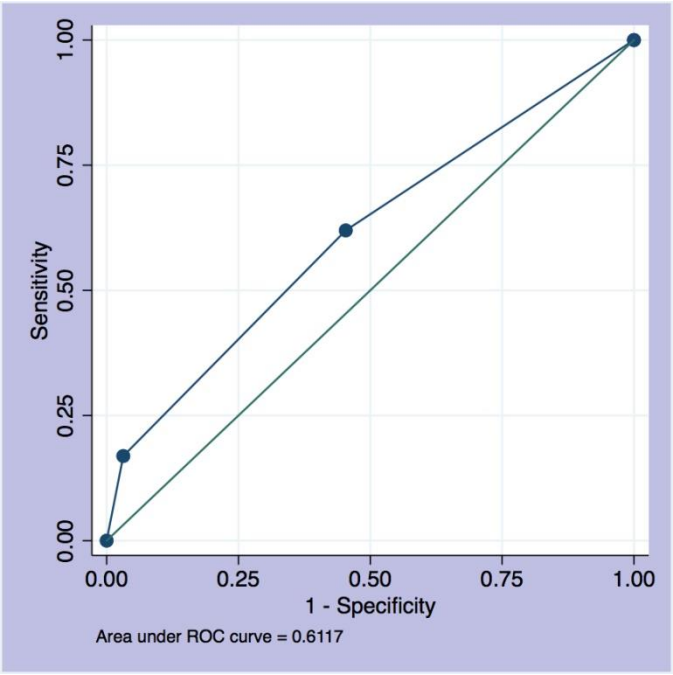


Figure 11.31 ROC curve for unadjusted MPI-ARS for in-hospital delirium.

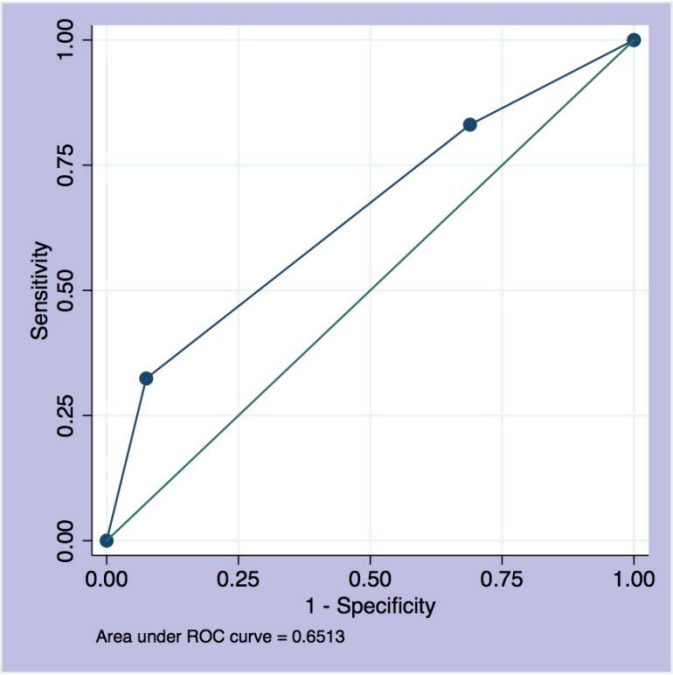


Figure 11.32 ROC curve for unadjusted MPI-RUDAS for in-hospital delirium.

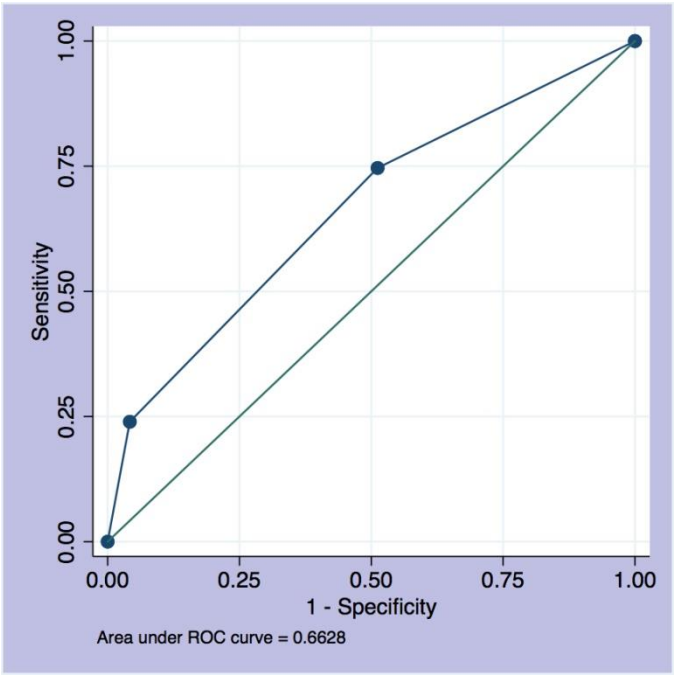


Figure 11.33 ROC curve for unadjusted OPT-MPI for in-hospital delirium.

11.2.2.5.3 Multivariate ROC curve

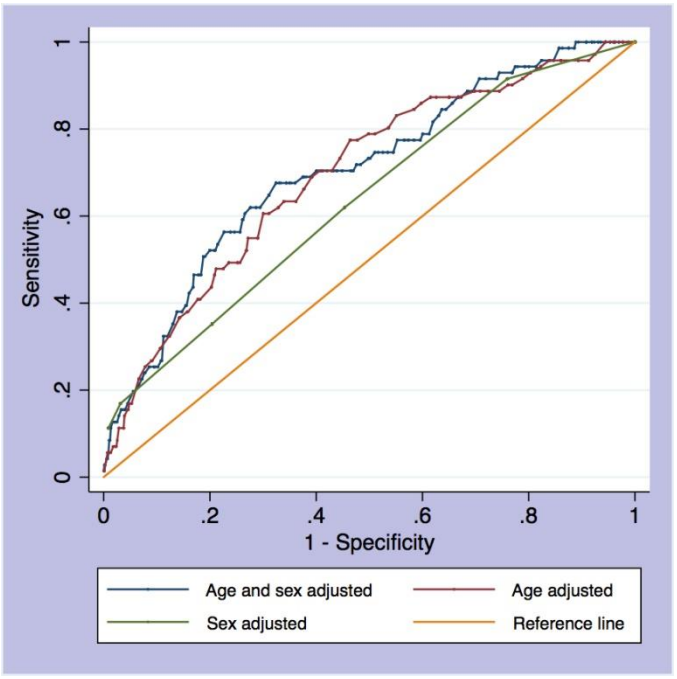


Figure 11.34 ROC curve for adjusted MPI-ARS for in-hospital delirium.

