Flinders University

Innovative Strategies to Improve Survivorship Care Across the Cancer Continuum

By

Alexandre Chan
Pharm.D., MPH, FCCP, FISOPP, BCPS, BCOP, APh

Thesis
Submitted to Flinders University
for the degree of

Doctor of Philosophy
College of Nursing and Health Sciences
November 6th, 2025

TABLE OF CONTENTS

ABSTRACT

Cancer survivorship is defined as the health and well-being of a person with cancer from the time of diagnosis through the end of their life. It aims to help people thrive after a cancer diagnosis and return to health or even improve their health and well-being. The number of people surviving with cancer is predicted to continue to rise due to a multitude of reasons, including early diagnosis, advances in cancer treatment, the growth and aging of the world population, and the increasing prevalence of risk factors. However, there are a number of unmet needs in cancer survivorship, such as the lack of patients' and care providers' perspectives, the lack of novel interventions for difficult-to-manage symptoms, and the lack of cultural adaptation to address disparities. Clinically relevant and novel strategies to optimize cancer survivorship are urgently needed.

To address the evolving needs in cancer survivorship, the overarching approach of this thesis is grounded in identifying and responding to the unmet needs of cancer survivors, applying a pragmatic, patient-centered approach to develop, evaluate, and implement novel interventions that directly address those needs. By aligning research with real-world clinical relevance, this thesis also explores the role of education in shaping the future of survivorship care, advocating the translation of research findings into university curriculum. The three specific aims of this thesis are: (1) to investigate the needs of cancer survivors from a patient and healthcare provider perspective; (2) to evaluate the impact of novel, multidisciplinary interventions, and implement them in routine care to address unmet needs of cancer survivors, and (3) to develop and evaluate an education-focused translational intervention embedding contemporary principles and research of survivorship care.

The overall structure of the thesis begins with an introduction of the current unmet needs surrounding cancer survivorship and the specific aims of the thesis (Chapter 1), followed by a discussion of the methodology and the methods (Chapter 2). The thesis then features six original research chapters (Chapters 3-8), with the first two chapters designed to gain insights from cancer survivors (Chapter

3) and healthcare professionals (Chapter 4) regarding unmet needs and strategies to optimize survivorship care. To address the specific unmet needs identified across diverse survivorship populations, Chapters 5 to 7 present distinct and innovative strategies to address the unmet needs within the treatment continuum. To examine the benefit of an undergraduate course on cancer survivorship, Chapter 8 describes the development and implementation of an education-focused translational intervention which embedded contemporary principles of survivorship care (Chapter 8). The thesis concludes with an in-depth discussion of the findings, along with concluding remarks (Chapter 9).

Collectively, the findings of the thesis highlight the interdisciplinary and patient-centered nature of survivorship care, emphasizing a holistic approach with three key strategies to address the unmet needs of cancer survivorship: (i) leveraging multidisciplinary teams, (ii) applying multilevel intervention designs, and (iii) utilizing culturally appropriate approaches to deliver survivorship care. Translating research findings related to cancer survivorship can enhance learners' perceptions and awareness of the subject matter, underscoring the value of integrating foundational and practical cancer survivorship content into undergraduate education. Overall, this thesis emphasizes the value of conducting pragmatic research to meet the evolving needs of cancer survivors.

Keywords: cancer, cancer survivorship, supportive care, pragmatic research, implementation science, clinical trials

DECLARATION

I certify that this thesis:

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

2. and the research within will not be submitted for any other future degree or diploma without the permission of Flinders University; and

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

4. has been completed without the use of generative artificial intelligence tools.

Signed.....Alex Chan (signed).....

Date.....November 6th, 2025.....

ACKNOWLEDGEMENTS

Knowing that the studies involved in this thesis span across a full decade in two different parts of the world (Singapore and the United States), I would like to express my most sincere gratitude to my family, friends, and colleagues, and dedicate this thesis to everyone who has provided me with tremendous support throughout my research journey.

To my dearest wife Professor Joyce Lee and my son Vincent Chan, I want to thank you for all your unwavering support and for giving me a love-filled home which allows me to pursue my research passion worry-free. You both have made me a better person, and your unconditional love and support have given me the faith to tackle any challenges that I face in life. I love you both.

To my parents Po Lun Chan and Clara Hong, I want to thank you both for bringing me to this world. Thank you for nurturing me and offering me lots of autonomy, which allows me to be successful. Yet, you are always there when I need support. I cannot be more grateful.

To my colleague Professor Raymond Chan, thank you for encouraging me to pursue a Ph.D. degree at Flinders. You are truly an inspiration.

To my mentor for this thesis, Professor Gillian Harvey, thank you for supervising my thesis, which has allowed me to deeply reflect on my research career.

To all my colleagues, my current/past trainees and staff, as well as patients who were involved in each of these individual studies, thank you for believing in me, as well as for sharing my holistic vision in improving cancer survivorship care through robust research.

PUBLICATIONS INCLUDED IN THIS THESIS

1. **Chan A**, Lum ZK, Ng T, Eyob T, Wang XJ, Chae JW, Raaj S, Shwe M, Gan YX, Fok R, Loh K, Tan YP, Fan G. Perceptions and Barriers of Survivorship Care in Asia: Perceptions from Asian Breast Cancer Survivors. *Journal of Global Oncology* 2016; 3(2): 98-104.

2. **Chan A**, Ports K, Ng DQ, Nasr R, Hsu S, Armenian S, Baca N, Freyer DR, Kuo DJ, Lin C, Milam J, Valerin J, Yun C, Torno L. Unmet Needs, Barriers, and Facilitators for Conducting Adolescent and Young Adult Cancer Survivorship Research in Southern California: A Delphi Survey. *J Adolesc Young Adult Oncol* 2023; 12(5):765-772.

3. **Chan A**, Ng DQ, Arcos D, Heshmatipour M, Lee BJ, Chen A, Duong L, Van L, Nguyen T, Green V, Hoang D. Electronic Patient-Reported Outcome-Driven Symptom Management by Oncology Pharmacists in a Majority-Minority Population: An Implementation Study. JCO Oncol Pract. 2024;20(12):1744-1754.

4. **Chan A,** Chan D, Ng DQ, Zheng HF, Tan QM, Tan CJ, Toh JHM, Yap NY, Toh YL, Ke Y, Wang ECA, Lim QPN, Ho HK, Chew L, Tan TJ. HEalth-Related Quality of Life-Intervention in Survivors of Breast and Other Cancers Experiencing Cancer-Related Fatigue and Associated Cognitive Symptoms Using TraditionAL Chinese Medicine: The 'HERBAL' Trial. *Integr Cancer Ther* 2025 Jan-Dec;24:15347354251314514. doi: 10.1177/15347354251314514. PMID: 39840742.

5. **Chan A**, Gan YX, Oh SK, Ng T, Shwe M, Chan R, Ng R, Goh B, Tan YP, Fan G. A Culturally Adapted Survivorship Program for Asian Early-Stage Breast Cancer Patients in Singapore: A Randomized, Controlled Trial. *Psychooncology* 2017;26(10):1654-1659.

6. **Chan A.** Implementing a cancer survivorship seminar course to non-healthcare professional undergraduate students. *Support Care Cancer* 2024; 32(4):227.

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AI	Artificial intelligence
AYA	Adolescent and young adults
BCS	Breast cancer survivors
CRF	Cancer-related fatigue
ePRO	Electronic patient-reported outcomes
IOM	Institute of Medicine
IO	Integrative oncology
HIC	High-income countries
LMIC	Low-middle income countries
MASCC	Multinational Association of Supportive Care Cancer
NIMDS	National Institute of Minority Health and Health Disparities
NCCS	National Cancer Centre Singapore
PRO	Patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PEG	Psychoeducational group
RCT	Randomized controlled trial
STCMI	Singapore Thong Chai Medical Institution
SC-PACS	Southern California Pediatric and Adolescent Cancer Survivorship
TCM	Traditional Chinese Medicine
XBYRT	Xiang Bei Yang Rong Tang

Chapter 1: Introduction

1.1 Concepts of cancer survivorship

With the advances in cancer prevention strategies and therapeutic approaches, survivorship is increasingly being recognized as an important issue among people diagnosed with cancer. According to the United States National Cancer Institute, cancer survivorship is defined as the health and well-being of a person with cancer from the time of diagnosis through the end of their life. (1) The field of cancer survivorship aims to help people thrive after a cancer diagnosis and return to health, or even improve their health and well-being. The definition includes the physical, mental, emotional, social, and financial effects of cancer that begin at diagnosis and continue through treatment and beyond. (2)

Cancer survivorship is increasingly relevant in today's society due to the continued surge of cancer incidence. It is estimated that there will be 28.4 million cancer survivors by 2040.(3) Globally, the number of cancer survivors is predicted to continue to rise due to a multitude of reasons, including early diagnosis, advances in cancer treatment, the growth and aging of the world population, and the increasing prevalence of risk factors. (3) Beyond the development of effective therapeutics that are essential to increase the lifespan of cancer survivors, it is also essential to proactively develop effective strategies to support cancer survivors during and after their treatment.

1.2 Treatment approaches and impact

Cancer survivors often report poorer health than people without cancer and often experience functional limitations. (4) Their health conditions are highly complicated by toxicities from both the cancer and the treatment that they experience after their cancer diagnosis, and the debilitating potential of these side effects is highly dependent on multiple factors. These factors include: the cancer type, the treatment type, the comorbidities that survivors had before the cancer diagnosis, alongside individual risk factors, including genetics, that survivors may possess. Collectively, these

characteristics may affect the clinical relevance, onset, and the severity of cancer-related toxicities.(5-7)

In the cancer supportive care arena, toxicities are generally classified into three different categories: acute toxicities (8), long-term toxicities, and late toxicities.(9) Acute toxicities are ones that generally occur while survivors are receiving treatment, and with the advances of cancer supportive care, these toxicities are relatively well managed.(8) Acute side effects may include and are not limited to: nausea and vomiting (10), constipation (11) and diarrhea (12), alopecia (13), bone marrow suppression (14), and hypersensitivity reactions. (15) Currently, guidelines are available for managing these side effects; often, survivors are given prophylactic medications and/or preventive strategies to ensure that these toxicities do not create a significant impact on their treatment, to ensure that the treatment outcomes are maximized.

Long-term side effects are those that begin during treatment and may extend beyond the cancer treatment period, and some of these long-term side effects may eventually resolve months or years after the cessation of therapies. (9) These side effects may include and are not limited to: pain (16), infertility (17), peripheral neuropathy (18), cancer-related fatigue (CRF) (19), insomnia (20), sexual dysfunction (21), and cognitive impairment. (22) On the other hand, late side effects are toxicities that tend to occur many months or years after treatment ends. Some of these toxicities include cardiac dysfunction (23), pulmonary dysfunction (24), and secondary cancers. (25) It is important to highlight that clinicians' and scientists' understanding of the mechanisms underlying long-term and late toxicities is very limited at this time. Although management guidelines are available for a number of these toxicities, effective strategies are still lacking, which helps to explain the substantial disease burden in this area and highlights the urgent need for effective supportive care interventions and models of care.

1.2.1 Supportive Care needs of cancer survivors

To effectively manage various treatment effects and toxicities, the field of cancer supportive care plays an indispensable role in the treatment journey of a cancer patient. (26) According to the Multinational Association of Supportive Care in Cancer, supportive care is defined as *'the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side effects across the continuum of the cancer journey from diagnosis through treatment to post-treatment care. Supportive care aims to improve the quality of rehabilitation, secondary cancer prevention, survivorship, and end-of-life care* (Paragraph 2).*'* (27) This includes managing the symptoms and toxicities of cancer treatment through both treatment and survivorship, to improve the quality of life of people who have an illness or disease by preventing or treating, as early as possible, the symptoms of the disease and the side effects caused by treatment of the disease. Common modalities include physical, psychological, social, and spiritual support for patients and their families. (28)

Numerous individual risk factors among cancer survivors have also been examined for their influence on supportive care needs. For instance, gender differences may reveal distinct supportive care requirements, as women tend to experience higher drug concentrations and slower drug elimination compared to men when given the same dosage of chemotherapy —primarily due to physiological differences. (29) This results in a higher risk of physical toxicities among women receiving chemotherapy. Age is another important factor; since cancer is most commonly diagnosed in older adults (particularly over 65 years), supportive care needs are often closely linked to coexisting comorbidities. (30) On the other hand, although cancer prevalence is lower among adolescents and young adults (AYA), there is increasing attention on the unique survivorship needs of this group. These include challenges such as returning to work or school and managing financial toxicity.

Financial toxicity is defined as economic burden that is associated with medical care which can lead to poor well-being and quality of life. (31)

Additionally, race and ethnicity can influence supportive care needs, underscoring disparities in cancer care. (32) For example, a large-scale study found that survivors from racial and ethnic minority groups, particularly those experiencing greater emotional or physical burdens, were more likely to report unmet needs related to side effect management and often experienced increased emergency room utilization. (33)

1.3 Tailored approaches to cancer supportive care

Ensuring appropriate and timely survivorship care is essential for all cancer survivors. However, because of the complex survivor profiles and differing preferences, it is not feasible for a one-size-fits-all care model to be implemented for all survivors across all phases of care. The literature supports applying a personalized approach to integrating different elements within a care model to address the heterogeneous survivorship trajectories of cancer survivors. (34, 35)

Patients diagnosed with cancer have significant supportive care needs throughout the disease trajectory. This is why a concerted effort to coordinate supportive care throughout the treatment continuum is critically important. Given the evolving needs of patients, it is important to develop effective strategies involving different professionals and implement these strategies to address patients' care needs within the cancer continuum.

1.3.1 Professional roles

In most high-income countries, the oncologists' role is primarily diagnostic and therapeutic. Typically, oncologists would play a central role in coordinating care, including supportive care, to cancer survivors within the treatment continuum. Cancer survivors visit their oncologists in public or private

healthcare settings, which can be located in specialized hospitals or within the community. Within this setup, supportive care needs are typically delivered by other members of the multidisciplinary care team, or may be outsourced to healthcare providers who are not within the oncology team. (36)

In addition to oncologists, nurses also play a major role throughout the care of cancer survivors. The most recent position statement provided by the Oncology Nursing Society outlined the scope and standards of practice for oncology nursing. (37) Roles include advocating for patients while they are undergoing care, delivering education, and providing support with treatment decision-making, coordinating care delivery, ensuring safe delivery of treatment, assessing complications of therapies, and working closely with patients to provide support.

Many other allied professionals also play important roles within the cancer care continuum. Pharmacists, for example, are poised to provide counseling and education on anticancer treatment to cancer survivors (38, 39), dieticians can provide nutritional support to cachectic cancer patients (40), and psychologists provide psychosocial care within psycho-oncology services (41).

Palliative care physicians and nurses, social workers, and chaplains provide palliative care in advanced cancer patients (42), whilst integrative oncology care providers such as acupuncturists and yoga therapists also play an important role in managing complementary and alternative medicine needs (43). Additionally, occupational health physicians and physical therapists can help with rehabilitation efforts to enable survivors to return to normalcy post-treatment. (44)

In summary, delivering high-quality supportive care to cancer survivors often requires a coordinated, multidisciplinary approach. This level of care demands significant collaboration and effort across various healthcare disciplines to ensure that survivors receive comprehensive and effective support.

1.3.2 Care models

There is an increasing amount of research suggesting that excellent supportive care and survivorship care should be multidisciplinary and integrative, involving the range of professionals identified above, to ensure that care delivery is not fragmented. (44, 45) This enables early identification of problems and timely intervention in patients with needs. As cancer survivors are generally managed by the tertiary healthcare system after diagnosis, it is recommended that all cancer survivors receive routine distress screening and care needs assessment, which can then facilitate the delivery of appropriate informational support on coping and self-management strategies.

The current literature describes several models of how supportive care can be delivered. They are designed to improve patients' and survivors' quality of life by effectively managing symptoms. Furthermore, these services can be standalone (46) but also integrated into existing services (47, 48), and the service model is highly driven by the structure of the primary treatment team. More importantly, these supportive care services can focus on specific patient populations (e.g., cancer-specific (49), stem cell transplantation (50), or they can be broad-based, which typically involves providers of different disciplines (48) to provide multiple facets of supportive care. However, few studies have undertaken a head-to-head comparison of different models to evaluate their impact on patient outcomes.

1.4 Unmet needs of cancer survivors

Despite the increased understanding of the need to provide high-quality supportive care to cancer survivors (51), there remain multiple challenges with the current approaches to the management of cancer survivorship care. The following summary is not comprehensive but captures some of the major challenges that can influence the experience of appropriate survivorship care within the treatment continuum of cancer survivors.

1.4.1 Current management approaches lack input from patient' and care providers' perspectives

Although healthcare delivery embraces general concepts of how toxicities from cancer treatment may affect survivors' health and quality of life, interventions are generally standardized based on recommendations from guidelines, policy or health system needs, which may neglect the perspectives and preferences of patients.

Work is ongoing to address this challenge, for example, through the conduct of mixed-method (52-54) and qualitative studies (55-57) to understand unmet needs among cancer survivors. These studies can improve researchers' understanding through the perspectives of both cancer survivors and healthcare professionals. Such studies are important because they provide rich insights for healthcare institutions and policymakers to develop and provide services that are appropriate to the patient's needs. (58)

An important advancement is the development and use of patient-reported outcome (PRO) measures in cancer care. (59) These tools have gained recognition because of their ability to provide valuable insights into patients' experiences, symptoms, functional status, and quality of life directly from the patient's perspective. In many cancer centers, PRO measures have been utilized for symptom monitoring in various populations, including cancer patients. (60-64) Efforts have been made to make PRO tools applicable for routine clinical use, such as identifying clinically meaningful cut points and changes in PRO scores (63), establishing real-time reporting of PRO scores (65-67), evaluating PRO effectiveness on clinical outcomes (68), and analyzing implementation-related factors. (69, 70) There is a need for more in-depth research on how to successfully implement PRO in clinical practice, to ensure survivors' perspectives are incorporated into their day-to-day management.

1.4.2 Lack of novel interventions for difficult-to-manage symptoms within the cancer continuum

Despite the wide prevalence of treatment-induced toxicities, effective management of toxicities is often hindered by the absence of effective, evidence-based management strategies, leading to many patients continuing to suffer from toxicities. Several reasons contribute to this problem. Firstly, there is a lack of understanding of the mechanisms associated with the toxicities of many anticancer agents, particularly with the off-target toxicity of many drugs. (71) Second, it is uncommon to provide medications that are effective in non-cancer settings as a remedy for treatment-induced toxicities in cancer. For example, numerous trials have evaluated the use of pharmacological interventions for cancer-related cognitive impairment, such as donepezil (72) (as in Alzheimer's Disease) or methylphenidate (73) (as in attention-deficit hyperactivity disorder). However, clinical trials of these therapies have not successfully demonstrated that these drugs are effective in managing these side effects. Additional studies to understand the biological mechanism, with rigorous study designs, are needed. For example, embedding appropriate biomarkers in clinical trials will allow researchers to objectively evaluate the effectiveness of the intervention, without solely relying on PRO, which might be influenced by placebo effects. (74) Lastly, different physical and psychological complications might affect survivors at different parts of their treatment continuum (acute versus delayed versus side effects), suggesting that the interventions they require can be different. Further research is required to evaluate the types of interventions that are effective at different parts of their treatment continuum.

1.4.3 Lack of cultural adaptation of interventions to address disparities in cancer survivorship

Despite the potential benefits of integrating supportive care into routine cancer care, there remains significant heterogeneity in integration and access across patient populations globally. This is similar to other areas of cancer care where there are well-recognized disparities. In a recent American Cancer Society report on cancer disparities in the United States, there was significant variability in screening rates, mortality, and survival between sociodemographic groups and by race and ethnicity. (75) There are similar disparities in access to supportive and/or end-of-life care with differences observed

between low-middle income countries (LMIC) and high-income countries (HIC) and within the United States and other HIC. (33, 76-78) Some factors influencing access to palliative and supportive care include race/ethnicity group, place of birth, geographical region (urban/rural), cultural beliefs around supportive/palliative care, and demographic factors (age, gender, income). (79) On a global level, some of the factors that may lead to disparities in supportive care include access to cancer/supportive care medicines, political/government environments, differences in the training of healthcare personnel and workforce, and the varying socio-demographic characteristics and clinical presentations of patients with cancer. (80, 81)

A recently conducted survey by the Multinational Association of Supportive Care Cancer (MASCC) evaluated global disparities in cancer supportive care. One factor that has been identified to contribute to the higher risk of care disparities is the inability to implement supportive care interventions within the local context. (32) While treatment guidelines for supportive care are widely available and recommend the use of various interventions, both patients and healthcare providers often lack confidence in implementing them. This hesitation may stem from concerns that these interventions are not adequately tailored to the local context or health care setting. In summary, it shows that supportive care interventions must undergo robust cultural adaptation to minimize health disparities and be acceptable to patients of various ethnic backgrounds.

1.4.4 Limited experience in translating cancer survivorship research and concepts into tertiary education

Given that cancer is highly prevalent on a global scale in the community and there are recognized unmet needs among cancer survivors, concerted efforts are needed to advocate for future survivorship care education and research. Currently, education on cancer management and supportive care is often broadly covered within medical and healthcare education in the classroom setting. (82, 83) However, fewer efforts are dedicated to introducing the discipline earlier in tertiary education, such as non-

healthcare professional undergraduate students. Within the United States, much of the cancer education within higher education is focused on prevention of skin cancer (84, 85) or human papillomavirus. (86, 87) Given that cancer is more likely to affect older individuals, most young adults do not have extensive experience in interacting with cancer patients or managing complications associated with cancer.

There is a growing amount of literature suggesting the benefits of increasing exposure to healthcare experiences to non-healthcare professional undergraduate students (88) in order to provide earlier exposure to cancer education for college students, and this space is not well-researched within the area of cancer survivorship. Survivors' and healthcare providers' voices need to be heard in the classroom as they can provide unique perspectives to students. Translating research findings in cancer survivorship as an approach in education pedagogy is rare, which may warrant research studies to evaluate its impact on students' knowledge and behavior.

1.5 Summary

As the global incidence of cancer continues to rise, the relevance of cancer survivorship has become increasingly prominent. This underscores the pressing need to address the supportive care needs of survivors, who are often significantly affected by both the diagnosis and its associated treatments. To ensure high-quality survivorship care throughout the treatment continuum, it is essential to identify and address existing barriers to high quality cancer survivorship. Innovative and targeted strategies are urgently required to meet the evolving needs of cancer survivors in an effective, feasible, and acceptable way.

To address the evolving needs in cancer survivorship, the overarching approach of this thesis is grounded in identifying and responding to the unmet needs of cancer survivors, applying a pragmatic, patient-centered approach to develop, evaluate, and implement novel interventions that

directly address those needs. By aligning research with real-world clinical relevance, this thesis also explores the role of education in shaping the future of survivorship care, advocating for enhanced training and further research to advance this critical area of healthcare. The three specific aims of this thesis are:

1. To investigate the needs of cancer survivors from a patient and healthcare provider perspective.
2. To evaluate the impact of novel, multidisciplinary interventions and implement them in routine care to address unmet needs of cancer survivors.
3. To develop and evaluate an education-focused translational intervention embedding contemporary principles and research evidence on survivorship care.

In the earlier chapters (Chapters 3 and 4) of my thesis, the papers present studies that focused on understanding the unmet needs and symptoms of cancer survivors, predisposing factors for survivors experiencing different types of toxicities of care, and the impact of these experiences on patients' health outcomes and quality of life. In the subsequent chapters of my thesis (Chapters 5, 6, and 7), the studies mainly focused on evaluating the effectiveness as well as the implementation of various types of interventions. In Chapter 8, an education-focused translational intervention which embedded contemporary principles of survivorship care was developed and implemented in an undergraduate course. A summary of how the individual chapters are linked to specific aims of the thesis is presented in the figure below. (Figure 1.1)

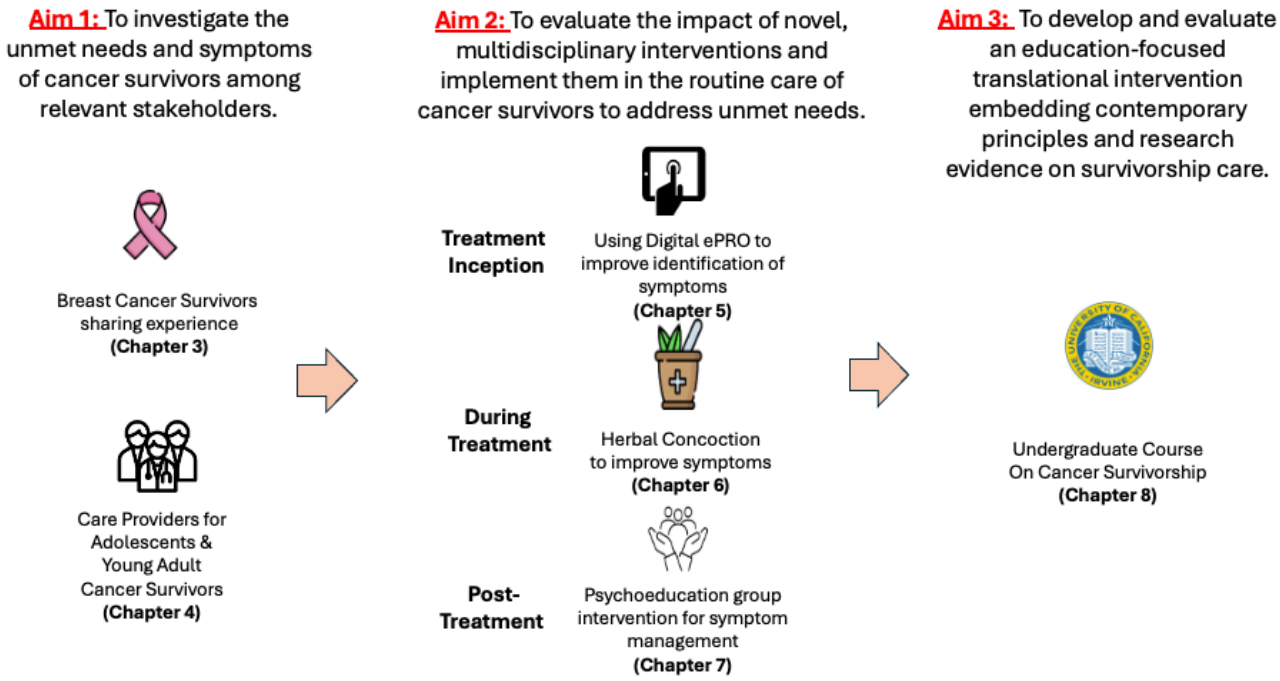

Figure 1.1. Relationship between the respective chapters of study aims and the respective chapters.

Chapter 2: Methodology and methods

2.1 Introduction

To recap, the introductory chapter characterized the current landscape of cancer survivorship and provided an overview of the challenges to meet cancer survivors' needs. With the anticipated global rise in the number of cancer survivors, it is critical to conduct research that identifies unmet needs in survivorship care involving physical, psychological, practical, and social issues, and explores innovative strategies to improve the management of care and survivors' overall quality of life.

This thesis adopts a holistic and multiple-methods approach to address key clinical and research questions in survivorship care. The first two studies focused on understanding the needs of cancer survivors from both patient and healthcare professional perspectives. Based on these insights, subsequent studies were designed and implemented to evaluate novel interventions tailored to the identified needs. To conclude the thesis, a final study was conducted to develop and assess an education-focused translational intervention aimed at integrating contemporary principles and research evidence on survivorship care into the classroom setting.

2.2 My positioning in the research

My own interest in researching cancer survivorship developed from my early career as an oncology pharmacist. This has shaped my ontological and epistemological positioning and, in turn, guided the methodology and methods for the published papers presented in this thesis. Before outlining the methodology and methods, I will briefly outline my career background and its influence of my research journey.

I began my career as an oncology pharmacist, primarily focused on educating newly diagnosed cancer patients about the side effects and toxicities of anticancer therapies. Early on, I developed a keen interest in understanding treatment-related toxicities, particularly acute side effects

such as nausea and vomiting, myelosuppression, and dermatological reactions—physical symptoms that often interfere with treatment adherence. Consequently, my initial research efforts centered on improving medication adherence, identifying patients at risk for toxicities, and contributing to the development of evidence-based clinical practice guidelines. Recognizing the need for robust methodological skills, I pursued a Master of Public Health in 2011 to strengthen my foundation in biostatistics and clinical epidemiology.

In 2012, following my promotion to tenured Associate Professor at my previous institution, my research focus began to shift. While I continued to explore toxicities relevant to supportive cancer care, I became increasingly interested in chemotherapy-induced toxicities—such as cancer-related fatigue (CRF), cognitive impairment, and peripheral neuropathy—whose underlying mechanisms remain poorly understood. The absence of effective, evidence-based interventions for these conditions often leaves patients with limited options and clinicians with few tools to offer. I began to appreciate the long-term impact these toxicities have on survivors' quality of life and overall well-being. This marked a turning point in my perspective; previously, my focus had been on ensuring patients completed their cytotoxic treatment, with limited attention to the survivorship journey that follows. During this same period (2009–2015), my maternal parents were undergoing treatment for breast and lung cancers, and I witnessed firsthand how symptoms disrupted their physical functioning, social roles, and quality of life. These personal and professional experiences deepened my commitment to designing pragmatic clinical trials that offer meaningful interventions with minimal disruption to survivors' daily lives.

My interest in cancer survivorship further evolved in 2015 when I joined a newly formed multidisciplinary workgroup at the National Cancer Centre Singapore. Our goal was to develop a sustainable model for delivering cost-effective survivorship care. I was fortunate to serve in a leadership role, which enabled me to contribute to both clinical practice design and research initiatives

aimed at improving care for cancer survivors. From that point onward, my research journey in survivorship care has continued to grow and evolve, as evidenced by the research publications presented in Chapters 3 to 8 of this thesis.

Having presented this background, the following sections are devoted to the research methodology and the related methods of each chapter.

2.3 Research methodology

My personal journey and commitment to facilitating real-world improvements in the experience of cancer survivors have guided the ontological framing of the thesis.

With a commitment to addressing practical issues in cancer survivorship, I have adopted a pragmatic research methodology. Pragmatism, as a paradigm, is grounded in the philosophical tradition of pragmatic thought and is distinguished by its flexibility in selecting the most suitable methods to investigate real-world problems, especially in patient-oriented research. (89) It operates on the assumption that human experiences shape justified beliefs, rather than relying on universal truths to determine outcomes. (90) Accordingly, knowledge gained is viewed not as a direct representation of reality, but as a tool for informed action. This is because knowledge is gained through the observed interactions between people and their environments. (91)

Within health services research, pragmatism as a research paradigm offers researchers an action-oriented framework that supports the use of appropriate methodologies to address issues emerging directly from the patients and the community. (92) This paradigm also enables the application of the most effective methods to explore and resolve patient-centered concerns—often through multipronged or mixed-method approaches. (93) This approach is then considered pluralistic,

as it acknowledges and values diverse perspectives, interests, and forms of knowledge as valid contributions to understanding. (94)

Through applying a pragmatic methodology, this thesis applies appropriate study designs in different chapters to address the questions of interest, moving from exploring cancer survivorship needs through to designing and testing novel interventions to address identified needs and applying a translational approach to embed research in an educational program. (95, 96)

2.4 Research methods for individual thesis aims

2.4.1. Aim 1: To investigate the needs of cancer survivors from a patient and healthcare provider perspective.

To understand the unmet care needs of cancer survivors, mixed-methods qualitative research was undertaken. I selected two specific groups of survivors as populations of interest for this aim, namely survivors of breast cancer (BCS) in Chapter 3 and adolescent and young adult (AYA) cancer survivors in Chapter 4. Both patient groups enjoy excellent cure rates and long survival rates, which implies that different needs arise throughout the treatment continuum. At the same time, numerous unique care concerns are associated with these two patient groups, making them excellent populations to evaluate survivorship concerns. These unique care concerns may also highlight the various health disparities observed in each of these populations.

To further elaborate on the uniqueness of these populations, I will outline the most common toxicities that are experienced by these two groups of cancer survivors in the following subsections. I will also address the implications of their cancer survivorship issues to clinical practice and research.

Globally, breast cancer is the most common cancer among women. With the advent of novel therapeutics and screening techniques, breast cancer is highly curable in high-income countries. (97) There are multiple treatment options available for breast cancer, and the modalities used are highly dependent on the stage of disease, the clinical pathology (including the staging of disease and the biomarkers involved). (98) Most BCS would receive at least one or more treatment modality, including surgery, radiation, chemotherapy, endocrine therapy, targeted therapy, and immunotherapy. The manifestation of toxicities and complications is therefore highly dependent on the drugs that they receive. (99, 100) Most individuals with breast cancer in developed countries present in early stages (Stage 1-3), where the prognosis is favorable. In patients with early-stage breast cancer, treatment is generally pursued with curative intent, utilizing several of the described modalities.(98) However, the physical and psychological toxicities associated with breast cancer are extensive and can significantly impact quality of life. (101) Toxicities may lead to unintended alteration of treatment, which include reduction of treatment intensity, discontinuation, as well as the need for costly healthcare services such as urgent care visits and hospitalization, and potentially increasing the risk for mortality. (102, 103)

Among BCS receiving chemotherapy, acute side effects such as chemotherapy-induced nausea and vomiting are often regarded as the most distressing adverse effects experienced by patients receiving anthracycline-containing chemotherapy. (104) Early management guidelines recommend the routine use of prophylactic antiemetics in contemporary clinical management, which have been shown to effectively prevent chemotherapy-induced nausea and vomiting in BCS. Neurological complications are also commonly reported among breast cancer patients. In BCS, two common categories of neurological complications are: peripheral symptoms and central nervous system-related symptoms. (105) BCS often receive taxane-type medications, which can manifest peripheral neuropathy, which is often characterized as burning or tingling sensations in their extremities. (106) The occurrence of these symptoms frequently leads to an irreversible loss of function of the peripheral

nerves, and management strategies are limited at this time. (107) On the other hand, cognitive dysfunction has detrimental effects on quality of life and daily functioning in BCS. (101) Cognitive dysfunction experienced by BCS encompasses a wide range of subtle cognitive changes, such as memory loss, the inability to concentrate, and difficulty in thinking. The mechanisms underlying cognitive dysfunction remain poorly understood at this time, with a resulting lack of effective pharmacological strategies to manage patients' cognitive changes. (108-110)

Although cancer is not a highly prevalent disease in AYAs, there is an increasing trend in the number of AYAs diagnosed with cancer. (111, 112) For most working definitions, AYAs are defined as individuals who are between 15 and 39 years old when they are diagnosed with cancer. The most common cancers diagnosed in this age group are breast, thyroid, and cervical, while the leading causes of death are breast, cervical, and leukemia. (111) Similar to BCS, AYA cancer survivors often receive more than one treatment modality (e.g., chemotherapy, radiation, surgery) to manage their underlying malignancy. Physical side effects such as nausea, vomiting, fatigue, and lack of sleep can negatively contribute to the well-being of AYA cancer patients. Survival rates of AYAs diagnosed with cancer can vary. For example, in a recent study conducted in the United States, it was observed that more survivors were female (66%) and long-term (>5 years from diagnosis, 83%) or very long-term survivors (>10 years from diagnosis, 68.8%). (113) A large percentage (44%) were more than 20 years from diagnosis. The most common cancer sites among female survivors were breast (24%) and thyroid cancers (23%), whereas among male survivors, testicular cancer (31%) is the most common. Interestingly, studies have shown that female AYAs are 1.9 times more likely to develop cancer than males. (111)

As AYAs are at a phase in life where multiple significant transitions and life events are occurring (114), these patients have to juggle their educational needs and social expectations, such as academic attainment, relationships with peers, and sexual coming-of-age. (114, 115) Especially

among the young adults, they must cope with newfound self-reliance, financial responsibilities, career goals, and family planning. (114, 115) The psychological stresses of cancer-related symptoms and treatment toxicities can result in missed school days, social isolation from peers, strained family relationships, financial difficulties, fertility concerns, and disruption to employment and training. (116) In addition, physical predicaments such as nausea, vomiting, fatigue, and lack of sleep contribute negatively to the well-being of AYA cancer patients. (117-119) In one study that evaluated the distress experienced by newly diagnosed AYA cancer patients, one out of two Asian AYA cancer patients experienced clinically significant distress at both the time of diagnosis and one month after diagnosis, with emotional and financial problems being highlighted as major concerns encountered by the patients. (120)

Psychological distress, such as anxiety and depression, is commonly observed in both AYA cancer survivors and BCS. Many factors may contribute to cancer survivors' distress, which could be related to the cancer itself as well as the treatment. Distress related to the recurrence of disease can also have a tremendous impact on survivors who have completed treatment. Untreated distress may elevate the risks of other side effects. (101, 121) Numerous studies have shown that distress tends to occur in younger patients, patients with lower education levels, and those who require mastectomy and chemotherapy as part of their breast cancer treatment. (122)

Clearly, the healthcare needs of AYA cancer survivors and BCS are tremendous during survivorship. However, most research has been conducted in North America (123), Australia (124), and Europe (125), with few studies devoted to Asian cancer survivors. Specifically in Singapore, a well-developed, multiethnic country located in Southeast Asia, there is a lack of understanding of the issues that are affecting Asian cancer survivors. Besides the unmet needs that are not well researched, it is also unknown what the barriers and facilitators are for delivering high-quality survivorship care.

Conducting research within Asian populations is valuable for addressing culturally specific needs that may differ from those of other ethnic groups. Health disparities in Asian cancer survivors may be significant and warrant focused attention on a range of issues, including academic and occupational performance, societal expectations, and financial burdens. Hence, a thorough investigation using a qualitative approach would enable greater understanding of unmet needs amongst this group of cancer survivors and inform the design of culturally appropriate interventions.

2.4.1.1 Chapter 3: To gather in-depth descriptions from multiethnic Asian breast cancer survivors on their perceptions and experiences of cancer survivorship and their perceived barriers to post-treatment follow-up

In this chapter, I present a qualitative study that was designed to identify existing unmet needs, barriers, and facilitators of survivorship care through the lens of breast cancer survivors. To facilitate the research, breast cancer survivors who completed their treatment at the National Cancer Centre Singapore were recruited to participate in focus group discussions. By involving cancer survivors, this study aimed to understand the perceived needs and inform the development of culturally and contextually relevant survivorship care strategies in the later chapters of the thesis.

2.4.1.2 Chapter 4: To identify the unmet needs, barriers, and facilitators for conducting AYA survivorship research from the providers' and researchers' perspectives.

In this chapter, I present a Delphi survey study designed to identify existing unmet needs, barriers, and facilitators among adolescent and young adult (AYA) cancer patients through the lens of healthcare professionals. In this study, I engaged with healthcare providers using Delphi survey as a methodology to gain insights into the perceived unmet needs, barriers, and facilitators in AYA cancer survivorship research. The Delphi technique was utilized because it is a systematic process of

forecasting using the collective opinion of panel members, and this structured method allows the development of consensus among panel members. (126) To facilitate the research, I conducted the study in close collaboration with the Southern California Pediatric and Adolescent Cancer Survivorship (SC-PACS) group, a multidisciplinary organization based in Southern California. Similar to the involvement of survivors in Chapter 3, by involving healthcare professionals, this approach aimed to generate expert consensus on research priorities and inform the development of culturally and contextually relevant survivorship care strategies.

2.4.2: Aim 2: To evaluate the impact of novel, multidisciplinary interventions and implement them in routine care to address unmet needs of cancer survivors.