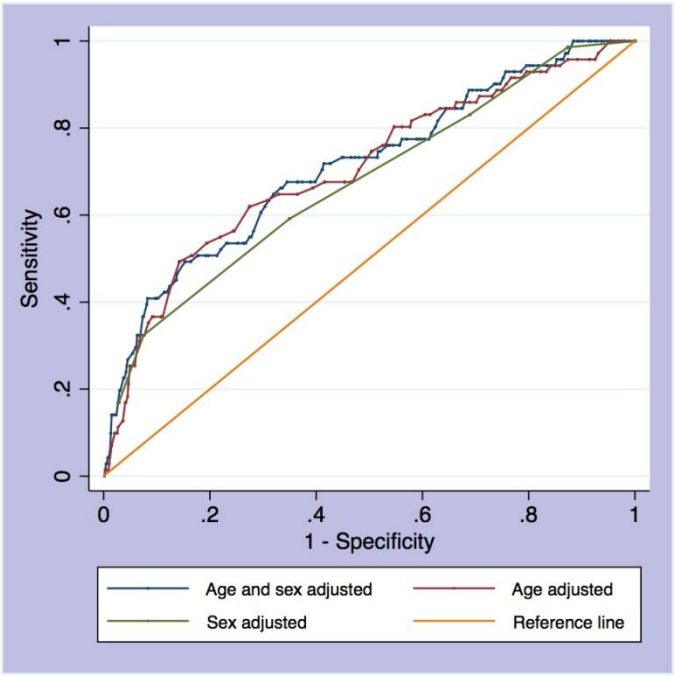


Figure 11.35 ROC curve for adjusted MPI-RUDAS for in-hospital delirium.

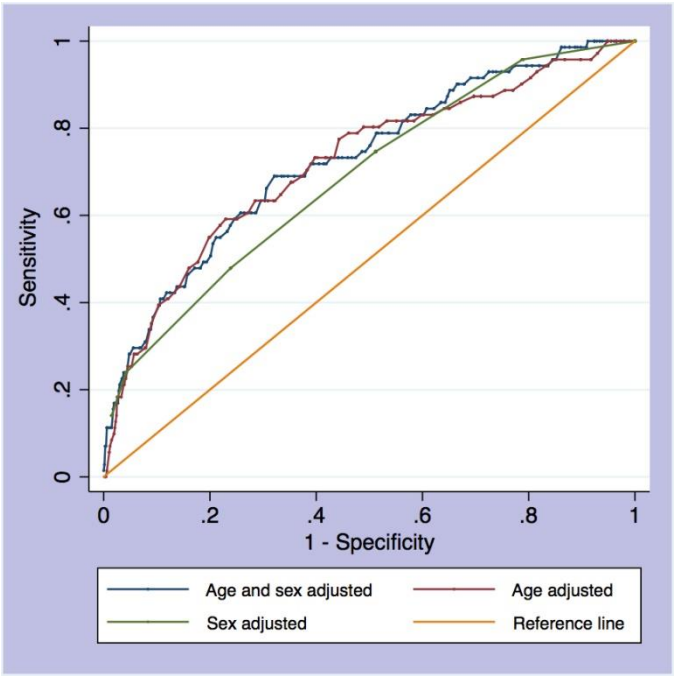


Figure 11.36 ROC curve for adjusted OPT-MPI for in-hospital delirium.

11.2.2.6 Length of stay

11.2.2.6.1 Mean LOS

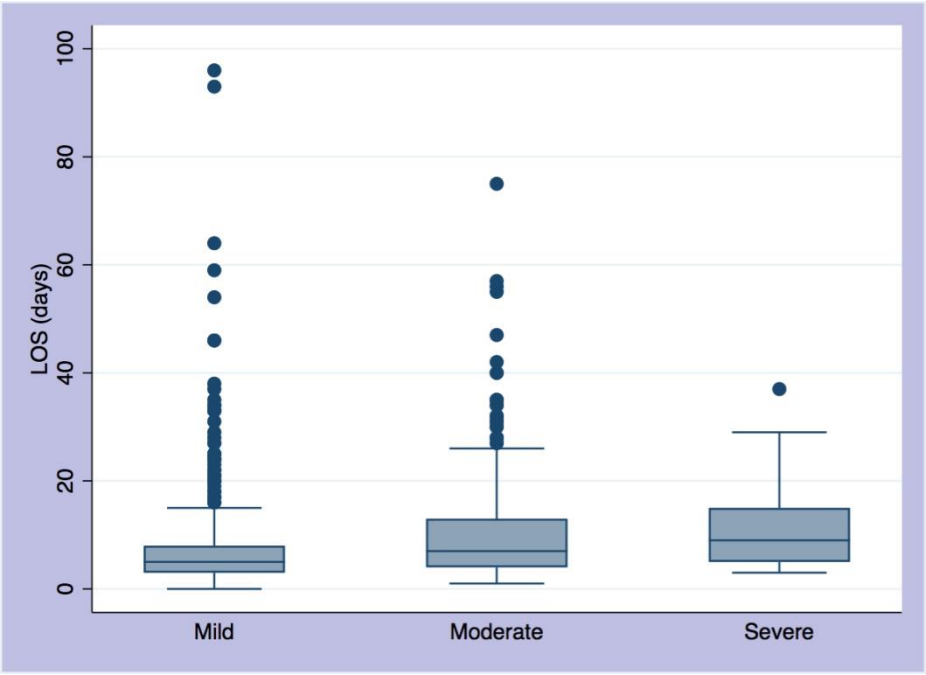


Figure 11.37 Boxplot for LOS in days according to MPI-ARS risk categories.

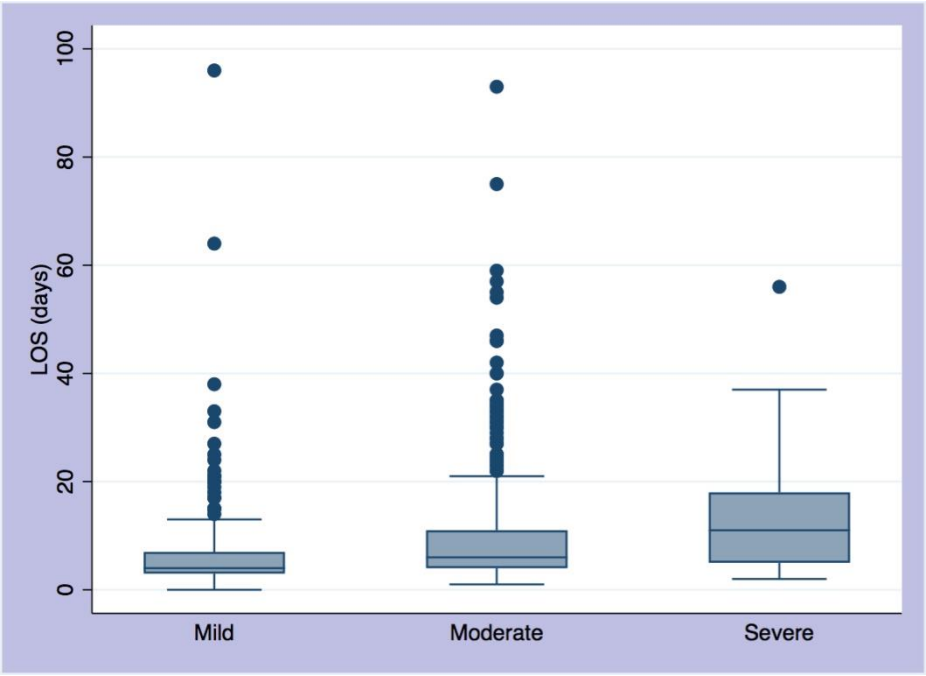


Figure 11.38 Boxplot for LOS in days according to MPI-RUDAS risk categories.

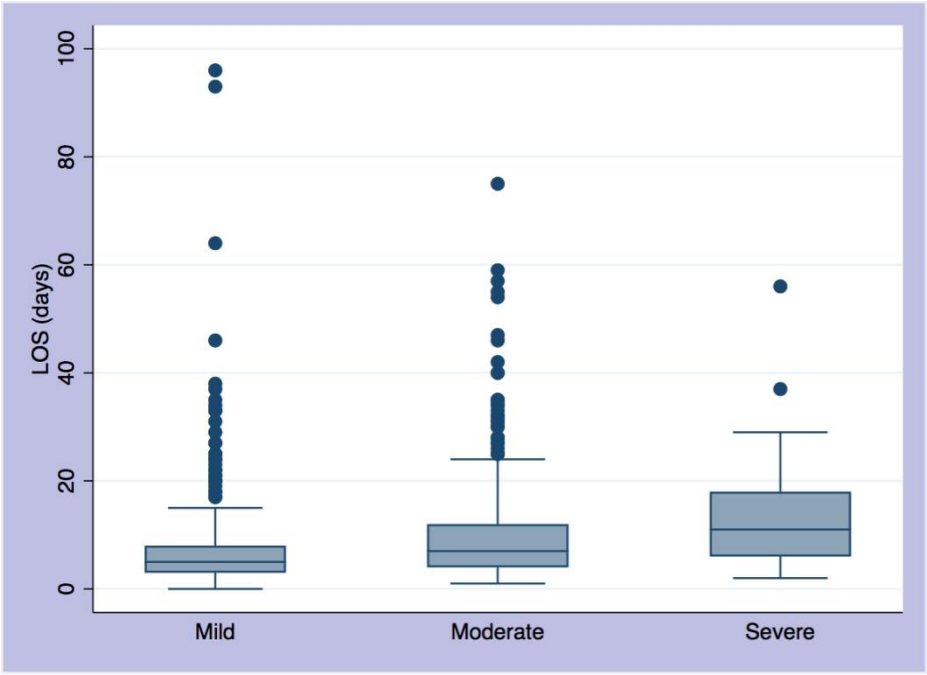


Figure 11.39 Boxplot for LOS in days according to OPT-MPI risk categories.

11.2.2.6.2 Univariate and multivariate Cox proportional hazards analyses

Table 11.24 Length of stay univariate and multivariate Cox proportional hazards of MPI-ARS items, age and sex.

Risk factors	HR	LOS Standard error	LCI	UCI	*p* value
Univariate					
MPI-ARS Categorical					
Mild x (follow-up)^2	0.9992	0.02363	0.9988	0.9997	*0.001*
Moderate (Y vs N)	0.7235	0.0610	0.6133	0.8534	*<0.0001*
Severe x (follow-up)^2	0.9997	0.0006	0.9986	1.0009	*0.680*
Multivariate					
MPI-ARS Categorical					
Mild	0.9992	0.0002	0.9988	0.9997	*0.001*
Moderate	0.7345	0.0620	0.6225	0.8668	*<0.0001*
Severe	0.9998	0.0006	0.9986	1.0009	*0.700*
Age	0.9863	0.0044	0.9777	0.9950	*0.002*
MPI-ARS Categorical					
Mild	0.9992	0.0002	0.9988	0.9997	*0.001*
Moderate	0.7131	0.0612	0.6028	0.8437	*<0.0001*
Severe	0.9998	0.0006	0.9986	1.0010	*0.693*
Sex	0.9327	0.0717	0.8023	1.0843	*0.364*
MPI-ARS Categorical					
Mild	0.9992	0.0002	0.9987	0.9997	*0.001*
Moderate	0.7215	0.0620	0.6098	0.8538	*<0.0001*
Severe	0.9998	0.0006	0.9986	1.0010	*0.716*
Age	0.9859	0.0044	0.9773	0.9947	*0.002*
Sex	0.9149	0.0705	0.7865	1.0641	*0.248*

Note: Reference group for the Moderate risk group was categorical Yes versus No. Mild and severe risk groups were time varying covariate of time of follow-up squared. Abbreviations: HR: hazard ratio; LCI: lower confidence interval; Ln: Natural log; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; N: No; UCI: upper confidence interval; Vs: Versus; Y: Yes.

Table 11.25 Length of stay univariate and multivariate Cox proportional hazards of MPI-RUDAS items, age and sex.

Risk factors	HR	LOS Standard error	LCI	UCI	*p* value
Univariate					
MPI-RUDAS Categorical					
Mild (Y vs N)	5.8094	2.3557	2.6241	12.8616	*<0.0001*
Moderate (Y vs N)	4.1864	1.6928	1.8952	9.2477	*<0.0001*
Severe x Ln(follow-up)	1.7481	0.3020	1.2460	2.4525	*0.001*
Multivariate					
MPI-RUDAS Categorical					
Mild	5.2031	2.1257	2.3361	11.5883	*<0.0001*
Moderate	3.8859	1.5725	1.7581	8.5890	*0.001*
Severe	1.7037	0.2938	1.2151	2.3889	*0.002*
Age	0.9921	0.0046	0.9831	1.0012	*0.087*
MPI-RUDAS Categorical					
Mild	6.0721	2.4882	2.7198	13.5564	*<0.0001*
Moderate	4.3302	1.7644	1.9483	9.6238	*<0.0001*
Severe	1.7774	0.3099	1.2690	2.5015	*0.001*
Sex	0.9303	0.0710	0.8011	1.0804	*0.344*
MPI-RUDAS Categorical					
Mild	5.4342	2.2422	2.4206	12.1996	*<0.0001*
Moderate	4.0181	1.6381	1.8072	8.9336	*0.001*
Severe	1.7328	0.3015	1.2320	2.4371	*0.002*
Age	0.9919	0.0046	0.9829	1.0010	*0.082*
Sex	0.9269	0.0707	0.7981	1.0764	*0.320*

Note: Reference group for the Mild and Moderate risk groups were categorical Yes versus No. Severe risk group was time varying covariate of natural log times follow-up Abbreviations: HR: hazard ratio; LCI: lower confidence interval; Ln: Natural log; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; N: No; UCI: upper confidence interval; Vs: Versus; Y: Yes.

Table 11.26 Length of stay univariate and multivariate Cox proportional hazards of OPT-MPI items, age and sex.

Risk factors	HR	LOS Standard error	LCI	UCI	*p* value
Univariate					
OPT-MPI Categorical					
Mild x (follow-up)^2	0.9993	0.000245	0.9989	0.9998	*0.007*
Moderate (Y vs N)	0.7439	0.0614	0.6328	0.8745	*<0.0001*
Severe x (follow-up)^2	0.9996	0.0003	0.9990	1.0003	*0.286*
Multivariate					
OPT-MPI Categorical					
Mild	0.9993	0.0002	0.9988	0.9998	*0.005*
Moderate	0.7560	0.0625	0.6429	0.8890	*0.001*
Severe	0.9996	0.0003	0.9989	1.0003	*0.245*
Age	0.9862	0.0044	0.9776	0.9949	*0.002*
OPT-MPI Categorical					
Mild	0.9993	0.0002	0.9988	0.9998	*0.006*
Moderate	0.7365	0.0616	0.6251	0.8678	*<0.0001*
Severe	0.9996	0.0003	0.9990	1.0003	*0.295*
Sex	0.9469	0.0725	0.8150	1.1002	*0.476*
OPT-MPI Categorical					
Mild	0.9993	0.0002	0.9988	0.9998	*0.004*
Moderate	0.7461	0.0626	0.6330	0.8794	*<0.0001*
Severe	0.9996	0.0003	0.9990	1.0003	*0.255*
Age	0.9859	0.0044	0.9773	0.9946	*0.001*
Sex	0.9299	0.0714	0.7999	1.0809	*0.344*

Note: Reference group for the Moderate risk group was categorical Yes versus No. Mild and severe risk groups were time varying covariate of time of follow-up squared. Abbreviations: HR: hazard ratio; LCI: lower confidence interval; Ln: Natural log; N: No; OPT-MPI: Optimised-Multidimensional Prognostic Index; UCI: upper confidence interval; Vs: Versus; Y: Yes.