Based on insights gained from Aim 1 (Chapters 3 and 4), novel interventions were developed and trialed to assess their effectiveness in addressing the specific needs of cancer survivors. These studies are presented in Chapters 5, 6, and 7 and involved the use of experimental research designs to avoid both systematic errors (due to study design) and statistical errors.

2.4.2.1 Chapter 5: To evaluate the implementation outcomes of an electronic patient-reported outcome (ePRO)-driven symptom management tool led by oncology pharmacists.

In order to address the need for early symptom identification, as highlighted by breast cancer survivors (Chapter 3) and the importance of personalized care planning discussed by healthcare providers (Chapter 4)— this study was designed to evaluate whether a culturally grounded supportive care navigation model supported by ePRO would improve provider-patient communication, with the ultimate aim to improve symptom identification and reduce health disparities. This research introduced a multilevel intervention which involved the implementation of electronic patient-reported

outcomes (ePRO) to guide supportive care navigation for patients receiving intravenous anticancer treatment at the infusion center.

In this study, the Patient-Reported Outcomes Measurement Information System (PROMIS) toolbox was utilized, and the toolbox was developed and made available by the National Institutes of Health of the United States. The toolbox serves as a validated electronic library of ePRO tools designed for use in both clinical research and point-of-care settings across the United States. (62) The additional use of computer adaptive tests can further facilitate symptom assessment precisely and rapidly by using the minimal possible number of items required. This can potentially reduce patients' reporting burden while ensuring that the desired range of health domains has been assessed. There are a number of benefits as we map the benefits of ePRO in addressing disparities issues. (Figure 2.1) On the *individual* level, PROMIS can facilitate the identification and active reporting of health problems to address variations in health-seeking behaviors. The use of translated tools also reduces language barriers in reporting health problems. In addition, providing access to the tool at the cancer center ensures that all patients have equal access to the digital platform. On the *interpersonal* level, supportive care navigators can utilize ePRO to improve communication with patients, which allows the personalization of therapy to enhance relevance and person-centricity, physician-patient communication, symptom awareness and management. (127-130) This approach also improves cultural relevance. Such screening can also facilitate patients' systematic access to supportive care services to address active care needs, mitigating the impact of clinical practice variability. (131)

It is important to emphasize that current solutions to improve health outcomes in ethnic minorities receiving cancer care mainly focus on targeting a specific factor in silo. (132) These solutions, however, do not tackle disparity issues on multiple levels, despite the United States National Institute of Minority Health and Health Disparities (NIMHD)'s recognition of multiple levels and domains of influence driving health disparities. (133) Tailoring care using an ePRO

measure may promote patient-centric care (134-136) for equitable health recovery within a specific patient population.

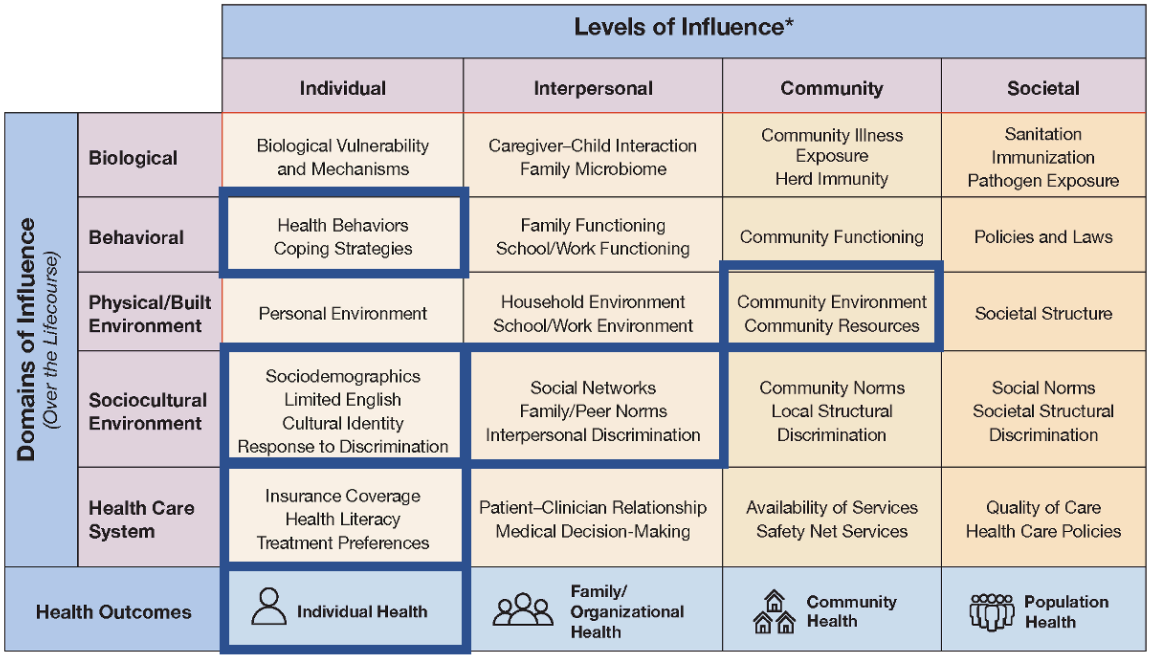

Figure 2.1: Potential impact of ePRO on NIMHD domains and level of influence

In this study, I leveraged implementation science methodologies to evaluate the real-world outcomes and sustainability of the intervention, particularly in populations with health disparities. Implementation science is defined as the rigorous study of the integration of evidence-based interventions into clinical and community health settings. (137) This includes the use of theory-informed implementation models and frameworks and the selection and application of evidence-informed implementation strategies that address identified contextual barriers and enablers that affect the integration of an intervention into practice and/or policy.

In the areas of cancer prevention and control, there is a considerable volume of studies that have applied implementation science approaches, and these have informed the implementation of interventions within cancer survivorship. These studies include the establishment of multidisciplinary supportive care models (138) in patients, the incorporation of survivorship care plans in routine

practice (139), and the incorporation of mental health (140) interventions for cancer survivors. There are study designs within implementation science that can help to improve the efficiency of evidence generation. For example, the introduction of hybrid effectiveness-implementation study designs help accelerate the transition from effectiveness trials to implementation trials in a single study. (141) Furthermore, trials incorporating implementation science allow the evaluation of multilevel interventions (142), which mimic the management for cancer survivors in real-life practice, as most supportive care services are multidisciplinary in nature.

There are numerous benefits to incorporating implementation science approaches to evaluate cancer survivorship interventions. (143) This approach allows the conduct of clinical trials that feature pragmatic design elements, allowing evidence generated from the clinical trial to be relevant, actionable, and reflective of how the trial results could be applied in real life. Most importantly, such a study design also helps to identify real-world implementation barriers and enablers, enabling future implementation interventions to overcome barriers, and subsequently informing spread and scale-up.

2.4.2.2 Chapter 6: **To evaluate and report the efficacy and safety of an herbal concoction on quality of life (QOL), cancer-related fatigue (CRF), and cognitive symptoms, compared to placebo.**

As part of Aim 2 to address unmet needs of cancer survivors as well as providing holistic, culturally relevant care to reduce health disparities, this paper evaluated the efficacy of a novel approach by integrating traditional Chinese medicine (TCM) herbs in conventional cancer care for symptom management, an approach also known as Integrative Oncology (IO). It is a patient-centered, evidence-informed approach to health care that utilizes mind-body therapies such as mindfulness-based interventions, acupuncture, natural products through TCM herbs and lifestyle modifications from different traditions alongside conventional cancer treatments, with the aim to optimize health, quality

of life, and clinical outcomes and to empower people to become active participants in their care during and beyond cancer treatment. (144) IO modalities are also specifically supportive to cancer survivors who, as described, face several health challenges that can impact their long-term quality of life, including CRF, cognitive impairment, pain, anxiety, and depression. (145, 146)

Since 2018, in collaboration with the supportive care services at NCCS, I have been investigating the use of TCM to manage symptoms and treatment-related toxicities in order to improve our culturally sensitive supportive care. As part of our efforts to integrate TCM into routine clinical practice, we chose to focus on a specific toxicity as a case study—CRF—to guide our approach. CRF, as we learned from our survivors (Chapter 3) and providers (Chapter 4), is an important symptom that needs to be better managed among survivors. This targeted exploration would also serve as a foundation for evaluating other IO modalities in symptom management.

In conventional medicine, CRF is a phenomenon attributed to mitochondria dysfunction and inflammation. CRF is also well characterized in the TCM setting. According to TCM principles, CRF is characterized as a deficiency of *qi* which is typically accompanied by fatigue/tiredness, shortness of breath, reduced activity, poor sleep, and/or poor appetite. (147-149) In TCM, this is known as qi and blood deficiency. *Qi* refers to the energy flow of the body or physical life force which helps to maintain the blood circulation. As chemotherapy indiscriminately destroys all rapidly growing cells and weakens body functions, the bone marrow is also affected, depleting both *qi* and blood which are considered as basic substances of our body constituent. Chemotherapy can also affect the intestinal lining, affecting the ability of the stomach to digest food and reducing the absorption of nutrients. In this aspect, TCM advocates invigoration of *qi* in patients with CRF, to strengthen the spleen which helps to improve the gastrointestinal system, transforms nutrients from food into qi and blood, and disperses food essence to all parts of the body. A Taiwanese study reported that breast cancer patients with *qi* deficiency were found to have a higher correlation with CRF and poorer quality of life. (150)

Through collaboration with TCM physicians from Singapore Thong Chai Medical Institution (STCMI), I codeveloped and studied a TCM herbal formula, namely Xiang Bei Yang Rong Tang (XBYRT), for the management of CRF. XBYRT has gone through extensive testing for drug-drug interactions and evaluation of organ toxicities in pre-clinical models. (151) With these data, we were interested in evaluating its role in managing CRF and related symptoms in cancer survivors who were undergoing chemotherapy. Findings from this study would also allow us to escalate to a large-scale clinical trial to robustly test the intervention in a larger population cohort.

A randomized, double-blind, placebo-controlled, parallel trial approach was chosen as the methodology for this research because it was important to account for potential placebo effects that could arise from patient-reported outcomes. (152) The research approach was prepared in accordance with the Standard Protocol Items: Recommendations for Interventional trials (SPIRIT-TCM extension statement 2018) (153) to ensure a high-quality trial design involving TCM. This randomized controlled trial allowed us to evaluate how IO, specifically TCM herb medicine, could improve CRF symptoms among cancer survivors undergoing chemotherapy, an area of unmet need identified by the survivors and providers interviewed in the first part of the thesis (Chapters 3 and 4). To capture physiological changes associated with symptom variation reported by participants, plasma biomarkers—specifically inflammatory and neurotrophin markers—were included in the analysis. These biomarkers are known to characterize the changes of CRF symptoms in cancer patients. (154)

2.4.2.3 Chapter 7: **To evaluate the effectiveness of a psychoeducation group (PEG) intervention program compared with usual care to reduce distress for physical symptoms and psychological aspects in Asian breast cancer survivors who have completed adjuvant chemotherapy.**

In this last chapter that addresses Aim 2, a study was designed to evaluate whether survivorship care can be improved by a multidisciplinary group intervention. In view of the lack of standardized post-treatment care programs in Singapore, our team at the National Cancer Centre Singapore developed a center-specific psychoeducation group (PEG) intervention program, with the goal to standardize the approach to deliver post-treatment survivorship care. The approach was based on a joint statement provided by the United States Institute of Medicine (IOM) and the National Research Council to ensure long-term cancer survivors receive appropriate transition care from active treatment to post-treatment care. (155) Upon discharge from treatment, it is recommended that all survivors receive a comprehensive survivorship care plan at the time of discharge. Among the post-treatment survivorship issues that raised by the IOM, three main areas were identified that should be addressed within a survivorship care program: intervention for consequences of cancer and its treatment, surveillance for cancer recurrence and coordination of care (Table 2.1).

Table 2.1. Recommendations made by IOM on components of a survivorship program

Intervention for consequences of cancer and its treatment
• Discuss information on peer support groups
• Conduct distress screening
• Discuss sexuality issues
• Discuss fertility issues
• Discuss long term physical effects
• Discuss exercise and physical activity
• Discuss healthy diet recommendations
• Discuss health behaviors
• Discuss management at home
• Discuss employment and financial issues
Surveillance for cancer recurrence
• Discuss how to identify signs of cancer recurrence
Coordination of care
• Link the patient with appropriate supportive services
• Discuss who to contact with questions
• Communicate survivorship care with multidisciplinary team
• Communicate survivorship care with primary healthcare team
• Ensure follow-up appointment schedule with oncologists
• Ensure follow-up appointment schedule with primary healthcare provider

To evaluate whether the PEG approach was effective in addressing psychological distress and physical symptoms that were not well controlled post-chemotherapy, a randomized trial was designed to assess the effectiveness of a PEG intervention that would allow the psychosocial oncology team at the cancer center to address supportive care and survivorship issues in BCS. The designed program took place on three individual days at the weekend, and the targeted symptoms were anxiety, depression, cognitive function, treatment-related physical symptoms, and health-related quality of life in early-stage BCS. These were all identified as unmet care needs in our qualitative focus group study (Chapter 3). For each session, three major topics were covered, with lectures and interactive workshops delivered in an integrated way. Sessions were conducted by healthcare professionals who were experts and well-versed in their respective professional domains (Table 2.2).

Table 2.2: Overview of PEG intervention program					
Session Number	**Speaker/ Facilitator**	**Content of individual component**	**Survivorship Issues addressed**	**Format**	**Duration (h)**
1	Dietitian	Introduce appropriate diet and supplements	Nutritional needs	Lecture and discussion	1.5
	Neuropsychologist	Improve awareness of cognitive functions and cognitive capacity	Cognitive abilities	Lecture, discussion and practice	1.5
	Social worker	Discuss acceptance of self as a breast cancer survivor	Psychological distress and acceptance of BCS identity	Discussion	1.5
2	Oncology Pharmacist	Discuss long-term toxicities management and use of medications during survivorship	Physical effects, fatigue, cognitive abilities and medication use	Lecture and discussion	1.5
	Advanced Practice Nurse	Discuss support network and review home management	Adjustment back to normal life	Lecture and discussion	1.5
	Focus group facilitators	Share survivorship problems and feelings by patients	Identification of survivorship issues	Discussion	1.5
3	Psychologist	Discuss emotional distress and coping strategies	Psychological distress	Lecture, discussion and practice	1.5
	Physiotherapist	Educate on the importance of physical activity and introduce simple exercises	Exercise and physical activity	Lecture, discussion and practice	1.5
	Breast cancer survivor	Discuss motivational sharing and reinforce the idea of living well	Psychological distress	Lecture and discussion	1.5

To address our proposed aim, a randomized, open-labeled, parallel trial approach was chosen as the methodology for this research to ensure that we are comparing the newly proposed intervention to usual care. Besides evaluating symptom outcomes from the intervention, we have also evaluated feasibility outcomes include patients' acceptance and satisfaction.

2.4.3: Aim 3: To develop and evaluate an education-focused translational intervention embedding contemporary principles and research evidence on survivorship care.

As described in Chapter 1, it is recognized that there is limited literature describing the process and success of translating scientific research findings to a broader scientific audience beyond implementation, particularly in the area of cancer survivorship. Translational education represents a pedagogical approach aimed at developing innovative educational activities that foster a deeper understanding of translational science strategies and solutions. (156, 157) This is achieved by leveraging the experiential knowledge generated through translational research initiatives.

As I was seeking opportunities to translate concepts and research findings of cancer survivorship through an educational intervention, I came across an opportunity where faculty members at the University of California, Irvine were invited to offer 1-unit seminars to undergraduate first-year students. Upperclassmen who are interested to learn about these seminar topics were also allowed to subscribe to these courses. Hence, between 2021-2023, I offered a 1-unit seminar series "Life After Cancer", with the aim to introduce the concepts of cancer survivorship to non-medical undergraduate students, incorporating findings from my different research projects. Through a series of seminars, students learned how cancer has evolved into a chronic condition in many survivors, especially among those who are cured. Students also learned about how cancer treatment can cause long-term complications, how cancer providers manage toxicities associated with cancer and treatment, as well as the cutting-edge research that is currently undertaken around the globe to mitigate these complications. The course was designed with a number of objectives (Table 2.3).

Table 2.3: Objectives of the "Life After Cancer" course at University of California, Irvine
1. Understand the definition and issues surrounding cancer survivorship. 2. Identify common toxicities and complications that are affecting various groups of cancer survivors. 3. Appreciate the disease trajectory of common cancers, from diagnosis to survivorship. 4. Discuss management strategies that are commonly employed to manage complications of cancer during survivorship. 5. Discuss the impact of cancer survivorship on the health care system. 6. Discuss the research directions that are taken to address the concerns related to cancer survivorship.

To ensure that the course served the original purposes that I had in mind, I designed a pre-/post-implementation study with the aim of evaluating the knowledge, attitude, and perception (KAP) changes related to the course, as well as its impact on undergraduate students. The KAP method was selected for its systematic framework, which could facilitate a comprehensive understanding of student behaviors, thus enabling the evaluation of the benefits of the intervention. (158) The overarching goal was to understand the potential for translation of research by embedding the concepts of cancer survivorship through a dedicated course for undergraduate students.

2.6 Summary

This chapter presents an overview of the pragmatic methodology that frames the thesis and the research methods used to address individual study aims within corresponding publications (Table 2.4). Research findings are presented in Chapters 3 to 7 that follow, to consider cancer survivorship concerns across the care continuum and, at the same time, ensure that the research remains grounded in real-world clinical relevance.

Table 2.4. Summary of specific aims, research questions, and study approaches.

Specific aim	Research question(s)	Study approach
1. To investigate the needs of cancer survivors from a patient and healthcare provider perspective.	To gather in-depth descriptions from multiethnic Asian breast cancer survivors on their perceptions and experiences of cancer survivorship and their perceived barriers to post-treatment follow-up	Qualitative focus group among survivors (*Chapter 3*)
	To identify the unmet needs, barriers, and facilitators for conducting AYA survivorship research from the providers' and researchers' perspectives.	Delphi study among healthcare professionals (*Chapter 4)*
2. To evaluate the impact of novel, multidisciplinary interventions and implement them in the routine care to address unmet needs of cancer survivors.	To evaluate the implementation outcomes of an electronic patient-reported outcome (ePRO)-driven symptom management tool led by oncology pharmacists.	Implementation Study (*Chapter 5*)
	To evaluate and report the efficacy and safety of a herbal concoction on quality of life (QOL), cancer-related fatigue (CRF), and cognitive symptoms, compared to placebo.	Prospective Randomized Controlled Trial (Chapter 6)
	To evaluate the effectiveness of a psychoeducation group (PEG) intervention program compared with usual care to reduce distress for physical symptoms and	Prospective Randomized Controlled Trial (Chapter 7)

	psychological aspects in Asian breast cancer survivors who have completed adjuvant chemotherapy.	
3. To develop and evaluate an education-focused translational intervention embedding contemporary principles and research evidence on survivorship care.	To evaluate the knowledge, attitude, and perception among university freshmen who have undergone a university course designed to educate fundamental concepts of cancer survivorship.	Prospective Cross-Sectional Study (Chapter 8)

Chapter 3: Unmet needs, barriers and facilitators of survivorship care among survivors of breast cancer

3.1 Introductory Comments

With improvements in the early detection and treatment of first malignancies, the number of BCS is anticipated to increase dramatically over the next decade. As described in the introductory chapters (Chapters 1 and 2), early-stage BCS are often at risk of long-term morbidities, related directly to the cancer itself, to pre-existing co-morbidities, and especially to their anti-cancer therapies. Clearly, the healthcare needs of BCS are tremendous during survivorship. However, the majority of studies have been conducted in North America (123), Australia (124), and Europe (125), with few studies devoted to Asian BCS. Conducting research within Asian populations is valuable for addressing culturally specific needs that may differ from those of other ethnic groups. Besides the unmet needs that are not well researched, it is also unknown what the barriers and facilitators are for delivering high quality survivorship care. As much of the existing literature on cancer survivorship lacks cultural adaptation, this can result in limited confidence among clinicians to implement these interventions in practice.