11.2.2.6.3 Kaplan-Meier survival plots

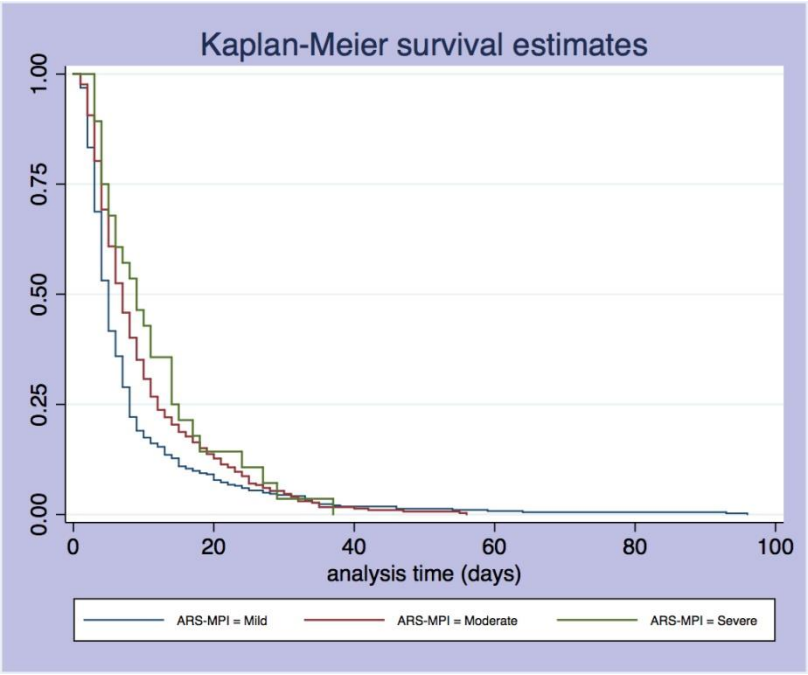


Figure 11.40 Unadjusted Kaplan-Meier survival cure for LOS in days according to MPI-ARS risk categories.

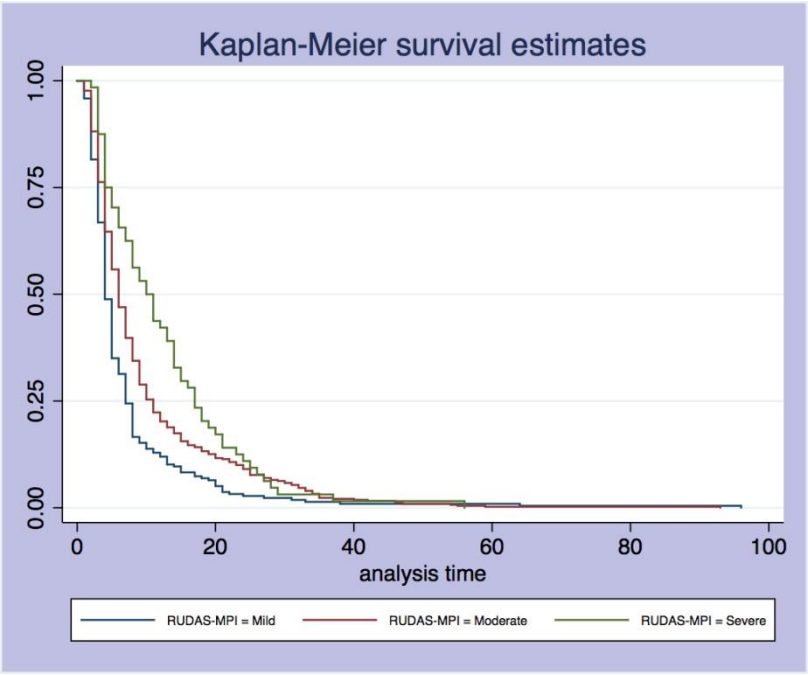


Figure 11.41 Unadjusted Kaplan-Meier survival cure for LOS in days according to MPI-RUDAS risk categories.

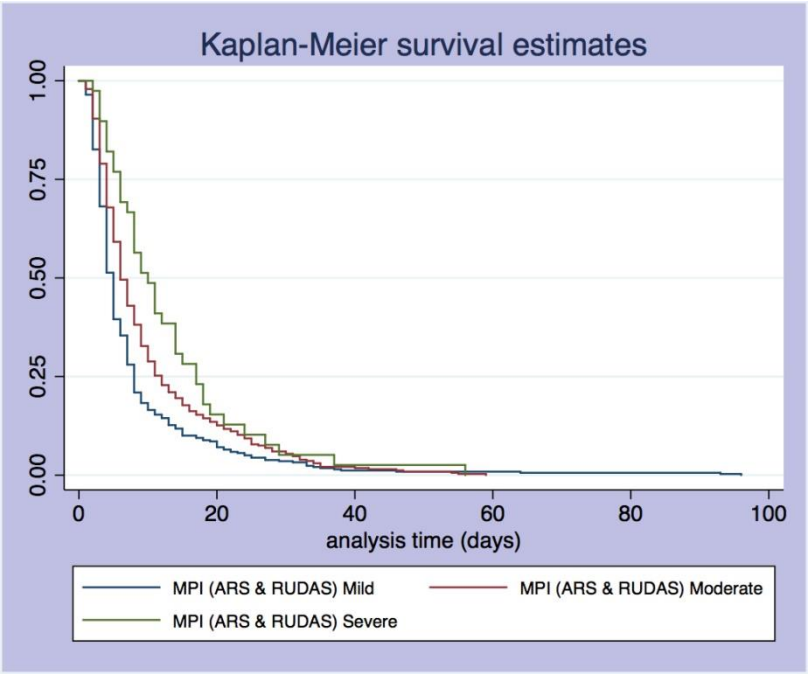


Figure 11.42 Unadjusted Kaplan-Meier survival cure for LOS in days according to OPT-MPI risk categories.

11.2.2.7 30-day re-admission rate

11.2.2.7.1 Univariate and multivariate competing risk regression analyses

Table 11.27 Thirty-day re-admission rate univariate and multivariate competing risk regression of MPI-ARS items, age and sex.

	30 day re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI-ARS Continuous	0.7796	0.1272	0.5662	1.0733	*0.127*
MPI-ARS Categorical					
Mild	1.00	reference group	-	-	-
Moderate	0.8851	0.1710	0.6061	1.2927	*0.528*
Severe	0.2263	0.2238	0.0326	1.5721	*0.133*
Multivariate					
MPI-ARS Continuous	0.7627	0.1277	0.5493	1.0590	*0.106*
Age	1.0093	0.0120	0.9860	1.0331	*0.439*
MPI-ARS Continuous	0.7841	0.1329	0.5624	1.0931	*0.151*
Sex	1.0337	0.2039	0.7022	0.1522	*0.866*
MPI-ARS Continuous	0.7678	0.1330	0.5467	1.0782	*0.127*
Age	1.0094	0.0120	0.9860	1.0333	*0.435*
Sex	1.0398	0.2057	0.7057	1.5322	*0.844*
MPI-ARS Categorical					
Moderate	0.8685	0.1694	0.5925	1.2730	*0.470*
Severe	0.2107	0.2127	0.0291	1.5241	*0.123*
Age	1.0102	0.0119	0.9871	1.0338	*0.391*
MPI-ARS Categorical					
Moderate	0.8936	0.1808	0.6010	1.3286	*0.578*
Severe	0.2287	0.2258	0.0330	1.5841	*0.135*
Sex	1.0487	0.2081	0.7107	1.5473	*0.811*
MPI-ARS Categorical					
Moderate	0.8776	0.1788	0.5887	1.3084	*0.522*
Severe	0.2132	0.2148	0.0296	1.5362	*0.125*
Age	1.0103	0.0120	0.9871	1.0340	*0.387*
Sex	1.0549	0.2097	0.7145	1.5575	*0.788*

Abbreviations: LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; SHR: sub-hazard ratio; UCI: upper confidence interval.

Table 11.28 Thirty-day re-admission rate univariate and multivariate competing risk regression of MPI-RUDAS items, age and sex.

	30 day re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI-RUDAS Continuous	1.0519	0.1597	0.7811	1.4166	*0.739*
MPI-RUDAS Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.2871	0.2885	0.8295	1.9971	*0.260*
Severe	0.8412	0.3622	0.3617	1.9563	*0.688*
Multivariate					
MPI-RUDAS Continuous	1.0263	0.1678	0.7449	1.4141	*0.874*
Age	1.0055	0.0123	0.9816	1.0299	*0.656*
MPI-RUDAS Continuous	1.0652	0.1660	0.7849	1.4456	*0.685*
Sex	1.1019	0.2150	0.7517	1.6151	*0.619*
MPI-RUDAS Continuous	1.0392	0.1729	0.7500	1.4399	*0.817*
Age	1.0057	0.0124	0.9817	1.0302	*0.646*
Sex	1.1049	0.2162	0.7529	1.6213	*0.610*
MPI-RUDAS Categorical					
Moderate	1.2557	0.2902	0.7984	1.9751	*0.324*
Severe	0.7988	0.3598	0.3304	1.9311	*0.618*
Age	1.0057	0.0122	0.9820	1.0299	*0.641*
MPI-RUDAS Categorical					
Moderate	1.3093	0.3002	0.8354	2.0520	*0.240*
Severe	0.8621	0.3756	0.3670	2.0251	*0.734*
Sex	1.1139	0.2169	0.7605	1.6315	*0.580*
MPI-RUDAS Categorical					
Moderate	1.2774	0.3007	0.8053	2.0263	*0.298*
Severe	0.8184	0.3714	0.3363	1.9919	*0.659*
Age	1.0059	0.0122	0.9822	1.0302	*0.630*
Sex	1.1170	0.2181	0.7618	1.6378	*0.571*

Abbreviations: LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; SHR: sub-hazard ratio; UCI: upper confidence interval.

Table 11.29 Thirty-day re-admission rate univariate and multivariate competing risk regression of OPT-MPI items, age and sex.

	30 day re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
OPT-MPI Continuous	0.8868	0.1396	0.6514	1.2072	*0.445*
OPT-MPI Categorical					
Mild	1.00	reference group	-	-	-
Moderate	0.9693	0.1868	0.6644	1.4142	*0.872*
Severe	0.5589	0.3171	0.1838	1.6992	*0.305*
Multivariate					
OPT-MPI Continuous	0.8699	0.1409	0.6333	1.1950	*0.390*
Age	1.0078	0.0119	0.9848	1.0314	*0.508*
OPT-MPI Continuous	0.8950	0.1443	0.6526	1.2276	*0.492*
Sex	1.0658	0.2078	0.7273	1.5618	*0.744*
OPT-MPI Continuous	0.8784	0.1452	0.6354	1.2144	*0.433*
Age	1.0080	0.0120	0.9849	1.0317	*0.500*
Sex	1.0719	0.2097	0.7305	1.5728	*0.723*
OPT-MPI Categorical					
Moderate	0.9524	0.1863	0.6490	1.3975	*0.803*
Severe	0.5334	0.3079	0.1721	1.6537	*0.276*
Age	1.0081	0.0118	0.9852	1.0316	*0.490*
OPT-MPI Categorical					
Moderate	0.9815	0.1946	0.6655	1.4475	*0.925*
Severe	0.5673	0.3226	0.1861	1.7291	*0.319*
Sex	1.0746	0.2102	0.7325	1.5766	*0.713*
OPT-MPI Categorical					
Moderate	0.9647	0.1936	0.6510	1.4297	*0.858*
Severe	0.5420	0.3133	0.1746	1.6826	*0.289*
Age	1.0083	0.0119	0.9853	1.0318	*0.482*
Sex	1.0803	0.2117	0.7357	1.5862	*0.694*

Abbreviations: LCI: lower confidence interval; OPT-MPI: Optimised-Multidimensional Prognostic Index; SHR: sub-hazard ratio; UCI: upper confidence interval.

11.2.2.8 3-month re-admissions

11.2.2.8.1 Univariate and multivariate competing risk regression analyses

Table 11.30 Three-month re-admission rate univariate and multivariate competing risk regression of MPI-ARS items, age and sex.

	3 month re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI-ARS Continuous	0.9573	0.1025	0.7761	1.1808	*0.684*
MPI-ARS Categorical					
Mild	1.00	reference group	-	-	-
Moderate	0.9874	0.1253	0.7700	1.2661	*0.920*
Severe	0.8194	0.2836	0.4158	1.6147	*0.565*
Multivariate					
MPI-ARS Continuous	0.9248	0.1008	0.7469	1.1450	*0.473*
Age	1.0139	0.0079	0.9986	1.0294	*0.075*
MPI-ARS Continuous	0.9697	0.1054	0.7836	1.2000	*0.777*
Sex	1.0807	0.1367	0.8433	1.3848	*0.540*
MPI-ARS Continuous	0.9369	0.1037	0.7542	1.1639	*0.556*
Age	1.0139	0.0079	0.9986	1.0295	*0.075*
Sex	1.0814	0.1370	0.8437	1.3861	*0.537*
MPI-ARS Categorical					
Moderate	0.9608	0.1228	0.7480	1.2342	*0.754*
Severe	0.7442	0.2654	0.3700	1.4972	*0.407*
Age	1.0141	0.0078	0.9989	1.0296	*0.070*
MPI-ARS Categorical					
Moderate	1.0038	0.1301	0.7786	1.2942	*0.977*
Severe	0.8338	0.2885	0.4232	1.6427	*0.599*
Sex	1.0851	0.1377	0.8461	1.3916	*0.520*
MPI-ARS Categorical					
Moderate	0.9766	0.1275	0.7562	1.2612	*0.856*
Severe	0.7586	0.2703	0.3773	1.5251	*0.438*
Age	1.0142	0.0079	0.9989	1.0297	*0.070*
Sex	1.0860	0.1378	0.8468	1.3927	*0.516*

Abbreviations: LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; SHR: sub-hazard ratio; UCI: upper confidence interval.

Table 11.31 Three-month re-admission rate univariate and multivariate competing risk regression of MPI-RUDAS items, age and sex.