This study aligns well with Aim 1 of the thesis, serving as an initial step in identifying the needs from the cancer survivors' perspective. Results of this study also helped to provide the necessary foundation for designing the culturally appropriate interventions presented in Chapters 5-7 of the thesis.

3.2 Aim

To gather in-depth descriptions from Asian BCS on their perceptions and experiences of cancer survivorship and the perceived barriers to post-treatment follow-up.

3.3 Summary

A number of clinically important findings were uncovered from our qualitative interviews with Asian BCS. Firstly, many survivors understood the term survivorship in its literal meaning. However, two opposing perspectives were observed through the discussions in terms of the definition of survivorship. Some survivors agreed that the connotation of survivorship is positive, but others viewed survivorship as a pessimistic description of their condition and disliked the term "survivorship," because it implies that survivors had undergone hardship during their treatment. I also uncovered that cognitive impairment and peripheral neuropathy were the physical symptoms that bothered survivors the most, and many indicated that they experienced emotional distress during survivorship, for which they turned to religion and peers as coping strategies. These are areas of unmet needs that are vital to address through subsequent experimental studies, providing the rationale for developing multimodal interventions in order to efficiently address these symptoms. Examples of such interventions are presented in subsequent thesis chapters (Chapters 5-7). Survivors reported that consultation time with physicians was often insufficient, and many expressed that allied health professionals could serve as valuable alternatives in providing support for survivorship care. These insights also formed a critical foundation for designing interventions that incorporated allied health professionals other than physicians and nurses —such as psychologists and pharmacists (Chapter 6), and integrative oncology providers (Chapter 7)—to effectively address the diverse care needs of cancer survivors.

Lastly, I learned that our BCS were affected by various types of symptoms throughout their treatment continuum, hence the need to incorporate effective screening tools (Chapter 5) in order to identify their symptoms earlier and to prevent them from experiencing clinically significant toxicities.

3.4 Publications

- **Chan A**, Lum ZK, Ng T, Eyob T, Wang XJ, Chae JW, Raaj S, Shwe M, Gan YX, Fok R, Loh K, Tan YP, Fan G. Perceptions and Barriers of Survivorship Care in Asia: Perceptions from Asian Breast Cancer Survivors. *Journal of Global Oncology* 2016; 3(2): 98-104.

3.5 Author's Contribution

- I conceived the research and obtained funding for the study. I led the data analysis, writing and editing of the publication. Additionally, I trained my research team members (comprising undergraduate and postgraduate students, and research coordinators) to conduct the focus group discussion components of the study.

original report

Perceptions and Barriers of Survivorship Care in Asia: Perceptions From Asian Breast Cancer Survivors

abstract

Purpose With the long-term goal to optimize post-treatment cancer care in Asia, we conducted a qualitative study to gather in-depth descriptions from multiethnic Asian breast cancer survivors on their perceptions and experiences of cancer survivorship and their perceived barriers to post-treatment follow-up.

Methods Twenty-four breast cancer survivors in Singapore participated in six structured focus group discussions. The focus group discussions were voice recorded, transcribed verbatim, and analyzed by thematic analysis.

Results Breast cancer survivors were unfamiliar with and disliked the term "survivorship," because it implies that survivors had undergone hardship during their treatment. Cognitive impairment and peripheral neuropathy were physical symptoms that bothered survivors the most, and many indicated that they experienced emotional distress during survivorship, for which they turned to religion and peers as coping strategies. Survivors indicated lack of consultation time and fear of unplanned hospitalization as main barriers to optimal survivorship care. Furthermore, survivors indicated that they preferred receipt of survivorship care at the specialty cancer center.

Conclusion Budding survivorship programs in Asia must take survivor perspectives into consideration to ensure that survivorship care is fully optimized within the community.

J Glob Oncol 00. © 2016 by American Society of Clinical Oncology

Alexandre Chan
Zheng Kang Lum
Terence Ng
Tewodros Eyob
Xiao Jun Wang
Jung-woo Chae
Sreemanee Dorajoo
Maung Shwe
Yan Xiang Gan
Rose Fok
Kiley Wei-Jen Loh
Yee Pin Tan
Gilbert Fan

Author affiliations appear at the end of this article.

Supported by the National Cancer Centre Community Cancer Fund Grant No. COMCF-YR2014-NOV-SD3 Call 2014 and Pretty in Pink 2014 Event.

Both A.C. and Z.K.L. contributed as first co-authors.

Authors' disclosures of potential conflicts of interest and contributions are found at the end of this article.

Corresponding author: Alexandre Chan, PharmD, Department of Pharmacy, Faculty of Science, National University of Singapore, Block S4A, 18 Science Dr 4, Singapore 117543; e-mail: phaac@nus.edu.sg.

INTRODUCTION

Cancer survivorship care is still in its infancy in Asia. The majority of the institutions lack formal and standardized survivorship programs for cancer survivors. Yet, numerous challenges exist in the management of post-treatment complications within Asia. An observational study showed that cancer survivors in Asia suffer significant post-treatment–related symptoms, including anxiety, fatigue, and cognitive disturbances, and that these treatment-related complications are likely to have a major effect on health-related quality of life during cancer recovery.[1] In addition, greater than 60% of the Southeast Asian oncology practitioners from numerous countries suggested that patient-specific barriers are the main barriers to follow-up care among the survivors they routinely treat.[2] Because the success of survivorship care also depends greatly on the cooperation and participation of the survivors, it would be prudent to fully understand cancer survivorship from the end user perspective. Much of what is known about survivorship care and the issues faced by cancer survivors originates from studies that were conducted in the West, so ethnocultural differences may contribute to the delivery and experience of survivorship care among Asian cancer survivors.

With the long-term goal to optimize post-treatment care in breast cancer survivors in Asia, we conducted a qualitative study to gather in-depth descriptions from Asian breast cancer survivors on their perceptions and experiences of cancer survivorship and their perceived barriers to post-treatment follow-up.

METHODS

Design and Participants

As part of a study to evaluate the performance of group psychoeducation to improve survivorship in breast cancer survivors, a qualitative study was conducted at the National Cancer Centre Singapore (NCCS) that involved focus group discussions.[3] NCCS is a leading regional center for cancer research and treatment in Southeast Asia, and it serves approximately 70% of all adult patients with cancer in Singapore.

The participants recruited for the focus group discussions fulfilled the following inclusion criteria: age older than 21 years, ability to read and understand English, diagnosis of early-stage breast cancer made by a medical oncologist, and completion of primary chemotherapy for early-stage breast cancer. This study was approved by the SingHealth Centralized Institutional Review Board, and informed consent was obtained from all of the participants.

Procedures

Six English-speaking structured focus groups were conducted over 2 separate days. Four to six participants were included in each focus group, and grouping of the participants was based on the type of cancer treatment they had received. Each focus group discussion was designed to be 60 to 90 minutes long and was coordinated by trained facilitators. These facilitators were medical social workers, and each facilitator was assisted by one of the investigators as a note taker. The discussions used an open-ended approach that proceeded from a general question to more specific questions, which thus reduced the influence of probing by the facilitators. Two training sessions were held before the focus group discussions to ensure consistency in the facilitation of the groups.

In each discussion, the facilitator would first understand the participant definitions and perception of the term survivorship and then gather information on the physical, emotional, social, and spiritual effects of cancer treatment on the survivor. Subsequently, the participants were asked to state the obstacles and factors that might deter them from joining survivorship programs (if offered; Table 1).

Data Analysis

The focus group discussions were voice-recorded, transcribed verbatim, and analyzed by thematic analysis.[4] The open-ended discussion guide and data-driven analytical methods used in this study were adopted from certain elements of the grounded theory.[5] Codes that described similar manifestations were grouped into themes. Two coders (L.Z.K. and A.C.) first familiarized themselves with the transcripts and generated initial codes independently. They then met to discuss and reach a consensus on the codes. Discrepancies were resolved with a consensus method.

RESULTS

Demographics

Twenty-four survivors participated in the six different focus groups. The mean (standard deviation) age was 56.4 years (± 7.0 years). Most of the survivors were Chinese (87.5%), were married (70.8%), and were diagnosed with stage II breast cancer (58.3%; Table 2).

Open codes were created and categorized into five broad themes: understanding the terminology: who is a cancer survivor, physical issues, psychological issues, barriers to follow-up care, and how can the health care system address participants' needs.

Understanding the Terminology: Who Is a Cancer Survivor?

A number of survivors understood the term survivorship as its literal meaning. However, two poles were observed through the discussions in terms of the definition of survivorship. Some survivors agreed that the connotation of survivorship is positive, but others viewed survivorship as a pessimistic description of their condition.

> "Survivorship brings [me] a different kind of hope."

> "I am not sure do you need to wait for 5 years to be called a cancer survivor, or is it immediately now when you finished all your treatment […] Don't really understand."

Some survivors viewed survivorship as a negative reflection of their condition, and being tagged with the term survivor caused them emotional discomfort. The Chinese translation of the term survivorship implies that the survivors had undergone hardship during their treatment, and this is a term that was not favored by the survivors.

> "Personally when I heard the word 'survivor,' it makes me go into sadness. I don't like the term because it somehow [has] this connotation of […] barely getting by."

Physical Symptoms

Cancer treatment brought about numerous physical adverse effects that affected the quality of life and personal relationships of survivors. Cognitive impairment, peripheral neuropathy, and fatigue were highlighted by most survivors. Hair loss, nausea, constipation, and mouth ulcers were other physical effects of cancer treatment that were experienced by numerous survivors during treatment.

Cognitive impairment. A number of survivors indicated that their memory loss had affected their daily functioning, and they became dependent on others around them for daily living. This group of survivors was saddened by their memory loss, which indirectly affected their self-esteem.

Table 1 – Guiding Questions That Were Used in the Focus Group Discussions

Theme	Question
Definitions and perceptions of the term survivorship	Do you understand the term "survivor" of breast cancer? What does the term mean to you? Has any health care professional mentioned this term to you?
Gather information on the survivors' physical effects of cancer treatment	What physical effects of cancer treatment bothered you the most during treatment and may continue to pose as problems/difficulties for you after treatment? How do you manage these side effects? What kind of role does your family and peers play in the management of these side effects?
Gather information on the survivors' emotional, social, and spiritual concerns.	What were the emotional, social, and spiritual concerns that you faced during cancer treatment and may continue to pose as problems/difficulties for you after treatment? How do you manage these side effects? What kind of role does your family and peers play in the management of these concerns?
Discuss the obstacles and factors that might deter them from joining survivorship programs.	What are some barriers to follow-up care after completion of active treatment? Why?
Discuss the opportunities that the public health system could improve post-treatment care.	What should the public health system do to address your needs after cancer treatment? Why?

> "Last time I do work very independent[ly] […] I can guide people, but now I cannot. I still have to ask."

These survivors overcame memory loss mainly through physical self-reminders by note-taking and by using certain tools to aid in memory recall. A small number of them turned to alternative medical therapies, such as traditional Chinese medicine and meditation, to improve their memory.

Peripheral neuropathy. The majority of the survivors claimed that the numbness that resulted from chemotherapy manifested as physical pain that caused disruptions to their daily living. Because neuropathy interferes with their daily living, the survivors were afraid that this effect would be permanent, and they were skeptical about recovering from the adverse effects.

> "It is painful [that] you couldn't open the [bottle] cap, [and] you couldn't do so many things. I remembered […] at one stage, splashing water on my face is also painful."

> "I am not that confident […] the nerves take time to recover."

This resulted in some survivors turning to alternative medical therapies to overcome this adverse effect, and a small number of them attempted to massage the areas of numbness.

> "The therapist that I went to, she does a mixture […] of […] Western, […] Japanese, [and] a little bit [of] traditional Chinese medicine."

Fatigue. Most of the survivors also complained that they experienced fatigue, especially after chemotherapy. They admitted that chemotherapy made them tired and very sleepy. However, they also acknowledged that this effect might not be significant, because healthy individuals can also get tired. Some survivors claimed that they had to find ways, such as taking afternoon naps, to keep themselves alert, and one survivor mentioned consuming coffee to stay awake.

Emotional, Social, and Spiritual Effects of Cancer Treatment

Fear and sadness were common among survivors. Some survivors were not optimistic about their prognosis, and this negative mindset led them to experience depression and anxiety.

Fear, sadness (uncertainty), and stress. The fear and uncertainty of the future resulted in a negative outlook on life for many survivors. As they suffered from the adverse effects of chemotherapy and the symptoms of breast cancer, the optimistic survivors grew to accept their fate and lost much hope in life.

Table 2 – Sociodemographic and Clinical Characteristics

Characteristic	No. (%) of Patients (N = 24)
Age, mean ± SD, years	56.4 ± 7.0
Level of education	
Secondary	9 (37.5)
Pre-university	9 (37.5)
Graduate/postgraduate	6 (25.0)
Race/ethnicity	
Chinese	21 (87.5)
Malay	1 (4.2)
Indian	1 (4.2)
Other	1 (4.2)
Marital status	
Single	5 (20.8)
Married	17 (70.8)
Divorced	1 (8.3)
Employment status	
Currently working	11 (45.8)
Not working	7 (29.2)
Retired	2 (8.2)
On long-term medical leave	4 (16.7)
Postmenopausal	20 (83.3)
Cancer stage	
1	5 (20.8)
2	14 (58.3)
3	5 (20.8)
Adjuvant chemotherapy received	
Anthracycline based	14 (58.3)
Comorbidity	
Hypertension	3 (12.5)
Diabetes	1 (4.2)
Dyslipidemia	1 (4.2)

Abbreviation: SD, standard deviation.

> "When you first started, you live from cycle to cycle, you can survive cycle to cycle, but then subsequently when it gets worse […], you start living from day to day […], then from day to day, it becomes meal to meal."

The majority of the survivors agreed that they were constantly under stress and did not have time to relax. One of the common concerns that arose from the various discussions was the fear of recurrence of their cancer.

Difficulty in coping with distress. With the variations in advice that they received, many survivors agreed that they were confused about whom to trust, and they had minimal avenues by which they could cope with this emotional distress. Controlling their emotions posed a great challenge to the survivors.

> "Initially [my husband kept] telling me […] to stay positive and things like that. I keep on telling him, you are not me, you don't know how I feel, can you let me [vent] out my feelings or not?"

Religious beliefs and support of family and friends. The majority of the survivors agreed that support from family and friends was important during their treatment and battle with cancer. For those survivors who did not know how to cope with emotional distress, they turned to religious support; many of them went to healing rooms or turned to prayer in churches or temples.

Post-Treatment Follow-Up: Patient-Related Barriers

Through the discussions, we aimed to establish the factors that might deter survivors from continuation of their treatment or participation in any post–active treatment programs.

Lack of consultation time with specialists. One common barrier reflected by the majority of the survivors was the issue of time spent with their oncologists. The survivors agreed that most of their questions were left unanswered because of the short consultation time with the oncologists.

> "Sometimes [during] the consultation, we do not have that much time to […] talk to the doctor."

Although lack of time is a concern, many survivors also agreed that generally this was not a significant barrier to their follow-up care, because there were other allied health care professionals to turn to who could answer their queries.

> "I find that when I talk to the oncologist and the doctor, I am a bit rush, but I find talking to the pharmacist, the time that I don't have to see the doctor right, I go and see the pharmacist just before the chemo, and I think that talking to the pharmacist, I have more time."

Unplanned hospitalization. Some survivors also mentioned the fear of unplanned hospitalization during their follow-up care. Some expressed their fear of diagnostic tests, including blood tests, because these tests may detect other health problems.

> "I don't like to be hospitalized […] because I already have very bad insomnia, even in my house at night I have difficulties sleeping, that is from young, I already have this problem, all the more when I am having this condition, I [find it] harder

for me to sleep [...] If [I] need to be hospitalized, [I don't have] to sleep [already]."

Post-Treatment Follow-Up: Health Care System–Related Barriers

Almost all of the survivors expressed their desire to continue their follow-up at the specialized cancer center. These survivors perceived the health care professionals at the cancer center as more knowledgeable in cancer treatment, and they thought that maintenance of treatment records at the cancer center was important. This confidence arose mainly as a result of prior experience with the center and was boosted by the services they received during active treatment.

Generally, the survivors were not confident with community cancer care, especially follow-up care with the community general practitioners (GPs). They perceived the GPs as not adequately knowledgable about cancer treatment, and some of the survivors reflected that they were turned away by GPs when they approached the community clinic for consultation. Thus, many survivors preferred to continue follow-up at the specialized cancer center, even for simple procedures, such as vaccinations.

"I go to the GP, he doesn't know how to do it [...]. They actually turn you off, they say 'No, I don't do things like that.' They turn you all away."

DISCUSSION

This qualitative study was conducted to gain an in-depth understanding of the health concerns identified by breast cancer survivors in Asia and the barriers that would hinder them from optimal care during survivorship. Although much of the perspectives carry similarities with known literature,[6,7] this study has identified a number of unique perspectives, particularly with the way survivors in Asia manage and cope with survivorship issues.

Survivors were overwhelmed by symptoms, including cognitive impairment, fatigue, and peripheral neuropathy, and they expressed concerns that these toxicities would become permanent over time. Although neurologic complications (both peripheral neuropathy and cognitive impairment) are significant after cancer treatment, it is clear to us that the survivors are not aware of strategies for coping with the physical effects of these complications. Thus, many of them resorted to complementary and alternative medicine (CAM). CAM is believed to have positive effects on psychological relief.[8] One study found that Asian survivors believe that gingko biloba may have beneficial effects to reverse cancer-related cognitive toxicity.[9] There is minimal evidence of the effectiveness of such CAM treatments to provide psychological symptom relief in cancer survivors.[10] Yet, our participants expressed their eagerness and willingness to try these unconventional therapies to attain relief. These findings highlight the importance of conducting studies to evaluate specific CAM therapies that could resolve cancer-related symptoms.

Asians are generally influenced by culture and beliefs, and it is apparent that peers and family play a major role in the road of cancer recovery among Asians. This finding is consistent with a number of studies conducted among Asian survivors who observe the importance of adequate family support on the road to cancer recovery. Previous studies have shown that Asians uphold family values and remain conservative and dependent upon the support of friends and family members during critical illnesses.[11,12] This is in contrast to a group of young breast cancer survivors in the United States, of whom most stated that they had lost family support or even interaction with their family members.[13] Although the current guidelines from the Institute of Medicine on the cancer survivorship care plan do not address how family and peer support should be incorporated into a patient's care plan, it is essential that survivorship programs implemented in Asia ensure sufficient involvement from family and peers. Such cultural differences between the Asian and Western societies should not be ignored.

We have also identified several patient- and health care–related barriers that are specific to Asian breast cancer survivors who participate in survivor care programs. Patient-related barriers were mainly personal in nature, such as the fear of unplanned hospitalizations or the receipt of inappropriate treatments. These barriers could be explained in part by the poor health literacy of our survivors.[14] Past studies have also suggested that Asian survivors who have migrated to the Western world suffer from cultural barriers that lead to poorer outcomes in survivorship care.[15] This highlights the importance of taking into account cultural sensitivity when survivorship programs for Asian breast cancer survivors are designed.