	3 month re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI-RUDAS Continuous	1.1908	0.1220	0.9742	1.4555	*0.088*
MPI-RUDAS Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.3374	0.1986	0.9997	1.7894	*0.050*
Severe	1.2873	0.3107	0.8021	2.0660	*0.295*
Multivariate					
MPI-RUDAS Continuous	1.1408	0.1241	0.9217	1.4120	*0.226*
Age	1.0098	0.0081	0.9940	1.0259	*0.224*
MPI-RUDAS Continuous	1.2084	0.1256	0.9857	1.4814	*0.069*
Sex	1.1252	0.1419	0.8788	1.4408	*0.350*
MPI-RUDAS Continuous	1.1586	0.1277	0.9336	1.4380	*0.182*
Age	1.0098	0.0081	0.9940	1.0259	*0.226*
Sex	1.1249	0.1422	0.8780	1.4411	*0.352*
MPI-RUDAS Categorical					
Moderate	1.2835	0.1957	0.9519	1.7306	*0.102*
Severe	1.1776	0.2989	0.7161	1.9365	*0.520*
Age	1.0100	0.0081	0.9943	1.0260	*0.214*
MPI-RUDAS Categorical					
Moderate	1.3646	0.2064	1.0145	1.8356	*0.040*
Severe	1.3234	0.3223	0.8211	2.1329	*0.250*
Sex	1.1331	0.1431	0.8847	1.4512	*0.322*
MPI-RUDAS Categorical					
Moderate	1.3106	0.2035	0.9667	1.7767	*0.081*
Severe	1.2129	0.3100	0.7350	2.0016	*0.450*
Age	1.0100	0.0081	0.9942	1.0260	*0.216*
Sex	1.1327	0.1433	0.8839	1.4514	*0.325*

Abbreviations: LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; SHR: sub-hazard ratio; UCI: upper confidence interval.

Table 11.32 Three-month re-admission rate univariate and multivariate competing risk regression of OPT-MPI items, age and sex.

	3 month re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
OPT-MPI Continuous	1.1137	0.1119	0.9146	1.3560	*0.284*
OPT-MPI Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.1712	0.1505	0.9105	1.5066	*0.219*
Severe	1.1080	0.3003	0.6514	1.8847	*0.705*
Multivariate					
OPT-MPI Continuous	1.0817	0.1107	0.8851	1.3220	*0.443*
Age	1.0118	0.0078	0.9966	1.0271	*0.128*
OPT-MPI Continuous	1.1306	0.1142	0.9274	1.3782	*0.225*
Sex	1.1154	0.1397	0.8726	1.4257	*0.383*
OPT-MPI Continuous	1.0985	0.1130	0.8978	1.3440	*0.361*
Age	1.0119	0.0078	0.9967	1.0273	*0.126*
Sex	1.1173	0.1402	0.8737	1.4289	*0.377*
OPT-MPI Categorical					
Moderate	1.1411	0.1477	0.8855	1.4705	*0.308*
Severe	1.0375	0.2879	0.6022	1.7875	*0.894*
Age	1.0119	0.0075	0.9968	1.0272	*0.122*
OPT-MPI Categorical					
Moderate	1.1946	0.1553	0.9260	1.5412	*0.171*
Severe	1.1341	0.3078	0.6662	1.9306	*0.643*
Sex	1.1210	0.1407	0.8765	1.4337	*0.363*
OPT-MPI Categorical					
Moderate	1.1634	0.1523	0.9002	1.5037	*0.247*
Severe	1.0641	0.2952	0.6178	1.8328	*0.823*
Age	1.0120	0.0078	0.9968	1.0273	*0.122*
Sex	1.1222	0.1410	0.8772	1.4357	*0.359*

Abbreviations: LCI: lower confidence interval; OPT-MPI: Optimised-Multidimensional Prognostic Index; SHR: sub-hazard ratio; UCI: upper confidence interval.

11.2.2.8.2 Univariate and multivariate Poisson regression analyses

Table 11.33 Number of re-admissions within 3 months univariate and multivariate Poisson regression of MPI-ARS items, age and sex.

	Number of re-admissions within 3 months				
Risk factors	**IRR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI-ARS Continuous	0.8730	0.0852	0.72101	1.0571	*0.164*
MPI-ARS Categorical					
Mild	1.00	reference group	-	-	-
Moderate	0.9647	0.1089	0.7731	1.2036	*0.750*
Severe	0.4608	0.1775	0.2166	0.9804	*0.044*
Multivariate					
MPI-ARS Continuous	0.8726	0.0864	0.7187	1.0594	*0.169*
Age	1.0002	0.0067	0.9871	1.0135	*0.977*
MPI-ARS Continuous	0.8845	0.0872	0.7290	1.0731	*0.213*
Sex	1.1019	0.1237	0.8843	1.3731	*0.387*
MPI-ARS Continuous	0.8835	0.0882	0.7265	1.0745	*0.215*
Age	1.0005	0.0067	0.9873	1.0138	*0.944*
Sex	1.1024	0.1239	0.8844	1.3740	*0.386*
MPI-ARS Categorical					
Moderate	0.9628	0.1093	0.7708	1.2026	*0.738*
Severe	0.4566	0.1775	0.2131	0.9783	*0.044*
Age	1.0012	0.0067	0.9881	1.0145	*0.862*
MPI-ARS Categorical					
Moderate	0.9823	0.1124	0.7849	1.2293	*0.876*
Severe	0.4684	0.1806	0.2200	0.9974	*0.049*
Sex	1.1148	0.1254	0.8942	1.3898	*0.334*
MPI-ARS Categorical					
Moderate	0.9800	0.1126	0.7823	1.2276	*0.860*
Severe	0.4632	0.1801	0.2161	0.9926	*0.048*
Age	1.0015	0.0067	0.9884	1.0148	*0.824*
Sex	1.1162	0.1257	0.8951	1.3918	*0.329*

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; UCI: upper confidence interval.

Table 11.34 Number of re-admissions within 3 months univariate and multivariate Poisson regression of MPI-RUDAS items, age and sex.

	Number of re-admissions within 3 months				
Risk factors	**IRR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI-RUDAS Continuous	1.1427	0.1056	0.9535	1.3695	*0.149*
MPI-RUDAS Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.5097	0.2021	1.1613	1.9626	*0.002*
Severe	1.0135	0.2345	0.6441	1.5949	*0.954*
Multivariate					
MPI-RUDAS Continuous	1.1707	0.1148	0.9659	1.4187	*0.108*
Age	0.9949	0.0070	0.9813	1.0086	*0.462*
MPI-RUDAS Continuous	1.1607	0.1079	0.9674	1.3926	*0.109*
Sex	1.1534	0.1291	0.9262	1.4362	*0.202*
MPI-RUDAS Continuous	1.1862	0.1164	0.9786	1.4378	*0.082*
Age	0.9952	0.0070	0.9817	1.0090	*0.493*
Sex	1.1497	0.1287	0.9232	1.4318	*0.213*
MPI-RUDAS Categorical					
Moderate	1.5414	0.2117	1.1776	2.0177	*0.002*
Severe	1.0601	0.2552	0.6614	1.6993	*0.808*
Age	0.9953	0.0069	0.9818	1.0090	*0.500*
MPI-RUDAS Categorical					
Moderate	1.5488	0.2091	1.1888	2.0179	*0.001*
Severe	1.0448	0.2427	0.6627	1.6472	*0.850*
Sex	1.1775	0.1318	0.9455	1.4663	*0.144*
MPI-RUDAS Categorical					
Moderate	1.5773	0.2178	1.2032	2.0676	*0.001*
Severe	1.0870	0.2619	0.6779	1.7430	*0.729*
Age	0.9957	0.0069	0.9822	1.0094	*0.537*
Sex	1.1742	0.1315	0.9428	1.4624	*0.152*

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; UCI: upper confidence interval.

Table 11.35 Number of re-admissions within 3 months univariate and multivariate Poisson regression of OPT-MPI items, age and sex.

	Number of re-admissions within 3 months				
Risk factors	**IRR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
OPT-MPI Continuous	0.9900	0.0911	0.8266	1.1858	*0.913*
OPT-MPI Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.0620	0.1207	0.8499	1.3270	*0.597*
Severe	0.8185	0.2153	0.4887	1.3707	*0.446*
Multivariate					
OPT-MPI Continuous	0.9937	0.0934	0.8265	1.1948	*0.946*
Age	0.9987	0.0067	0.9856	1.0120	*0.845*
OPT-MPI Continuous	1.0036	0.0931	0.8368	1.2037	*0.969*
Sex	1.1267	0.1262	0.9046	1.4033	*0.287*
OPT-MPI Continuous	1.0063	0.0951	0.8361	1.2111	*0.947*
Age	0.9990	0.0068	0.9859	1.0124	*0.885*
Sex	1.1258	0.1262	0.9037	1.4025	*0.291*
OPT-MPI Categorical					
Moderate	1.0639	0.1219	0.8499	1.3319	*0.589*
Severe	0.8235	0.2202	0.4876	1.3909	*0.468*
Age	0.9991	0.0067	0.9860	1.0124	*0.899*
OPT-MPI Categorical					
Moderate	1.0833	0.1246	0.8647	1.3573	*0.486*
Severe	0.8328	0.2195	0.4969	1.3958	*0.487*
Sex	1.1364	0.1276	0.9120	1.4161	*0.255*
OPT-MPI Categorical					
Moderate	1.0844	0.1256	0.8642	1.3608	*0.484*
Severe	0.8356	0.2235	0.4946	1.4115	*0.502*
Age	0.9995	0.0068	0.9864	1.0128	*0.942*
Sex	1.1360	0.1277	0.9114	1.4159	*0.257*

Abbreviations:IRR: Incidence-rate ratio; LCI: lower confidence interval; PT-MPI: Optimised-Multidimensional Prognostic Index; UCI: upper confidence interval.

11.2.2.9 6-month re-admissions

11.2.2.9.1 Univariate and multivariate competing risk regression analyses

Table 11.36 Six-month re-admission rate univariate and multivariate competing risk regression of MPI-ARS items, age and sex.

	6 month re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI-ARS Continuous	0.9599	0.0908	0.7975	1.1554	*0.665*
MPI-ARS Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.0031	0.1101	0.8089	1.2438	*0.978*
Severe	0.7802	0.2559	0.4103	1.4838	*0.449*
Multivariate					
MPI-ARS Continuous	0.9557	0.0916	0.7920	1.1533	*0.637*
Age	1.0019	0.0068	0.9887	1.0152	*0.778*
MPI-ARS Continuous	0.9498	0.0908	0.7876	1.1454	*0.590*
Sex	0.9341	0.1021	0.7539	1.1573	*0.533*
MPI-ARS Continuous	0.9462	0.0916	0.7827	1.1438	*0.568*
Age	1.0017	0.0068	0.9886	1.0151	*0.798*
Sex	0.9352	0.1025	0.7543	1.1593	*0.541*
MPI-ARS Categorical					
Moderate	0.9993	0.1105	0.8045	1.2412	*0.995*
Severe	0.7688	0.2550	0.4014	1.4726	*0.428*
Age	1.0022	0.0067	0.9891	1.0155	*0.740*
MPI-ARS Categorical					
Moderate	0.9912	0.1105	0.7966	1.2332	*0.937*
Severe	0.7706	0.2520	0.4060	1.4626	*0.425*
Sex	0.9386	0.1030	0.7569	1.1638	*0.564*
MPI-ARS Categorical					
Moderate	0.9880	0.1108	0.7929	1.2310	*0.914*
Severe	0.7603	0.2514	0.3976	1.4536	*0.407*
Age	1.0021	0.0067	0.9889	1.0154	*0.758*
Sex	0.9400	0.1035	0.7576	1.1663	*0.574*

Abbreviations: LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; SHR: sub-hazard ratio; UCI: upper confidence interval.

Table 11.37 Six-month re-admission rate univariate and multivariate competing risk regression of MPI-RUDAS items, age and sex.

	6 month re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI-RUDAS Continuous	1.0709	0.1009	0.8904	1.2882	*0.467*
MPI-RUDAS Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.1699	0.1517	0.9074	1.5085	*0.226*
Severe	1.0492	0.2338	0.6779	1.6238	*0.829*
Multivariate					
MPI-RUDAS Continuous	1.0713	0.1056	0.8831	1.2997	*0.485*
Age	0.9999	0.0070	0.9864	1.0136	*0.990*
MPI-RUDAS Continuous	1.0647	0.1016	0.8831	1.2836	*0.511*
Sex	0.9542	0.1046	0.7697	1.1828	*0.699*
MPI-RUDAS Continuous	1.0655	0.1061	0.8765	1.2952	*0.524*
Age	0.9998	0.0070	0.9863	1.0136	*0.980*
Sex	0.9541	0.1047	0.7694	1.1830	*0.668*
MPI-RUDAS Categorical					
Moderate	1.1697	0.1553	0.9017	1.5173	*0.238*
Severe	1.0488	0.2427	0.6664	1.6506	*0.837*
Age	1.0000	0.0070	0.9865	1.0138	*0.995*
MPI-RUDAS Categorical					
Moderate	1.1625	0.1522	0.8994	1.5024	*0.250*
Severe	1.0388	0.2329	0.6694	1.6119	*0.865*
Sex	0.9573	0.1047	0.7727	1.1861	*0.690*
MPI-RUDAS Categorical					
Moderate	1.1627	0.1556	0.8944	1.5113	*0.260*
Severe	1.0391	0.2416	0.6588	1.6390	*0.869*
Age	1.0000	0.0070	0.9864	1.0137	*0.995*
Sex	0.9573	0.1048	0.7725	1.1864	*0.690*

Abbreviations: LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; SHR: sub-hazard ratio; UCI: upper confidence interval.

Table 11.38 Six-month re-admission rate univariate and multivariate competing risk regression of OPT-MPI items, age and sex.