ASCO has recently provided recommendations to guide the management of breast cancer survivorship, which emphasize the role of a primary care provider to deliver survivorship care.[16] Given the wide disparity of health care resources among different Asian countries, the ASCO standards must be carefully tailored and adopted, particularly in resource-limited countries. In Asia,

confidence remained an issue in this context; many of the breast cancer survivors noted that primary care clinicians were not adequately trained to handle the complexity of their conditions. This issue has also been greatly discussed in the literature within the Western context.[17] As the breast cancer burden in Asia increases, it might not be feasible to solely depend on the specialized cancer center to adequately meet the needs of these survivors. A few strategies could be implemented to improve the seamless transition of care between the specialized cancer center and the GPs: greater use of electronic resources, such as web-based survivorship care plans, to ensure that care plans are accessible by GPs; improvement in the knowledge and confidence of GPs about care of cancer survivors by using different platforms, including didactic workshops, certification courses, and distance learning; and safe distribution of some services to a multidisciplinary team that comprises primary care providers and allied health professionals, such as nurses, pharmacists, and medical social workers (under a shared model) to provide holistic care for Asian cancer survivors. Currently, a randomized controlled trial is ongoing to evaluate the effectiveness of a standardized multidisciplinary survivorship program that is culturally adapted for Asian breast cancer survivors who have completed chemotherapy.[3] The results from this study will drive the directions of survivorship care and provide insights into how such a structured program might be implemented on a larger scale and on a national level.

There are a few limitations to this qualitative study. Given that all of the participants of the focus group discussions were breast cancer survivors, findings of this study may not be generalizable to other cancer populations. Furthermore, participants of these focus groups were relatively highly educated; hence, their perspectives may not represent women who are less educated.

In conclusion, with the increase of cancer survivors in the next few decades, cancer survivorship is recognized as an important issue on a global scale. As interest in cancer survivorship grows in Asia, a more comprehensive understanding of Asian breast cancer survivors is needed to create transitional programs that suit their needs. Our data suggest that breast cancer survivors in Asia are still unfamiliar with the term survivorship and have a multitude of physical health and psychological issues to address to allow the transition to normalcy. Budding survivorship programs in Asia must take survivor perspectives into consideration to ensure that survivorship care is more fully optimized within the community.

DOI: 10.1200/JGO.2016.004929
Published online on jgo.ascopubs.org on June 8, 2016.

AUTHOR CONTRIBUTIONS

Conception and design: Alexandre Chan, Terence Ng, Yee Pin Tan, Gilbert Fan

Collection and assembly of data: Alexandre Chan, Zheng Kang Lum, Terence Ng, Tewodros Eyob, Xiao Jun Wang, Jung-woo Chae, Sreemanee Dorajoo, Maung Shwe, Yan Xiang Gan, Yee Pin Tan, Gilbert Fan

Data analysis and interpretation: Alexandre Chan, Zheng Kang Lum, Terence Ng, Rose Fok, Kiley Wei-Jen Loh, Yee Pin Tan, Gilbert Fan

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Alexandre Chan

Honoraria: Merck Sharp & Dohme

Consulting or Advisory Role: Merck Sharp & Dohme

Speakers' Bureau: Merck Sharp & Dohme

Travel, Accommodations, Expenses: Merck Sharp & Dohme

Zheng Kang Lum
No relationship to disclose

Terence Ng
No relationship to disclose

Tewodros Eyob
No relationship to disclose

Xiao Jun Wang
No relationship to disclose

Jung-woo Chae
No relationship to disclose

Sreemanee Dorajoo
No relationship to disclose

Maung Shwe
No relationship to disclose

Yan Xiang Gan
No relationship to disclose

Rose Fok
No relationship to disclose

Kiley Wei-Jen Loh
No relationship to disclose

Yee Pin Tan
No relationship to disclose

Gilbert Fan
No relationship to disclose

Affiliations

Alexandre Chan, **Zheng Kang Lum**, **Terence Ng**, **Tewodros Eyob**, **Xiao Jun Wang**, **Jung-woo Chae**, **Sreemanee Dorajoo**, **Maung Shwe**, **Yan Xiang Gan**, National University of Singapore; **Alexandre Chan**, **Terence Ng**, **Tewodros Eyob**, **Xiao Jun Wang**, **Jung-woo Chae**, **Sreemanee Dorajoo**, **Maung Shwe**, **Yan Xiang Gan**, **Rose Fok**, **Kiley Wei-Jen Loh**, **Yee Pin Tan**, and **Gilbert Fan**, National Cancer Centre Singapore; and **Alexandre Chan**, Duke–National University of Singapore Medical School Singapore, Singapore

REFERENCES

1. Cheung YT, Shwe M, Chui WK, et al: Effects of chemotherapy and psychosocial distress on perceived cognitive disturbances in Asian breast cancer patients. Ann Pharmacother 46:1645-1655, 2012
2. Ng T, Toh MR, Cheung YT, et al: Follow-up care practices and barriers to breast cancer survivorship: Perspectives from Asian oncology practitioners. Support Care Cancer 23:3193-3200, 2015
3. Chan A. Effectiveness of a psychoeducational group (PEG) intervention on supportive care and survivorship issues in early-stage breast cancer survivors who have received systemic treatment. Bethesda, MD, ClinicalTrials.gov, National Library of Medicine, 2015
4. Attride-Stirling J: Thematic networks: An analytic tool for qualitative research. Qual Res 1:385-405, 2001
5. Martin PY, Turner BA: Grounded theory and organisational research. J Appl Behav Sci 22:141-157, 1986
6. Documet PI, Trauth JM, Key M, et al: Breast cancer survivors' perception of survivorship. Oncol Nurs Forum 39:309-315, 2012
7. Fouladi N, Ali-Mohammadi H, Pourfarzi F, et al: Exploratory study of factors affecting continuity of cancer care: Iranian women's perceptions. Asian Pac J Cancer Prev 15:133-137, 2014
8. Lengacher CA, Bennett MP, Kip KE, et al: Relief of symptoms, side effects, and psychological distress through use of complementary and alternative medicine in women with breast cancer. Oncol Nurs Forum 33:97-104, 2006
9. Cheung YT, Shwe M, Tan YP, et al: Cognitive changes in multiethnic Asian breast cancer patients: A focus group study. Ann Oncol 23:2547-2552, 2012
10. Kinsel JF, Straus SE: Complementary and alternative therapeutics: Rigorous research is needed to support claims. Annu Rev Pharmacol Toxicol 43:463-484, 2003
11. Mehta KK: Multigenerational relationships within the Asian family: Qualitative evidence from Singapore. Int J Sociol Fam 33:63-77, 2007
12. Yi C, Chang C: Chang Y: The intergenerational transmission of family values: A comparison between teenagers and parents in Taiwan. J Comp Fam Stud 35:523-545, 2004
13. Ruddy KJ, Greaney ML, Sprunck-Harrild K, et al: Young women with breast cancer: A focus group study of unmet needs. J Adolesc Young Adult Oncol 2:153-160, 2013
14. Cheung YT, Ong YY, Ng T, et al: Assessment of mental health literacy in patients with breast cancer. J Oncol Pharm Pract 22:437-447, 2015
15. Kwok C, Koo FK, D'Abrew N, et al: East meets West: A brief report of a culturally sensitive breast health education program for Chinese-Australian women. J Cancer Educ 26:540-546, 2011
16. Runowicz CD, Leach CR, Henry NL, et al: American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. J Clin Oncol 34:611-635, 2016
17. Mayer EL, Gropper AB, Neville BA, et al: Breast cancer survivors' perceptions of survivorship care options. J Clin Oncol 30:158-163, 2012

Chapter 4: Unmet needs, barriers and facilitators of cancer survivorship research among adolescent and young adult cancer patients

4.1 Introductory Comments

As discussed in the introductory chapters (Chapters 1 and 2), AYA cancer survivors often face unique challenges that make them a particularly vulnerable group within the broader cancer community. While many researchers have advocated for a standardized approach to delivering survivorship care for AYAs, such a model may not be feasible in practice due to the heterogeneous and complex needs of this group. As we work toward developing an optimal survivorship care model for AYA cancer survivors, it is essential to first understand and address the core issues affecting survivorship.

Within this thesis, this chapter presents an alternative strategy under Aim 1 for evaluating unmet needs among cancer populations experiencing health disparities. It explores whether strategies can be developed to overcome existing barriers and leverage facilitators to conduct practice-changing research in order to enhance survivorship care in this unique population.

4.2 Aim

To identify the unmet needs, barriers, and facilitators for conducting AYA cancer survivorship research in Southern California from the providers' and researchers' perspectives.

4.3 Summary

Using the Delphi method, this study employed two rounds of surveys to establish consensus among participating healthcare providers. Building on insights from BCS, who reported a wide range of symptoms throughout their treatment journey, providers caring for AYA cancer survivors identified

similar complications—such as anxiety, psychological distress, and neurocognitive disorders—that significantly impact quality of life. These findings underscore the urgent need for innovative and effective strategies to mitigate these symptoms, suggesting that these symptoms can be outcomes that should be measured in future interventional studies.

This chapter also offers key insights that lay the groundwork for designing experimental clinical trials and refining methodological approaches for subsequent chapters of this thesis. First, providers emphasized the importance of exploring the use of telehealth platforms to obtain patient consent and deliver interventions in clinical trials. These strategies will help with conducting research post pandemic as telehealth is becoming more accessible among survivors. Second, it was noted that oncologists often lack the time to engage in survivorship research, highlighting the important role allied health professionals—previously identified by BCS as essential contributors—can play as facilitators in addressing unmet needs. Lastly, personalizing survivorship goals was identified as a key facilitator for enhancing patient engagement and enrollment in survivorship research. This strategy is particularly important for populations affected by health disparities (such as AYA), where individualized care approaches may be more effective in addressing diverse needs. One practical method for enabling personalized care is the integration of PRO tools into routine clinical practice. These tools can support the identification of patient-specific concerns and guide tailored interventions. In summary, the insights gained from this consensus-building exercise helped inform the design and implementation of experimental trials discussed in the subsequent chapters of this thesis.

4.4 Publications

- **Chan A**, Ports K, Ng DQ, Nasr R, Hsu S, Armenian S, Baca N, Freyer DR, Kuo DJ, Lin C, Milam J, Valerin J, Yun C, Torno L. Unmet Needs, Barriers, and Facilitators for Conducting Adolescent and Young Adult Cancer Survivorship Research in Southern California: A Delphi

Survey. *J Adolesc Young Adult Oncol*. 2023 Jan 25. doi: 10.1089/jayao.2022.0086. Epub ahead of print. PMID: 36695742. (Reprinted with permission from Mary Ann Liebert, Inc.)

4.5 Author's Contribution

- I conceived the research idea and presented the idea to SC-PACS for execution. I led the data collection, data analysis, writing, and editing of the publication. Furthermore, I supervised and worked closely with my research coordinator and students to conduct the two rounds of Delphi Surveys.

JOURNAL OF ADOLESCENT AND YOUNG ADULT ONCOLOGY
Volume 00, Number 00, 2023

DOI: 10.1089/jayao.2022.0086

Unmet Needs, Barriers, and Facilitators for Conducting Adolescent and Young Adult Cancer Survivorship Research in Southern California: A Delphi Survey

Alexandre Chan, PharmD, MPH,[1] Kayleen Ports, MS,[1] Ding Quan Ng, BSc (Pharm),[1] Reem Nasr,[1] Steffi Hsu,[1] Saro Armenian, DO, MPH,[2,3] Nicole Baca, MD,[4] David R. Freyer, DO, MS,[5,6] Dennis John Kuo, MD, MS,[7,8] Carol Lin, MD,[9] Joel Milam, PhD,[10] Jennifer Valerin, MD, PhD,[11] Christine Yun, NP,[9] and Lilibeth Torno, MD[9]

Introduction: An adolescent and young adult cancer (AYAC) patient is an individual who has received a cancer diagnosis between 15 and 39 years of age. They require significant survivorship care due to a combination of practical, physical, and mental health problems, but research in these areas is sparse. This study aimed to identify the unmet needs, barriers, and facilitators for conducting AYAC survivorship research in Southern California (SoCal) from the providers' and researchers' perspectives.

Methods: A two-round, electronically administered Delphi survey study was conducted, involving a panel of 12 health care professionals and/or researchers with substantial work experience in AYAC. A 10-point Likert scale was used to evaluate 24 areas of unmet needs in AYAC survivors, 39 barriers, and 25 facilitators.

Results: The top unmet needs in AYAC survivorship requiring research were in mental health issues, improving school/occupational performance, neurocognitive disorders, subsequent malignant neoplasms, and reproductive health. The top barriers identified were as follows: (1) institutions are too short-staffed to administer survivorship studies; (2) oncologists do not have the time/resources; and (3) lack of available funding. The top facilitators identified were as follows: (1) development of a mechanism/program to fund AYAC survivorship research studies; (2) in-person or virtual investigator engagement between children's hospitals and adult cancer centers to discuss research studies; and (3) developing personalized survivorship goals with AYAC patients and survivors to facilitate enrollment into survivorship studies.

Conclusion: Experts identified the lack of time, manpower, funding, and resources as major barriers in AYAC survivorship research. Enhancing communication and collaboration with different stakeholders may facilitate AYAC survivorship research efforts within the SoCal region.

[1]Department of Clinical Pharmacy Practice, School of Pharmacy & Pharmaceutical Sciences, University of California, Irvine, Irvine, California, USA.
[2]Department of Pediatrics, City of Hope, Duarte, California, USA.
[3]Department of Population Sciences, City of Hope, Duarte, California, USA.
[4]Department of Pediatric Hematology and Oncology, Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute, Los Angeles, California, USA.
[5]Cancer and Blood Disease Institute, Children's Hospital Los Angeles, Los Angeles, California, USA.
[6]USC Norris Comprehensive Cancer Center, Los Angeles, California, USA.
[7]Division of Pediatric Hematology/Oncology, Rady Children's Hospital—San Diego, San Diego, California, USA.
[8]Department of Pediatrics, University of California, San Diego, San Diego, California, USA.
[9]Department of Pediatric Hematology/Oncology, Hyundai Cancer Institute at Children's Healthcare of Orange County, Orange, California, USA.
[10]Department of Epidemiology and Biostatistics, Program in Public Health, University of California, Irvine, Irvine, California, USA.
[11]Division of Hematology/Oncology, School of Medicine, University of California, Irvine, Irvine, California, USA.

Keywords: adolescent and young adults, survivorship, research, cancer, Delphi survey

Background

Southern California (SoCal) is home for ~24 million residents, and the racial makeup is immensely diverse, with up to 40% of the state residents being Hispanic, followed by 35% non-Hispanic white and 15% Asian American or Pacific Islander. A recent population-based study in the Los Angeles County reported that close to half of the young adult survivors were ethnic minorities, with Hispanics less likely to receive survivorship follow-up care than non-Hispanic whites.[1] This suggests that disparities in health outcomes in cancer, as a function of the race and ethnicity, are likely to exist and create clinical gaps and specific research needs in this region.

An adolescent and young adult cancer (AYAC) patient is defined as an individual 15 to 39 years of age at the time of cancer diagnosis.[2] Globally, interest in the AYAC population has risen in recent years for various reasons. Most importantly, AYAC patients receive their cancer diagnoses at a critical stage in life characterized by major physical, emotional, cognitive, and social developments and changes.[2] As a result, AYAC patients raise concerns distinct from other age groups such as learning challenges, career developments, and fertility concerns.[2] In addition, they experience a wide range of health problems and are reportedly at high risk of developing chronic comorbidities postcancer treatment (such as hearing loss, stroke, thyroid disorders, and diabetes) due to exposure to chemotherapy and radiation therapy compared with age-matched healthy controls.[3]

Furthermore, the developments in life that occur in the AYAC patient age range create challenges that can impede consistent medical follow-up, such as insurance coverage, social transitions, and geographic mobility.[4] The racial-ethnic diversity in SoCal and distinctive health issues of AYAC patients highlight the opportunities for dedicated AYAC survivorship research in this region.

Unfortunately, many of the postcancer-related complications currently lack evidence-based screening guidelines.[5,6] There is also a lack of research dedicated to investigating the clinical management of these complications in AYAC patients. Besides the rarity of AYAC patients in the community, patients in this age range are also generally less involved in clinical studies. Over the past years, there has been a growth in studies reporting barriers and facilitators that would affect enrollment of AYAC patients in clinical studies, spanning from the individual patient to the health care system level. Clearly, there are tremendous unmet needs in the management of AYAC patients in SoCal and further research is needed to improve the enrollment of AYAC patients in survivorship research studies.

With the aim of improving the engagement of AYAC patients on survivorship clinical studies in SoCal, research is needed to understand the challenges associated with enrollment of AYAC patients from the providers' perspective. In this investigation, we evaluated (1) the unmet needs within AYAC survivorship care that require further research; (2) barriers to enrollment of AYAC patients in survivorship research studies, and (3) facilitators that may improve the enrollment of the AYAC patients into survivorship research studies among health care professionals and researchers with AYAC expertise.

Methods

Study design

This prospective study was conducted between January and December 2021 and was exempted for approval by the Ethics Board of the University of California, Irvine. The Delphi technique[7] was utilized for this investigation to obtain consensus on experts' opinions through two rounds of structured surveys, and we have adapted our methodology from another Delphi survey study that we have previously conducted.[8] Individuals identified as experts in the field were asked to complete the questionnaires anonymously. Responses from the first round of the survey were analyzed and summarized to develop the second round of the survey. This methodology allowed experts the opportunity to refine and clarify their views in consideration of other panel members' responses, without being pressured by those on the panel with strong opinions.

Delphi survey

Creation of the questionnaire. Four investigators (A.C., K.P., R.N., and S.H.) conducted a literature review between January and May 2021 to identify (1) the potential unmet needs in AYAC survivorship as well as the (2) barriers and (3) facilitators associated with enrolling AYAC patients in survivorship research studies. Unmet needs within AYAC survivorship care were identified through relevant literature and guidelines,[9–13] and were classified into physical problems, psychosocial problems, and practical issues. Barriers to enrollment of AYAC patients into survivorship research studies identified in the literature included existence of studies, accessibility to studies, eligibility, presentation of studies to AYAC patients, and acceptability by the patients.[14–16] Lastly, facilitators to enrollment identified in the literature included patient-level, health care professional-level, and system-level facilitators.[14–16] All identified items were entered into a survey developed within the Research Electronic Data Capture (REDCap®) v.11.2.4 platform, and panelists are required to provide responses to all items in the questionnaire.

Expert panel selection. Health care professionals and researchers who self-identified as having been involved with AYA cancer patient care for at least 10% of the time for 2 or more years were eligible to serve on the expert panel and participate in the Delphi process. Study information was disseminated to prospective expert panelists through the Southern California Pediatric and Adolescent Cancer Survivorship (SC-PACS) consortium by email and word of mouth by expert panelists. The SC-PACS consortium comprised cancer survivorship specialists experienced with childhood and adolescent cancers from multiple cancer treatment centers located in SoCal, with a demographic reach that is ~40% of the California population, thus making it an appropriate site for the recruitment of the panelists.[17]

First round. The first survey round was conducted in July 2021. In the first survey round, panelists independently scored each survey item based on perceived importance

and/or relevance. In addition, panelists were given the opportunity to contribute additional items to each portion of the survey in designated free-text fields. The survey took ~20 to 30 minutes to complete. After the conclusion of the first survey round, the results were analyzed by investigators of the study, including whether the free texts contained new information that had not existed in the first round. Items that met the consensus criteria and additional items that were recorded by panelists within the free-text fields were included in the second survey round.

Second round. The second round of the Delphi survey was conducted 2 months after the conclusion of the first round, engaging the same panel. In this round, panelists were provided a list of the items that met qualification for escalation in the first survey round, the median score and interquartile range (IQR) of each item across all 12 panelists, as well as their personal scoring of each item from the first survey round. Participants were asked to reappraise their response in consideration of the full panelists' responses in the first survey round.

In addition, panelists were asked to score the newly incorporated items derived from the free-text portions of the first survey. Panelists were also asked regarding the items that should be prioritized in the case of limited resources. The completion of the second survey round took ~10 to 15 minutes. Following the completion of the second survey round, responses were analyzed and a consensus was formulated.

Endpoints

Consensus. For both the first and second survey rounds, consensus regarding an item's significance (scored as 1 being ''the least important/relevant,'' to 10 being ''the most important/relevant'') was defined as an item receiving a score of ≥ 8 by at least 75% of panelists.