	6 month re-admission rate				
Risk factors	**SHR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
OPT-MPI Continuous	1.0489	0.0950	0.8783	1.2527	*0.598*
OPT-MPI Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.1077	0.1240	0.8895	1.3795	*0.361*
Severe	0.9600	0.2494	0.5770	1.5974	*0.875*
Multivariate					
OPT-MPI Continuous	1.0469	0.0961	0.8746	1.2532	*0.617*
Age	1.0008	0.0067	0.9877	1.0141	*0.903*
OPT-MPI Continuous	1.0422	0.0947	0.8722	1.2455	*0.649*
Sex	0.9512	0.1033	0.7689	1.1767	*0.645*
OPT-MPI Continuous	1.0406	0.0957	0.8690	1.2462	*0.665*
Age	1.0007	0.0067	0.9876	1.0140	*0.919*
Sex	0.9517	0.1037	0.7687	1.1781	*0.649*
OPT-MPI Categorical					
Moderate	1.1055	0.1248	0.8861	0.1379	*0.374*
Severe	0.9551	0.2500	0.5718	1.5954	*0.861*
Age	1.0010	0.0067	0.9879	1.0142	*0.884*
OPT-MPI Categorical					
Moderate	1.0998	0.1240	0.8818	1.3717	*0.399*
Severe	0.9519	0.2462	0.5733	1.5804	*0.849*
Sex	0.9554	0.1038	0.7721	1.1822	*0.675*
OPT-MPI Categorical					
Moderate	1.0980	0.1246	0.8790	1.3716	*0.410*
Severe	0.9476	0.2470	0.5685	1.5795	*0.836*
Age	1.0009	0.0067	0.9878	1.0141	*0.899*
Sex	0.9556	0.1042	0.7721	1.1837	*0.680*

Abbreviations: LCI: lower confidence interval; OPT-MPI: Optimised-Multidimensional Prognostic Index; SHR: sub-hazard ratio; UCI: upper confidence interval.

11.2.2.9.2 Univariate and multivariate Poisson regression analyses

Table 11.39 Number of re-admissions within 6 months univariate and multivariate Poisson regression of MPI-ARS items, age and sex.

	Number of re-admissions within 6 months				
Risk factors	**IRR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI-ARS Continuous	1.0017	0.0718	0.8704	1.1529	*0.981*
MPI-ARS Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.0931	0.0930	0.9252	1.2914	*0.296*
Severe	0.7205	0.1749	0.4477	1.1595	*0.177*
Multivariate					
MPI-ARS Continuous	1.0169	0.0742	0.8814	1.1733	*0.818*
Age	0.9940	0.0050	0.9842	1.0039	*0.237*
MPI-ARS Continuous	1.0137	0.0734	0.8795	1.1683	*0.851*
Sex	1.0951	0.0927	0.9278	1.2927	*0.283*
MPI-ARS Continuous	1.0278	0.0756	0.8897	1.1872	*0.710*
Age	0.9943	0.0050	0.9844	1.0042	*0.258*
Sex	1.0900	0.0923	0.9233	1.2868	*0.309*
MPI-ARS Categorical					
Moderate	1.1022	0.0942	0.9322	1.3032	*0.255*
Severe	0.7499	0.1845	0.4630	1.2144	*0.242*
Age	0.9949	0.0050	0.9851	1.0048	*0.313*
MPI-ARS Categorical					
Moderate	1.1117	0.0959	0.9388	1.3164	*0.220*
Severe	0.7316	0.1779	0.4543	1.1782	*0.199*
Sex	1.1067	0.0938	0.9372	1.3067	*0.232*
MPI-ARS Categorical					
Moderate	1.1197	0.0969	0.9450	1.3267	*0.192*
Severe	0.7588	0.1868	0.4684	1.2292	*0.262*
Age	0.9952	0.0051	0.9853	1.0051	*0.343*
Sex	1.1021	0.0936	0.9331	1.3016	*0.252*

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; MPI-ARS: Multidimensional Prognostic Index-Anticholinergic Risk Scale; UCI: upper confidence interval.

Table 11.40 Number of re-admissions within 6 months univariate and multivariate Poisson regression of MPI-RUDAS items, age and sex.

	Number of re-admissions within 6-months				
Risk factors	**IRR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
MPI-RUDAS Continuous	1.1715	0.0816	1.0220	1.3428	*0.023*
MPI-RUDAS Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.5906	0.1628	1.3015	1.9439	*<0.0001*
Severe	1.0560	0.1851	0.7490	1.4889	*0.756*
Multivariate					
MPI-RUDAS Continuous	1.2319	0.0911	1.0657	1.4240	*0.005*
Age	0.9893	0.0052	0.9791	0.9996	*0.042*
MPI-RUDAS Continuous	1.1864	0.0832	1.0341	1.3611	*0.015*
Sex	1.1229	0.0947	0.9518	1.3247	*0.169*
MPI-RUDAS Continuous	1.2438	0.0921	1.0758	1.4381	*0.003*
Age	0.9896	0.0052	0.9794	0.9999	*0.048*
Sex	1.1149	0.0940	0.9450	1.3152	*0.197*
MPI-RUDAS Categorical					
Moderate	1.6638	0.1745	1.3546	2.0436	*<0.0001*
Severe	1.1641	0.2122	0.8143	1.6640	*0.405*
Age	0.9898	0.0052	0.9797	1.0001	*0.052*
MPI-RUDAS Categorical					
Moderate	1.6255	0.1677	1.3278	1.9898	*<0.0001*
Severe	1.0836	0.1907	0.7675	1.5299	*0.648*
Sex	1.1482	0.0969	0.9733	1.3547	*0.101*
MPI-RUDAS Categorical					
Moderate	1.6946	0.1787	1.3782	2.0836	*<0.0001*
Severe	1.1868	0.2165	0.8300	1.6970	*0.348*
Age	0.9902	0.0052	0.9800	1.0005	*0.061*
Sex	1.1406	0.0962	0.9668	1.3457	*0.119*

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; MPI-RUDAS: Multidimensional Prognostic Index-Rowland University Dementia Assessment Scale; UCI: upper confidence interval.

Table 11.41 Number of re-admissions within 6 months univariate and multivariate Poisson regression of OPT-MPI items, age and sex.

	Number of re-admissions within 6 months				
Risk factors	**IRR**	**Standard error**	**LCI**	**UCI**	***p* value**
Univariate					
OPT-MPI Continuous	1.0877	0.0746	0.9509	1.2442	*0.220*
OPT-MPI Categorical					
Mild	1.00	reference group	-	-	-
Moderate	1.2305	0.1061	1.0392	1.4571	*0.016*
Severe	0.8819	0.1760	0.5964	1.3042	*0.529*
Multivariate					
OPT-MPI Continuous	1.1106	0.0780	0.9678	1.2745	*0.135*
Age	0.9927	0.0050	0.9829	1.0027	*0.150*
OPT-MPI Continuous	1.1004	0.0760	0.9611	1.2599	*0.166*
Sex	1.1099	0.0937	0.9407	1.3096	*0.216*
OPT-MPI Continuous	1.1217	0.0791	0.9768	1.2880	*0.104*
Age	0.9930	0.0051	0.9831	1.0030	*0.168*
Sex	1.1035	0.0932	0.9351	1.3022	*0.244*
OPT-MPI Categorical					
Moderate	1.2477	0.1084	1.0524	1.4793	*0.011*
Severe	0.9236	0.1874	0.6206	1.3745	*0.695*
Age	0.9935	0.0050	0.9837	1.0035	*0.201*
OPT-MPI Categorical					
Moderate	1.2536	0.1093	1.0566	1.4873	*0.010*
Severe	0.8962	0.1792	0.6057	1.3262	*0.584*
Sex	1.1265	0.0953	0.9544	1.3297	*0.159*
OPT-MPI Categorical					
Moderate	1.2694	0.1115	1.0687	1.5077	*0.007*
Severe	0.9348	0.1897	0.6281	1.3914	*0.740*
Age	0.9938	0.0051	0.9840	1.0038	*0.226*
Sex	1.1212	0.0950	0.9497	1.3236	*0.177*

Abbreviations: IRR: Incidence-rate ratio; LCI: lower confidence interval; PT-MPI: Optimised-Multidimensional Prognostic Index; UCI: upper confidence interval.

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