Priority. For the second survey round, panelists were asked to prioritize the top three unmet needs, barriers, and facilitators that they believed, with limited available resources, would have the greatest impact if targeted first. These responses were scored numerically (first = 3 points, second = 2 points, third = 1 point) for each item and summed across panelists, where higher summated scores represent a higher overall priority for the item in the domain as rated by the panel. The top 3 priority items were identified for each domain.

Statistical analysis

Descriptive statistics were calculated to describe the panelists' characteristics. Medians and IQRs for scores regarding item significance, and proportions of panelists scoring 8 or more were described for both the survey rounds. Items with the three highest priority scores, determined in the second survey round, were presented with their corresponding priority scores. All analyses were conducted in Microsoft Excel.

Results

Expert panelists

A total of 18 experts were identified through the SC-PACS network. Of the 18 identified experts, 12 agreed to participate as panelists in the Delphi survey and participated in both the survey rounds. The panel included nine physicians, two nurse practitioners, and one psychologist, representing nine institutions located in SoCal. The median number of years of work experience with AYAC patients within the expert panel was 12.5 years (IQR: 8.25, 18.75), with an average of 40% (IQR: 25%, 57.5%) time spent on caring for AYAC patients on a regular basis.

First round

Nineteen areas of unmet need in AYAC survivorship research, 29 barriers, and 21 facilitators of AYAC patient enrollment into survivorship studies were presented to the panel in the

Table 1. Consensus for Unmet Needs in Adolescent and Young Adult Cancer Survivorship Care from the Second Delphi Survey Round

Unmet needs	*Median score*[a] *(IQR)*	*Proportion of experts scoring* ≥ 8 *(n = 12)*	*Met consensus criteria*[b]*?*
Carried over from the first Delphi survey round			
Depression	9 (8.25, 10)	100%	Y
Neurocognitive disorders	9 (8, 10)	91.7%	Y
Secondary malignancy Neoplasms	8 (8, 9)	91.7%	Y
Anxiety	9 (8.25, 10)	91.7%	Y
Fertility issues/family planning	9 (8.25, 9.75)	83.3%	Y
Lifestyle/substance use	8.5 (8, 9.75)	83.3%	Y
Behavioral disorders	9 (7.25, 9)	75.0%	Y
Financial toxicities	9 (7.25, 10)	75.0%	Y
New items identified from free text in the first Delphi survey round			
School/occupational performance	8.5 (8, 9)	100%	Y
Relationship skills/relationship building	8.5 (8, 9)	83.3%	Y
Sexual health	8.5 (7, 9.75)	66.7%	
Body image	8 (7, 8.75)	66.7%	
Goal setting	8 (7, 9)	66.7%	

[a]The expert panelists were asked to rate an item's significance on a Likert scale from 1 (''the least important/relevant'') to 10 (''the most important/relevant'').

[b]Consensus regarding an item's significance was defined as an item receiving a score of ≥ 8 by at least 75% of participants.

IQR, interquartile range; Y, yes.

first round of the Delphi survey (Supplementary Tables S1–S3). Of the presented items, eight areas of unmet need (42.1%), one barrier (3.4%), and six facilitators (28.5%) met the criteria for escalation to the second round. The free-text fields within each domain revealed several items that could be added into the second round of the survey (Supplementary Table S4).

Second round

Areas of unmet need. A total of 18 areas of unmet need were scored by the panel in the second survey round, including five items that were introduced by panelists in the free-text portion of the first survey round. After evaluation by the panel, 10 (76.9%) areas of unmet need met the criteria for consensus (rated ≥ 8 out of 10 by at least 75% of the panelists). Areas of unmet need that achieved consensus included depression, school/occupational performance, neurocognitive disorders, secondary malignant neoplasms, anxiety, and fertility issues/family planning (Table 1).

Barriers. A total of 11 barriers were scored by panelists in the second survey round, including 10 barriers derived from the free-text feedback in the first survey round. After evaluation by the panel, 3 barriers (27.2%) met the criteria for consensus (rated ≥ 8 out of 10 by 75% of the panelists). These barriers included the following: (1) the institution is too understaffed to handle AYAC survivorship research studies, (2) oncologists do not have the time or sufficient research resources/support to conduct AYAC survivorship studies, and (3) lack of funding available for AYAC survivorship research studies (Table 2).

Facilitators. A total of 10 facilitators were scored by panelists in the second survey round, including four facilitators derived from the free-text portion of the first survey round. After evaluation by the panel, 6 facilitators (60.0%) met the criteria for consensus (rated ≥ 8 out of 10 by 75% of the panelists).

These facilitators included the following: (1) the development of a mechanism/program to fund AYAC survivorship research studies, (2) conduct survivorship meetings at both the children's hospital and adult cancer centers to discuss AYAC survivorship research studies, (3) help develop personalized survivorship goals with AYAC patients and survivors to facilitate enrollment into survivorship research studies, (4) allowing for AYAC survivorship research studies consenting and interventions to be conducted by telehealth, (5) improve the communication between medical oncology research officers and pediatric oncologists to discuss new enrollment protocols for AYAC survivorship research studies, and (6) expand the inclusion criteria of AYAC survivorship research studies to allow more patients to be eligible (Table 3).

Table 2. Consensus for Barriers of Adolescent and Young Adult Cancer Survivorship Studies from the Second Delphi Survey Round

Barriers	*Median score*[a] *(IQR)*	*Proportion of experts scoring* ≥ 8 *(*n = *12)*	*Met consensus criteria*[b]*?*
Carried over from the first Delphi survey round			
Institution is too short-staffed to handle AYAC survivorship studies	9 (8, 9)	91.7%	Y
New items identified from free text in the first Delphi survey round			
Oncologists do not have the time or sufficient research resources/support to conduct AYAC survivorship studies	9 (8, 9.75)	83.3%	Y
Lack of funding available for AYAC survivorship studies	9 (7.5, 10)	75.0%	Y
Multiple priorities that providers need to satisfy	9 (6.25, 9)	66.7%	
AYAC age group crosses adult and pediatric treatment center ages	8 (7, 8.75)	58.3%	
AYAC survivorship study visits are time-consuming (longer visits are needed to capture data and support the research)	8 (5.25, 9)	58.3%	
AYAC survivorship study visits happen during school and work hours	7 (5.25, 8)	41.7%	
AYAC experience information overload and do not want to add survivorship research studies on top of everything else	6 (5,8)	41.7%	
AYAC are reluctant to be back in an oncology setting for survivorship research studies and refocus on issues that they would prefer to forget	6 (5, 8)	33.3%	
Transportation costs related to participation in survivorship studies, especially if the caregiver must miss work to bring an AYAC patient to survivorship research studies visits	7 (6, 7.75)	25%	
AYAC age group is difficult to interest in survivorship research	5 (6, 7)	16.7%	

[a]The expert panelists were asked to rate an item's significance on a Likert scale from 1 (''the least important/relevant'') to 10 (''the most important/relevant'').

[b]Consensus regarding an item's significance was defined as an item receiving a score of ≥ 8 by at least 75% of participants.

AYAC, adolescent and young adult cancer; IQR, interquartile range; Y, yes.

Table 3. Consensus for Facilitators of Adolescent and Young Adult Cancer Survivorship Research Studies from the Second Delphi Survey Round

Facilitators	*Median score*[a] *(IQR)*	*Proportion of experts scoring* ≥ 8 *(*n = *12)*	*Met consensus criteria*[b]*?*
Carried over from the first Delphi survey round			
Development of a mechanism/program to fund AYAC survivorship research studies	9 (9, 10)	91.7%	Y
Conduct survivorship meetings at BOTH the children's hospital and adult cancer centers to discuss AYAC survivorship research studies	8.5 (8, 9)	83.3%	Y
Help develop personalized survivorship goals with AYAC to facilitate enrollment into survivorship research studies	8 (8, 9)	83.3%	Y
Improve the communication between medical oncology research officers and pediatric oncologists to discuss new enrollment protocols for AYAC survivorship research studies	8 (7.25, 9)	75.0%	Y
Expand inclusion criteria of AYAC survivorship research studies to allow more AYAC patients to be eligible	8 (7.25, 8)	75.0%	Y
Development of a survivorship program specific to just AYAC patients	8.5 (5.5, 9.75)	66.7%	
New items identified from free text in the first Delphi survey round			
Allowing for AYAC survivorship research study consenting and interventions to be conducted by telehealth	9.5 (7.25, 10)	75.0%	Y
Offering reimbursement for the patient's/caregiver's time and transportation costs related to participation in AYAC survivorship research studies	9 (6.25, 9)	66.7%	
Incentivizing adult care hospitals to open AYAC survivorship research studies	8 (7, 10)	54.5%	
Regular interval notices (e.g., every 3 months) with information about locally available AYAC survivorship research studies	7 (6, 8)	41.7%	

[a]The expert panelists were asked to rate an item's significance on a Likert scale from 1 (''the least important/relevant'') to 10 (''the most important/relevant'').
[b]Consensus regarding an item's significance was defined as an item receiving a score of ≥ 8 by at least 75% of participants.
AYAC, adolescent and young adult cancer; IQR, interquartile range; Y, yes.

Priority. The unmet needs with the highest priority scores include school/occupational performance (top priority with 13 points), followed by secondary malignancy, anxiety, and depression (all at 10 points), and relationship skills/building (7 points).

Barriers of highest priority include institution is too short-staffed to handle AYAC survivorship research studies (25 points), oncologists do not have the time or sufficient research resources/support to conduct AYAC survivorship research studies (16 points), and lack of funding available for AYAC survivorship research studies (11 points).

Facilitators deemed significant to prioritize include allowing for AYAC survivorship research studies consenting and interventions to be conducted by telehealth (13 points), developing a mechanism/program to fund AYAC survivorship research studies (11 points), developing personalized survivorship goals with AYAC patients to facilitate enrollment into survivorship research studies, improving the communication between medical oncology research officers and pediatric oncologists to discuss new enrollment protocols for AYAC survivorship research studies, and incentivizing adult care hospitals to open AYAC survivorship research studies (all at 10 points) (Table 4).

Discussion

In this Delphi investigation, key insights were gained regarding priorities, barriers, and facilitators to the enrollment of AYAC patients and survivors in survivorship studies, from the perspective of providers engaged in AYAC care. Through 2 iterative survey rounds, consensus was established among a panel of 12 SoCal health care professionals and researchers regarding the significance of 10 areas of unmet need, 3 barriers, and 6 facilitators. Important themes identified across domains included limited institutional resources, support, and funding available in support of AYAC survivorship research, the need for improved collaboration between pediatric and adult health care, and the unmet needs related to the emotional well-being of AYAC patients.

Interestingly, as we compared the results generated through panel consensus against the prioritization actions that were ranked by the panelists in all three areas (unmet needs, barriers, and facilitators), the results show that the data were highly congruent. Although our findings were reported by panelists who are practicing in the SoCal region, these findings offer actionable opportunities for intervention and improvement in AYAC survivorship research in SoCal.

Through the Delphi exercise, our panel successfully established consensus with regard to the unmet needs among AYAC

Table 4. Consensus on the Unmet Needs, Barriers, and Facilitators Regarding Adolescent and Young Adult Cancer Survivorship Research Studies to Prioritize

Rank	Items	Priority score[a]
Unmet needs		
1	School/occupational performance	13
2	Secondary malignancy	10
	Anxiety	
	Depression	
3	Relationship skills/building	7
Barriers		
1	Institution is too short-staffed to handle AYAC survivorship research studies.	25
2	Oncologists do not have the time or sufficient research resources/support to conduct AYAC survivorship studies.	16
3	Lack of funding available for AYAC survivorship research studies.	11
Facilitators		
1	Allowing for AYAC survivorship research study consenting and interventions to be conducted by telehealth.	13
2	Development of a mechanism/program to fund AYAC survivorship research studies.	11
3	Help develop personalized survivorship goals with AYAC to facilitate enrollment into survivorship research studies.	10
	Improve the communication between medical oncology research officers and pediatric oncologists to discuss new enrollment protocols for AYAC survivorship research studies.	
	Incentivizing adult care hospitals to open AYAC survivorship research studies.	

[a]In the second survey round, experts were asked to rank the top three unmet needs, barriers, and facilitators to prioritize when resources are limited. Consensus on priority is calculated by adding up priority scores for each item (first = 3 points, second = 2 points, third = 1 point), where higher scores represent a higher overall priority for the item in the domain as rated by the expert panel.

AYAC, adolescent and young adult cancer.

patients. Practical problems (such as school/occupational performance) and mental health (anxiety/depression) were identified by the panelists as the top unmet needs, with 90% of the panelists agreeing with the consensus. These findings are congruent with the existing literature, suggesting that AYAC patients have significant challenges in transitioning back into their age normative routines after cancer treatment, which may be due to the lack of resolution of practical and psychological issues after treatment.[18–20] More importantly, in the literature there is a lack of effective and robust interventions that clinicians can routinely recommend; therefore, clinicians do not have evidence-based recommendation to help AYAC patients navigate and overcome these challenges.

Although previous qualitative studies[4,9,21] have shown that AYAC patients were eager to enter or return to the workforce and resume their previous roles and career trajectories after achieving disease remission, there is a lack of standardized methodologies on how to incorporate back-to-work and back-to-school programs in rehabilitating AYAC. In the current literature, there is also no consensus established with regard to screening and monitoring for psychological problems including depression and anxiety, and these symptoms are known to contribute to neurocognitive disorders and several other survivorship complications, which are also lacking evidence-based monitoring and management strategies at this point.[22,23]

In terms of barriers identified in conducting AYAC survivorship research, only 1 of the 29 (institution is too short-staffed to handle AYA survivorship studies) originally identified barriers from the literature contributed to the final consensus list. This discrepancy between the panelists and our literature review emphasizes that providers and survivors do not identify the same barriers that are interfering with the conduct of survivorship research in AYAC. In our consensus exercise, the key barrier to AYAC survivorship research studies was resource limitations, in terms of funds and manpower. This suggests that AYAC survivorship studies are less prioritized in cancer centers in comparison with other clinical oncology studies, such as therapeutic trials or translational laboratory science studies.

Remaining barriers that have achieved consensus are specific to providers and institutions instead of the patients, which points toward the importance of increasing interest in and resources for AYAC survivorship research studies at the institution level in addition to addressing patient-level barriers.

The panel also established consensus on facilitators for improving AYAC research, with the majority of facilitators achieving consensus originating from the literature search.[14–16] A key facilitator of AYAC survivorship research identified was to improve the communication between adult and pediatric oncologists and cancer centers. As survivorship care starts during treatment and continues into adulthood during remission in younger cancer patients, survivorship care will be impacted by the complexities of the transition from pediatric to adult-centered care (including the lack of adult primary providers experienced with survivorship care, the lack of interest in or capacity in adult oncology centers to care for the needs of pediatric cancer survivors after treatment is completed, and patient attachment to their pediatric provider).[24] Thus, enhancing communication and collaboration between adult and pediatric institutions through survivorship meetings and strategizing on study enrollments, as well as streamlining administrative and regulatory procedures, is crucial to addressing AYAC survivorship needs.[25]

Most patients graduating from a pediatric cancer care have their care transitioned to adult primary care providers, who are not oncologists and have neither the expertise in nor knowledge of cancer survivorship studies. One strategy to keep these patients in contact with future AYAC studies, which is used by the Children's Oncology Group through Project:EveryChild,[26] is to consent adult survivors of pediatric cancer to potential follow-up for cancer survivorship studies before they graduate from the care of pediatric cancer specialists. In this way, the Children's Oncology Group serves as the locus for continued outreach to these AYAC patients as they mature into adulthood, away from their original institution of treatment without regard to who their subsequent care providers are. Correspondingly, many

facilitators agree that targeting oncologists and institutions by innovations, such as developing a mechanism to fund AYAC survivorship research studies and conducting survivorship meetings, to focus specifically on AYAC.

Implementation of virtual investigator support may also provide additional support to clinicians who have difficulties conducting research at their practice sites. Altogether, the experts concluded that efforts to enhance the recognition of AYAC survivorship issues as a key clinical and research need for health care institutions and funding agencies must be prioritized.

In collaborating with health care professionals and researchers in the SC-PACS consortium, we generated consensus regarding AYAC survivorship research needs and enrollment challenges across major cancer treatment institutions in SoCal. However, generalizability of our findings to other regions of California as well as other parts of the country may be limited. In addition, the makeup of the panel can also affect the generalizability of our data. While variations may exist regarding AYAC survivorship research facilitators and barriers across geographical locations, our findings in unmet needs are unlikely to differ greatly as they reflect the current gaps in the management of AYAC treatment complications. We were also unable to calculate a response rate in view that we recruited panelists through word of mouth.

Additionally, we observed the lack of consensus regarding patient-level barriers and facilitators in our results. Other than indicating the higher priority for institution-level changes, this finding also illustrates a possible bias due to our focus on providers' perspectives.

Another limitation of the study is that the survey participants were survivorship experts based in pediatric institutions, a subsequent study investigating the perceptions among adult oncologists or other providers who care for AYAC patients of pediatric cancer would be useful. To create a more complete picture regarding survivorship research engagement among AYAC patients and survivors in SoCal, future research will be needed to include patient perspectives. Interestingly, a recent needs assessment study of young cancer survivors (including AYAC patients), conducted by the SC-PACS consortium, has reported high importance regarding secondary malignancy, practical support (e.g., scholarships and jobs), and care coordination between institutions, suggesting that patients and providers are in agreement regarding many of the unmet needs and barriers on AYAC survivorship care in SoCal.[13]

Conclusion

Through reaching consensus, experts have established areas of unmet needs and priorities in AYAC care, as well as appraised existing strategies to improve the conduct of AYAC survivorship studies. Experts identified the lack of time, manpower, funding, and resources as major barriers in AYAC survivorship research. Enhancing communication and collaboration with different stakeholders may facilitate AYAC survivorship research efforts within the SoCal region. Increasing funding opportunities to facilitate AYAC survivorship research will also address the resource limitations that were highly cited by the experts. Data from this study will also establish directions and key elements that must be considered to ensure the success of future AYAC studies. Ultimately, data from this research will inform researchers on how to tackle systemic barriers for AYAC patients to be enrolled in survivorship research studies.

Acknowledgment

The investigators would like to thank Victoria Yi, PharmD, for providing assistance with this study.

Authors' Contributions

A.C.: Conceptualization, methodology, formal analysis, supervision, and writing (original draft preparation, review, and editing). K.P.: Methodology, data curation, investigation, formal analysis, and writing (original draft preparation, review, and editing). D.Q.N.: Methodology, investigation, formal analysis, and writing (original draft preparation, review, and editing). R.N.: Methodology, formal analysis, and writing (original draft preparation, review, and editing). SH: Methodology, formal analysis, and writing (original draft preparation, review, and editing). S.A.: Investigation, formal analysis, and writing (original draft preparation, review, and editing). N.B.: Investigation, formal analysis, and writing (original draft preparation, review, and editing). D.R.F.: Investigation, formal analysis, and writing (original draft preparation, review, and editing). D.J.K.: Investigation, formal analysis, and writing (original draft preparation, review, and editing). C.L.: Investigation, formal analysis, and writing (original draft preparation, review, and editing). J.M.: Methodology, investigation, formal analysis, and writing (original draft preparation, review, and editing).

J.V.: Investigation, formal analysis, and writing (original draft preparation, review, and editing). C.Y.: Investigation, formal analysis, and writing (original draft preparation, review, and editing). L.T.: Conceptualization, methodology, formal analysis, and writing (original draft preparation, review, and editing).

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received for this article.

Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4

References

1. Milam J, Freyer DR, Miller KA, et al. Project forward: A population-based cohort among young adult survivors of childhood cancers. JNCI Cancer Spectr. 2021;15(5): pkab068; doi: 10.1093/jncics/pkab068
2. Janssen SHM, van der Graaf WTA, van der Meer DJ, et al. Adolescent and young adult (AYA) cancer survivorship practices: An overview. Cancers (Basel) 2021;13(19); doi: 10.3390/cancers13194847

3. Chao C, Bhatia S, Xu L, et al. Chronic comorbidities among survivors of adolescent and young adult cancer. J Clin Oncol 2020;38(27):3161–3174; doi: 10.1200/JCO.20.00722
4. Zebrack B, Kent EE, Keegan THM, et al. ''Cancer sucks,'' and other ponderings by adolescent and young adult cancer survivors. J Psychosoc Oncol 2014;32(1):1–15; doi: 10.1080/07347332.2013.855959
5. Coccia PF, Pappo AS, Beaupin L, et al. Adolescent and young adult oncology, version 2.2018: Clinical practice guidelines in oncology. JNCCN J Natl Compr Cancer Netw 2018;16(1):66–97; doi: 10.6004/jnccn.2018.0001
6. Adams SC, Herman J, Lega IC, et al. Young adult cancer survivorship: Recommendations for patient follow-up, exercise therapy, and research. JNCI Cancer Spectr 2021; 5(1); doi: 10.1093/jncics/pkaa099
7. Brown BB. Delphi Process: A Methodology Used for the Elicitation of Opinions of Experts. RAND Corporation: Santa Monica, California; 1968.
8. Chan A, Tan SH, Wong CM, et al. Clinically significant drug-drug interactions between oral anticancer agents and nonanticancer agents: A delphi survey of oncology pharmacists. Clin Ther 2009;31(PART. 2):2379–2386; doi: 10.1016/j.clinthera.2009.11.008
9. Wong AWK, Chang T-T, Christopher K, et al. Patterns of unmet needs in adolescent and young adult (AYA) cancer survivors: In their own words. J Cancer Surviv 2017;11(6): 751–764; doi: 10.1007/s11764-017-0613-4
10. Galán S, de la Vega R, Tomé Pires C, et al. What are the needs of adolescents and young adults after a cancer treatment? A Delphi study. Eur J Cancer Care (Engl) 2017; 26(2); doi: 10.1111/ecc.12488
11. Kent EE, Parry C, Montoya MJ, et al. ''You're too young for this'': Adolescent and young adults' perspectives on cancer survivorship. J Psychosoc Oncol 2012;30(2):260–279; doi: 10.1080/07347332.2011.644396
12. Nass SJ, Beaupin LK, Demark-Wahnefried W, et al. Identifying and addressing the needs of adolescents and young adults with cancer: Summary of an Institute of Medicine Workshop. Oncologist 2015;20(2):186–195; doi: 10.1634/theoncologist.2014-0265
13. Tsangaris E, Johnson J, Taylor R, et al. Identifying the supportive care needs of adolescent and young adult survivors of cancer: A qualitative analysis and systematic literature review. Support Care Cancer 2014;22(4):947–959; doi: 10.1007/s00520-013-2053-7
14. Roth M, Mittal N, Saha A, et al. The Children's Oncology Group Adolescent and Young Adult Responsible Investigator Network: A new model for addressing site-level factors impacting clinical trial enrollment. J Adolesc Young Adult Oncol 2020;9(4):522–527; doi: 10.1089/jayao.2019.0139
15. Cheung YT, Zhang H, Cai J, et al. Identifying priorities for harmonizing guidelines for the long-term surveillance of childhood cancer survivors in the Chinese Children Cancer Group (CCCG). JCO Glob Oncol 2021;7(7):261–276; doi: 10.1200/go.20.00534
16. Siembida EJ, Loomans-Kropp HA, Trivedi N, et al. Systematic review of barriers and facilitators to clinical trial enrollment among adolescents and young adults with cancer: Identifying opportunities for intervention. Cancer 2020;126(5):949–957; doi: 10.1002/cncr.32675
17. Lin C, Baca N, Yun C, et al. Southern California Pediatric and Adolescent Cancer Survivorship (SC-PACS): Establishing a multi-institutional childhood, adolescent, and young adult cancer survivorship consortium in Southern California. Cureus 2022;14(2):e21981; doi: 10.7759/cureus .21981
18. Smith AW, Keegan T, Hamilton A, et al. Understanding care and outcomes in adolescents and young adult with Cancer: A review of the AYA HOPE study. Pediatr Blood Cancer 2019;66(1):e27486; doi: 10.1002/pbc. 27486
19. Leuteritz K, Friedrich M, Sender A, et al. Return to work and employment situation of young adult cancer survivors: Results from the Adolescent and Young Adult-Leipzig Study. J Adolesc Young Adult Oncol 2021;10(2):226–233; doi: 10.1089/jayao.2020.0055
20. Chan A, Poon E, Goh WL, et al. Assessment of psychological distress among Asian adolescents and young adults (AYA) cancer patients using the distress thermometer: A prospective, longitudinal study. Support Care Cancer 2018; 26(9):3257–3266; doi: 10.1007/s00520-018-4189-y
21. Tan CJ, Ke Y, Ng T, et al. Work- and insurance-related issues among Asian adolescent and young-adult cancer survivors: A qualitative study. Support Care Cancer 2020; 28(12):5901–5909; doi: 10.1007/s00520-020-05430-z
22. Zebrack B, Kwak M, Salsman J, et al. The relationship between posttraumatic stress and posttraumatic growth among adolescent and young adult (AYA) cancer patients. Psychooncology 2015;24(2):162–168; doi: 10.1002/pon.3585
23. Lauer AL. Treatment of anxiety and depression in adolescents and young adults with cancer. J Pediatr Oncol Nurs 2015;32(5):278–283; doi: 10.1177/1043454214563406
24. Kenney LB, Melvin P, Fishman LN, et al. Transition and transfer of childhood cancer survivors to adult care: A national survey of pediatric oncologists. Pediatr Blood Cancer 2017;64(2):346–352; doi: 10.1002/pbc.26156
25. Siembida EJ, Loomans-Kropp HA, Tami-Maury I, et al. Comparing barriers and facilitators to adolescent and young adult clinical trial enrollment across high- and low-enrolling community-based clinics. Oncologist 2022;27(5): 363–370; doi: 10.1093/oncolo/oyac030
26. The Children's Oncology group. Project:EveryChild. Available from: http://projecteverychild.org [Last accessed: June 3, 2022].

Address correspondence to:
Alexandre Chan, PharmD, MPH
Department of Clinical Pharmacy Practice
School of Pharmacy & Pharmaceutical Sciences
University of California, Irvine
Irvine, CA 92697
USA

Email: a.chan@uci.edu

Lilibeth Torno, MD
Department of Pediatric Hematology/Oncology
Hyundai Cancer Institute at Children's Healthcare of Orange County
Orange, CA 92868
USA

Email: ltorno@choc.org

Chapter 5: Implementation of an Electronic Patient-Reported Outcome-driven Symptom Management tool to Reduce Health Disparities and Improve Cancer Survivorship Care

5.1 Introductory Comments

Building on the insights gained from cancer survivors (Chapter 3) and healthcare professionals (Chapter 4) regarding unmet needs and strategies to optimize survivorship care, the following three chapters address aim 2 of the thesis, describing three clinical trials (Chapters 5 to 7). Each trial incorporates a distinct and innovative strategy aimed at addressing the specific unmet needs identified across diverse survivorship populations.

The first of these chapters focuses on ethnic and racial minority cancer survivors who are disproportionately affected by health disparities. As highlighted by both patients (Chapter 3) and providers (Chapter 4), personalized care—supported by appropriate screening tools—is essential for optimizing survivorship outcomes by early identification of symptoms. This project was undertaken as part of a broader effort to reduce health disparities and implement culturally responsive approaches to symptom management among vulnerable cancer survivors receiving care at the Chao Family Comprehensive Cancer Center. The study aimed to design and implement an intervention that could enable tailored approaches to meet the specific care needs of racial and ethnic minority cancer survivors.

5.2 Aim

To evaluate whether a multilanguage electronic patient-reported outcome (ePRO)–driven symptom management tool, led by oncology pharmacists, addresses supportive care issues among patients undergoing anticancer treatment in a racial/ethnic majority-minority cancer center.

5.3 Summary

This implementation trial, conducted among patients newly initiated on cancer treatment, yielded several important insights. First, the approach was innovative in that it shifted the traditional care paradigm by highlighting the role of oncology pharmacists in delivering personalized care through the use of ePRO. This strategy was informed by earlier observational findings from both patients and healthcare providers. Second, the use of real-time assessments and multilingual, validated tools enabled the timely identification and management of patients' unique care needs. The inclusive nature of the study—inviting all newly diagnosed patients at the infusion center to participate—resulted in a cohort that closely reflected the racial and ethnic diversity of the center's catchment area.

This inclusivity represents a meaningful step toward addressing disparities in cancer care. In summary, this chapter within the thesis demonstrates that the integration of ePRO tools, coupled with follow-up by pharmacists, facilitates the early identification of clinically significant symptoms—potentially preventing symptom escalation and improving the overall quality of survivorship care. Although the use of ePRO tools is helpful when survivors are receiving care at the cancer center, the tool may not be as effective when survivors are treated in the community. Other innovative approaches to managing cancer survivors residing in the community will be explored in a future chapter of this thesis (Chapter 7).

5.4 Publications

- **Chan A**, Ng DQ, Arcos D, Heshmatipour M, Lee BJ, Chen A, Duong L, Van L, Nguyen T, Green V, Hoang D. Electronic Patient-Reported Outcome-Driven Symptom Management by Oncology Pharmacists in a Majority-Minority Population: An Implementation Study. JCO Oncol Pract. 2024 Jul 15:OP2400050. doi: 10.1200/OP.24.00050. Epub ahead of print. PMID: 39008806.

5.5 Author's Contribution

- I conceived the idea and obtained funding from the Hematology/Oncology Pharmacy Association to conduct the study. I led the data analysis, writing, and editing of the publication. I have also supervised my undergraduate and postgraduate students and clinical trial coordinators to perform data collection, and oncology pharmacists to deliver the intervention.

Electronic Patient-Reported Outcome-Driven Symptom Management by Oncology Pharmacists in a Majority-Minority Population: An Implementation Study

Alexandre Chan, PharmD, MPH, BCOP, FCCP[1,2]; Ding Quan Ng, BScPharm(Hon)[1]; Daniela Arcos, MS[1]; Matthew Heshmatipour, BS[1]; Benjamin J. Lee, PharmD[1,2]; Alison Chen, PharmD[2]; Lan Duong, PharmD[2]; Linda Van, PharmD[2]; Thomas Nguyen, PharmD[2]; Vuong Green, PharmD[2]; and Daniel Hoang, PharmD[1,2]

DOI https://doi.org/10.1200/OP.24.00050

ABSTRACT

PURPOSE There is a lack of systematic solutions to manage supportive care issues in racial/ethnic minorities (REM) receiving treatment for cancer. We developed and implemented an electronic patient-reported outcome (ePRO)–driven symptom management tool led by oncology pharmacists in a majority-minority cancer center located in Southern California. This study was designed to evaluate the implementation outcomes of our multilevel intervention.

METHODS This was a prospective, pragmatic, implementation study conducted between July 2021 and June 2023. Newly diagnosed adult patients with cancer receiving intravenous anticancer therapies completed symptom screening using ePRO that consists of the Patient-Reported Outcomes Measurement Information System measures at each infusion visit during the study. ePRO results were presented to an oncologist pharmacist for personalized symptom management and treatment counseling. The RE-AIM framework was used to guide implementation outcomes. Differences in symptom trajectories and clinical outcomes between groups were tested using generalized estimating equations.

RESULTS We screened 388 patients of whom 250 were enrolled (acceptance rate: 64.4%), with 564 assessments being completed. The sample consisted of non-Hispanic White (NHW, 42.4%), Hispanic/Latinx (H/L, 30.8%), and non-Hispanic Asian (20.4%), with one (21.6%) of five participants preferring speaking Spanish. Compared with NHW, H/L participants had greater odds of reporting mild to severe pain interference (odds ratio [OR], 1.91 [95% CI, 1.18 to 3.08]; $P = .008$) and nausea and vomiting (OR, 2.08 [95% CI, 1.21 to 3.58]; $P = .008$), and higher rates of urgent care utilization (OR, 1.92 [95% CI, 1.04 to 3.61]; $P = .04$) within 30 days. Nausea and vomiting (n = 131, 23.2%), pain (n = 91, 16.1%), and fatigue (n = 72, 12.8%) were most likely to be intervened, with 90% of the participants expressing satisfaction across all visits.

CONCLUSION Our multilevel ePRO-driven intervention led by oncology pharmacists helps facilitate symptom assessments and management and potentially reduce health disparities among REM.

ACCOMPANYING CONTENT

Appendix

Accepted May 23, 2024
Published July 15, 2024

JCO Oncol Pract 00:1-11

View Online Article

INTRODUCTION

Studies have reported that racial and ethnic disparities can affect clinical outcomes related to symptom burden and severity, causing minoritized patients to perceive unmet needs for supportive care services.[1] These disparities persist, although supportive care is increasingly recognized as an essential component of cancer care.[2] Current solutions to improve cancer supportive care and related outcomes in racial/ethnic minorities (REM) mainly focus on targeting a specific factor in silo.[3] However, these solutions do not tackle health disparity issues on both individual and interprofessional levels and seldom engage oncology pharmacists as a resource.

Oncology pharmacists play a critical role in caring for patients with cancer as they provide education to patients and their caregivers on the respective anticancer regimen.[4] Studies have demonstrated that pharmacist-led clinical interventions improve patients' understanding of their

CONTEXT

Key Objective

Can the utilization of a multilanguage electronic patient-reported outcome (ePRO)–driven symptom management tool, led by oncology pharmacists, address supportive care issues among patients undergoing anticancer treatment in a racial/ethnic majority-minority cancer center?

Knowledge generated

Through implementing this ePRO intervention, we found that Hispanic/Latinx participants showed increased odds of reporting pain interference and nausea/vomiting compared with non-Hispanic White participants, prompting corresponding interventions by pharmacists. Across race/ethnicities, most participants expressed satisfaction with the intervention.

Relevance

The use of this monitoring tool shows potential in facilitating symptom assessment and management, which may mitigate disparities in health care outcomes among racial/ethnic minorities.

treatment and their ability to effectively manage side effects, ultimately improving quality of life and decreasing anxiety and depression.[5-7] However, early recognition of these health issues by pharmacists is often impeded by patients' limited health literacy or poor communication due to language barriers, issues that are highly prevalent among REM.[8,9] Improving early recognition of health issues among REM may also facilitate timely interventions.[10]

There are few solutions developed to improve symptom identification to reduce health disparities in newly diagnosed patients with cancer undergoing anticancer treatment. In this study, we developed and implemented a multilevel intervention involving the incorporation of electronic patient-reported outcome (ePRO) tools and active personalization to guide symptom management. We hypothesize that a multilanguage ePRO-driven symptom management tool led by oncology pharmacists will help reduce health disparities at a majority-minority county in Southern California. We also hypothesize that REM patients undergoing anticancer treatment will find the program satisfactory and acceptable.

METHODS

Study Design

This prospective, pragmatic, implementation study was conducted at the Chao Family Comprehensive Cancer Center (CFCCC) infusion unit from July 2021 to June 2023. This study was designed to evaluate a clinical intervention in a real-world setting.[11] CFCCC is located in Orange County, California, a majority-minority county (ie, >50% in terms of ethnic representation) with Hispanic/Latinx (H/L) and Asian Americans accounting for 35.0% and 21.1% of the population, respectively.[12] With such diversity, CFCCC serves as an excellent environment to evaluate interventions aimed at reducing health disparities in REM. The study protocol received ethics approval from the University of California Irvine Institutional Review Board (#2021-6431), and all study participants provided written informed consent before participation.

Eligibility Criteria

Adult patients (age ≥18 years) newly diagnosed with cancer and receiving intravenous anticancer treatment at CFCCC were selected for inclusion in the study. Eligible patients were screened through the pharmacy schedule by oncology pharmacists within the electronic health record (EHR). Patients of all race/ethnic groups were included. Patients who did not wish to perform the research procedures or were physically and/or mentally incapable of providing written consent were excluded.

Intervention

Our multilevel intervention incorporates ePRO measures to assist oncology pharmacists with symptom management in patients undergoing anticancer treatment. There were three components for our intervention (Fig 1):

1. *Screening of symptoms using ePRO:* Standardized ePRO assessments were administered through REDCap using computer adaptive tests (CAT). Patients were provided a dedicated iPad before or during their infusion and completed their assessments at their infusion chair. The ePRO comprised the Patient-Reported Outcomes Measurement Information System (PROMIS) measures developed by the National Institutes of Health. Our ePRO measured seven health domains: nausea and vomiting, physical impairment, anxiety, depression, fatigue, cognitive impairment, and pain interference. All domains were administered as CAT, except nausea and vomiting (short form of four items used; CAT version unavailable). Measures were chosen to holistically assess toxicities of treatment and physical, mental, and social health. Patients' sociodemographic characteristics, responses to individual PROMIS items,

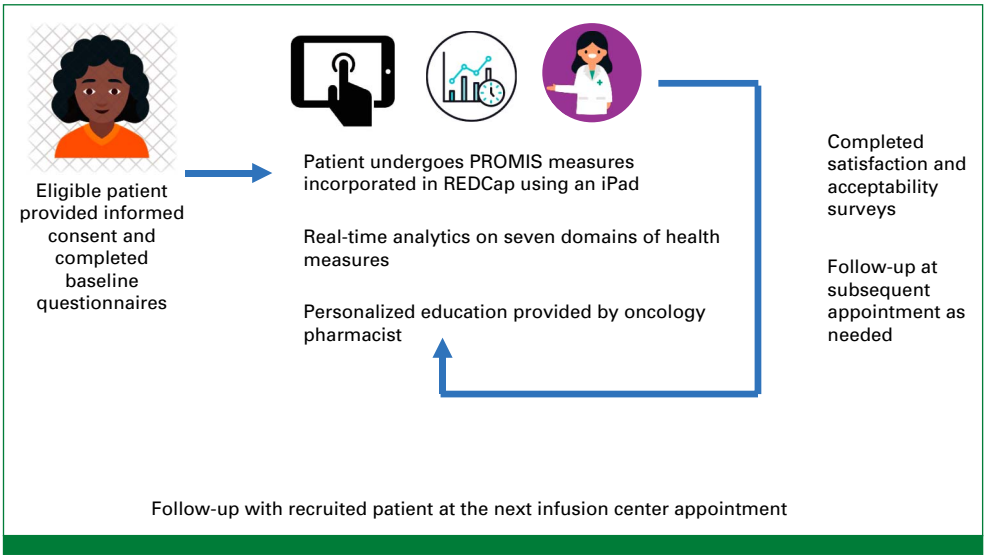

FIG 1. An overview of the study procedures. PROMIS, Patient-Reported Outcomes Measurement Information System.

and metrics of PROMIS utilization (eg, duration of completion) were also captured. Both English and Spanish versions were available. When a specific language (eg, Vietnamese or Korean) was unavailable, we engaged medical interpreters through video remote technology. After a patient completed the ePRO, raw scores were transformed to degrees of severity (normal, mild, moderate, and severe) on the basis of normative thresholds in real time.[13]

2. *Symptom management provided by trained oncology pharmacists:* An oncology pharmacist immediately reviewed the results from symptom screening and delivered personalized symptom management and treatment counseling to the patient, with content that aligns with current requirements provided by the ASCO QOPI certification program standards. Participating pharmacists attended an in-person training session to understand the workflow and to review existing care pathways. In addition, pharmacists could communicate and document treatment decisions, including ordering prescriptions, with other members of the oncology care team via the EHR.
3. *Study wrap-up and patients' follow-up:* After each visit, patients were asked about their satisfaction and acceptability of the program. Satisfaction was assessed using a single item: How satisfied are you with the counseling provided by your pharmacist? on a five-point Likert scale (very dissatisfied to very satisfied) as adapted from similar studies.[14,15] Acceptability of the length of the ePRO and education session was similarly assessed. Finally, on the basis of pharmacist's assessment of patients' symptomatology, participants would either be discharged from the study on the basis of mutual agreement or followed up at a subsequent visit. This allowed the pharmacist to provide reassessment of patients' symptoms, additional interventions, and/or counseling as necessary.

Outcomes

To assess the success of our intervention, we applied the RE-AIM framework[16] (Appendix Table A1, online only) to formulate the primary outcomes. RE-AIM guides the planning and evaluation of programs according to five key outcomes: Reach, Effectiveness, Adoption, Implementation, and Maintenance. For the secondary outcomes, we investigated differences in the following outcomes across racial/ethnic groups: (1) duration to complete ePRO, (2) symptom severity, (3) worsening and improving symptoms, (4) urgent care utilization within 30 days of assessment, (5) education delivery and patients' satisfaction, and (6) clinical interventions.

Statistical Analysis and Sample Size Calculation

All hypotheses were tested at a 5% significance level, and analysis was completed using Stata v16.1 and R v4.3.2. Descriptive statistics were used to summarize implementation science outcomes: medians and IQR or mean and standard deviations (SD) for continuous variables, and counts and percentages for categorical variables. We performed a chi-square test to compare our study's distribution of race/ethnicity with our catchment area demographics in Orange, California.[12] Four health and implementation science outcomes were compared between non-Hispanic White (NHW) participants and other racial/ethnic groups (H/L, non-Hispanic Asian [NHA], Others [OTH]):

1. Time to complete the PROMIS tool was compared between groups with linear mixed models adjusted for visit number (categorical) with random intercepts for individual participants.
2. Differences in symptom severities (proportions of mild to severe symptoms), as well as worsening and improving symptoms, between groups were tested using generalized

estimating equations (GEE) with a sandwich variance estimator, binomial family, logit link function, and an exchangeable correlation matrix, adjusted for visit number (categorical). Sources of differences were evaluated with cross-sectional logistic regression at each visit, given significant findings from GEE longitudinal analyses. Context for observed differences in symptom severities was further explored using chi-square comparisons in primary cancer diagnoses between the groups.

3. Urgent care utilization was evaluated using Poisson regression, with person-days as the offset variable.
4. Delivery of education was compared between groups in two domains: frequency of completed visits using Poisson regression and patient satisfaction with pharmacists' education using GEE analysis as described in 2.
5. Clinical interventions were descriptively evaluated, stratified by symptom types and race/ethnicity groups. The proportion of intervened visits for each symptom was compared across different race/ethnicity groups (NHW being the reference) using GEE as described in 2 and 4.

Sample size was calculated on the basis of the expected number of newly diagnosed patients at CFCCC in a single year. We anticipated that 295 patients were eligible in 1 year. With an estimated nonparticipation rate of 15%, our final sample size was 250.

RESULTS

Participant Characteristics

A total of 250 patients were recruited. Participants had a median age of 61 years, with half being female (51.6%) and NHW (42.4%). Most participants preferred speaking in English (69.6%) or Spanish (29.6%; Table 1). Reasons for stopping study participation included treatment cessation (n = 171, 68.4%), discharge by pharmacists (n = 43, 17.2%), patient declined continuation (n = 18, 7.2%), and death (n = 16, 6.4%).

Symptoms Severities

Of the 250 participants, 193 (77.2%) completed two visits, 89 (35.6%) completed three, 28 (11.2%) completed four, and four (1.6%) completed five. A total of 564 unique visits were conducted. The median (days) duration between the baseline (first visit, V1) and subsequent follow-up visits (V2, V3, V4, and V5) is as follows: 21, 43, 68, and 120 days, respectively.

Before chemotherapy initiation (V1), the counts and prevalence of mild to severe symptoms were as follows: physical impairment (n = 138, 55.4%), anxiety (n = 115, 46.3%), pain interference (n = 112, 45.3%), fatigue (n = 74, 30.0%), depression (n = 66, 26.6%), nausea and vomiting (n = 49, 19.8%), and cognitive impairment (n = 49, 19.7%). From V1 to V3, the proportions of participants with mild to severe symptoms increased for physical impairment, cognitive

TABLE 1. Sociodemographic and Clinical Characteristics of Participants (N = 250)

Characteristics	Participants (N = 250)
Age at recruitment, median (Q1, Q3)	61.0 (50.0, 70.8)
Female, No. (%)	129 (51.6)
Race/ethnicity, No. (%)	
Non-Hispanic White	106 (42.4)
Hispanic/Latinx	77 (30.8)
Non-Hispanic Asian	51 (20.4)
Other racial/ethnic groups[a]	16 (6.4)
Education attainment, No. (%)	
Less than high school	71 (28.5)
High school diploma	54 (21.7
College/associate's degree/technical school	34 (13.7)
Bachelor	60 (24.1)
Master or more	30 (12.0)
Employment before cancer diagnosis, No. (%)	
Unemployed/student/homemaker/retired/ disabled	129 (51.6)
Full-time employment	86 (34.4)
Part-time employment or freelance	24 (9.6)
Self-employed	11 (4.4)
Health insurance, No. (%)	
Private	83 (33.2)
Medicare/dual eligibility	90 (36.0)
Medicaid	66 (26.4)
Others	8 (3.2)
Own but unsure	2 (0.8)
Uninsured	1 (0.4)
Has caregiver, No. (%)	85 (34.0)
Preferred language, No. (%)	
English	174 (69.6)
Spanish	54 (21.6)
Vietnamese	13 (5.2)
Others[b]	14 (5.6)
Primary cancer, No. (%)	
Gynecological	49 (19.6)
Head and Neck	31 (12.4)
Melanoma	28 (11.2)
Breast	27 (10.8)
Upper GI[c]	26 (10.4)
Genitourinary	24 (9.6)
Lower GI[d]	23 (9.2)
Lung and Bronchus	22 (8.8)
Lymphoma	9 (3.6)
Bone	8 (3.2)
Others[e]	3 (1.2)
Metastatic disease, No. (%)	50 (20.0)
Treatment agents, No. (%)	
Cisplatin-containing	67 (26.8)
Carboplatin-containing	54 (21.6)
Doxorubicin-containing	24 (9.6)

(continued on following page)

TABLE 1. Sociodemographic and Clinical Characteristics of Participants (N = 250) (continued)

Characteristics	Participants (N = 250)
Immunotherapy combination	39 (15.6)
Immunotherapy-containing	74 (29.6)
Oxaliplatin-containing	27 (10.8)
Taxane-containing	59 (23.6)
Comorbidities, No. (%)	
Hypertension	69 (27.6)
Hyperlipidemia	42 (16.8)
Diabetes	33 (13.2)
Depression	12 (4.8)
Anxiety	11 (4.4)
Hypothyroidism	8 (3.2)

Abbreviations: n, counts; Q1, quartile 1; Q3, quartile 3.
[a]Other racial/ethnic groups include Black or African American (5), Native Hawaiian or Other Pacific Islander (3), American Indian or Alaska Native (1), Mexican (1), Filipino/Mexican (1), North African (1), Mediterranean (1), Persian (1), Middle Eastern (1), and Unknown (1).
[b]Other preferred languages include Mandarin (three participants), Korean (2), Tagalog (1), Hindi (1), Tongan (1), Russian (1), Farsi (1), Burmese (1), and Ukrainian (1).
[c]Upper GI cancers: stomach cancer, pancreatic cancer, hepatobiliary cancer.
[d]Lower GI cancers: colon cancer, rectal cancer, anal cancer.
[e]Other primary cancers include peritoneal carcinomatosis, multiple myeloma, and acute myeloblastic leukemia.

impairment, depression, fatigue, and nausea and vomiting (Appendix Fig A1).

Implementation Science Outcomes (RE-AIM)

Reach

A total of 138 patients did not enroll in the study. Common reasons for nonparticipation included lack of interest (n = 61, 44.2%), not eligible (n = 26, 18.8%), and feeling overwhelmed, stressed, tired, sick, or uncomfortable (n = 23, 16.7%). The average age of nonparticipants was 61.4 years (SD = 14.6), with an even distribution of male and female patients. None of these characteristics were significantly different from recruited patients ($P > .05$). There was also no significant difference in race/ethnicity distribution of our participants (NHW = 42.4%, H/L = 30.8%, NHA = 20.4%, OTH = 6.4%) when compared with our catchment area demographics (NHW = 38.6%, H/L = 35.0%, NHA = 21.1%, OTH = 5.3%, $P = 1.000$).

Effectiveness

Regarding participants' satisfaction with pharmacists' counseling, over 90% reported satisfied or very satisfied with their pharmacists across all visits (Table 2).

Of the 564 visits, 311 (55.1%) had one or more documented pharmacist interventions. The most intervened PROMIS-measured symptoms were nausea and vomiting (n = 131, 23.2%), followed by pain (n = 91, 16.1%), fatigue (n = 72, 12.8%), physical impairment (n = 67, 11.9%), anxiety (n = 58, 10.3%), depression (n = 24, 4.3%), and cognitive impairment (n = 15, 2.7%). A total of 153 visits (27.1%) recorded interventions of symptoms not captured by the PROMIS tool; these included neuropathy (n = 32, 5.7%), constipation (n = 23, 4.1%), diarrhea (n = 15, 4.8%), rash (n = 11, 2.0%), appetite loss (n = 9, 1.6%), and edema (n = 9, 1.6%).

The types of interventions included pharmacist education/re-education (n = 311, 100%), pharmacologic interventions (n = 107, 34.4%), and communication with other health care providers (n = 54, 17.4%).

Among 314 visits with a follow-up visit, the top three worsening symptoms were nausea and vomiting (n = 86, 27.4%), physical impairment (n = 86, 27.4%), and fatigue (n = 69, 22.0%). On the other hand, the top three improved symptoms were anxiety (n = 76, 24.2%), pain interference (n = 76, 24.2%), and physical impairment (n = 64, 20.4%).

During the study duration, there were 64 unplanned urgent care (including emergency department) visits within 30 days from PROMIS assessment; 40 (62.5%) required overnight admission. Infection-related visits were most common (n = 28, 43.8%), followed by GI complications (n = 12, 18.8%) and cardiovascular complications (n = 11, 17.2%), which were the top three reasons for unplanned medical care.

Adoption

Five pharmacists were actively involved in the program. The median (IQR) number of years of experience in oncology pharmacy was 8 (3-12) years. All participating pharmacists have professional (or greater) working proficiency in English, and three pharmacists have also reported proficiency in Vietnamese.

Implementation

Each patient participated in a median (IQR) of two (2-3) visits, and the median (IQR) duration for completion of the PROMIS tool was 7 (5-9) minutes. Over 90% of participants stated that the length of the PROMIS tool was acceptable across all visits (Table 2). The completion rate across all visits was 91.1%.

Maintenance

When asked for their opinions on the use of the PROMIS tool on every visit to the infusion center, more than 70% of participants felt that the frequency was just right across the five visits (Table 3).

TABLE 2. Patient Satisfaction and Acceptability From Visit 1 to 5 (V1-V5)

	V1 (N = 250), No. (%)	V2 (n = 193), No. (%)	V3 (n = 89), No. (%)	V4 (n = 28), No. (%)	V5 (n = 4), No. (%)
Effectiveness: How satisfied are you with the counseling (education) provided by your pharmacist?					
Very satisfied	182 (77.5)	130 (72.6)	66 (77.7)	19 (73.1)	4 (100.0)
Satisfied	51 (21.7)	48 (26.8)	19 (22.5)	7 (26.9)	0 (0.0)
Dissatisfied	1 (0.4)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Very dissatisfied	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Implementation: How do you find the length of the electronic survey tool (PROMIS tool)?					
Acceptable	219 (92.8)	166 (91.7)	81 (95.3)	25 (96.2)	4 (100.0)
Too long	15 (6.4)	14 (7.7)	3 (3.5)	1 (3.9)	0 (0.0)
Too short	2 (0.9)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Maintenance: What do you think if this electronic survey (PROMIS tool) is offered to you during every visit to the infusion center?					
Just right	192 (81.7)	136 (75.1)	67 (78.8)	22 (84.6)	3 (75.0)
Too frequent	39 (16.6)	43 (23.8)	18 (21.2)	4 (15.4)	1 (25.0)
Too infrequent	4 (1.7)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System.

Outcomes Comparison On the Basis of Racial/Ethnic Differences

Cancer Types

The distribution of primary cancer types was significantly different across race/ethnicity ($P < .001$; Table 3). The two most prevalent cancers for each group were melanoma (21.6%) and head and neck (17.9%) cancers among NHW, gynecological (29.9%) and breast (18.2%) cancers among H/L, lung and bronchus (21.6%) and gynecological (19.6%) cancers among NHA, and lung and bronchus (37.5%) and breast (25.0%) cancers among OTH (Table 3).

Duration to Complete ePRO

Compared with NHW, H/L patients spent an additional 2.2 minutes (95% CI, 1.0 to 3.4, $P < .001$), NHA patients spent an additional 1.7 minutes (95% CI, 0.3 to 3.0, $P = .016$), and OTH patients spent an additional 2.7 minutes (95% CI, 0.5 to 4.8, $P = .017$) to complete the PROMIS tool (Table 4).

Symptoms Severities

Compared with NHW, H/L participants had greater odds of reporting mild to severe pain interference (odds ratio [OR], 1.91 [95% CI, 1.18 to 3.08]; $P = .008$) and nausea and vomiting (OR, 2.08 [95% CI, 1.21 to 3.58]; $P = .008$), whereas OTH participants had greater odds of pain interference (OR, 3.17 [95% CI, 1.22 to 8.25]; $P = .018$; Table 3). The above-mentioned disparities in symptoms (nausea and vomiting, and pain interference) among H/L and OTH participants were statistically significant ($P < .05$) at V1 and V2 (Table 5).

Changes of Symptoms Over Visits

Compared with NHW, H/L (OR, 2.16 [95% CI, 1.16 to 4.00]; $P = .015$) and NHA (OR, 2.09 [95% CI, 1.06 to 4.12]; $P = .033$) participants had greater odds of reporting the worsening of pain interference symptoms. Nevertheless, H/L also reported greater odds of improving pain symptoms (OR, 2.49 [95% CI, 1.38 to 4.50]; $P = .003$) compared with NHW. We observed near significance for improving pain symptoms among NHA compared with NHW (OR, 1.83 [95% CI, 0.93 to 3.62]; $P = .080$; Table 3). Further stratified analysis found that these significant differences between the racial/ethnic groups were concentrated between V1 and V2 (Appendix Table A2).

Urgent Care Utilization

Compared with NHW, H/L and OTH participants were 1.92 times (95% CI, 1.04 to 3.61, $P = .04$) and 4.82 times (95% CI, 2.25 to 10.03, $P < .001$) more likely to receive urgent care within 30 days from assessments, respectively. OTH were associated with a higher rate of urgent care utilization with overnight admissions than NHW participants (rate ratio [RR], 3.42 [95% CI, 1.19 to 8.80]; $P = .014$; Table 3). Further analysis revealed that these disparities were largely found from V1 to V2 (Appendix Table A2).

Symptom Management and Satisfaction

Across racial/ethnic groups, pharmacists performed interventions most frequently among OTH for other symptoms, fatigue, depression, and cognitive impairment; among H/L for nausea and vomiting, pain interference, and anxiety; and among NHW for physical impairment (Appendix Fig A2). Compared with NHW participants, pharmacists were more likely to intervene for nausea and vomiting (OR, 1.93 [95%

TABLE 3. Comparison of Primary Cancer Types and Longitudinal Mild-Severe Symptoms Among Racial/Ethnic Minorities Compared With NHW Participants

Primary Cancer	NHW (n = 106)	H/L (n = 77)	NHA (n = 51)	OTH (n = 16)
	No. (%)	No. (%)	No. (%)	No. (%)
Gynecological	16 (15.1)	23 (29.9)	10 (19.6)	0 (0.0)
Head and Neck	19 (17.9)	5 (6.5)	6 (11.8)	1 (6.3)
Melanoma	24 (21.6)	3 (3.9)	0 (0.0)	1 (6.3)
Breast	4 (3.8)	14 (18.2)	5 (9.8)	4 (25.0)
Upper GI	9 (8.5)	10 (13.0)	5 (9.8)	2 (12.5)
Genitourinary	10 (9.4)	9 (11.7)	4 (7.8)	1 (6.3)
Lower GI	9 (8.5)	8 (10.4)	6 (11.8)	0 (0.0)
Lung and bronchus	4 (3.8)	1 (1.3)	11 (21.6)	6 (37.5)
Lymphoma	7 (6.6)	1 (1.3)	0 (0.0)	1 (6.3)
Bone	3 (2.8)	1 (1.3)	4 (7.8)	0 (0.0)
Others[b]	1 (0.9)	2 (2.6)	0 (0.0)	0 (0.0)

Association Analyses

Outcomes	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)
Mild to severe[c]				
Physical impairment	1.0 (ref)	1.24 (0.75 to 2.06)	1.05 (0.86 to 0.59)	2.60 (0.86 to 7.82)
Cognitive impairment	1.0 (ref)	0.93 (0.52 to 1.64)	1.12 (0.58 to 2.17)	1.89 (0.72 to 4.95)
Pain interference	1.0 (ref)	1.91** (1.18 to 3.08)	1.51 (0.85 to 2.66)	3.17* (1.22 to 8.25)
Depression	1.0 (ref)	1.28 (0.72 to 2.28)	1.47 (0.78 to 2.77)	0.88 (0.29 to 2.70)
Anxiety	1.0 (ref)	1.20 (0.73 to 1.96)	1.10 (0.62 to 1.96)	0.89 (0.39 to 2.01)
Fatigue	1.0 (ref)	0.97 (0.57 to 1.67)	1.37 (0.77 to 2.44)	1.70 (0.68 to 4.25)
Nausea and vomiting	1.0 (ref)	2.08** (1.21 to 3.58)	1.30 (0.70 to 2.41)	2.29 (0.91 to 5.75)
Worsening symptoms[c]				
Physical impairment	1.0 (ref)	1.46 (0.82 to 2.58)	1.21 (0.65 to 2.27)	0.60 (0.18 to 1.96)
Cognitive impairment	1.0 (ref)	0.84 (0.43 to 1.64)	0.94 (0.46 to 1.92)	2.12 (0.81 to 5.58)
Pain interference	1.0 (ref)	2.16* (1.16 to 4.00)	2.09* (1.06 to 4.12)	1.96 (0.70 to 5.50)
Depression	1.0 (ref)	0.91 (0.43 to 1.91)	0.88 (0.36 to 2.15)	0.62 (0.13 to 2.92)
Anxiety	1.0 (ref)	1.28 (0.60 to 2.73)	0.92 (0.40 to 2.14)	1.69 (0.51 to 5.61)
Fatigue	1.0 (ref)	1.17 (0.62 to 2.23)	1.34 (0.70 to 2.23)	1.03 (0.34 to 3.13)
Nausea and vomiting	1.0 (ref)	1.30 (0.71 to 2.38)	1.50 (0.77 to 2.89)	1.51 (0.49 to 4.70)
Improving symptoms[c]				
Physical impairment	1.0 (ref)	1.11 (0.59 to 2.10)	1.09 (0.49 to 2.41)	0.76 (0.23 to 2.54)
Cognitive impairment	1.0 (ref)	1.61 (0.72 to 3.60)	1.01 (0.40 to 2.53)	1.17 (0.27 to 5.13)
Pain interference	1.0 (ref)	2.49** (1.38 to 4.50)	1.83 (0.93 to 3.62)	0.98 (0.35 to 2.75)
Depression	1.0 (ref)	1.09 (0.49 to 2.45)	2.16 (0.99 to 4.72)	0.37 (0.05 to 2.89)
Anxiety	1.0 (ref)	1.48 (0.83 to 2.66)	1.19 (0.59 to 2.37)	0.94 (0.32 to 2.76)
Fatigue	1.0 (ref)	1.37 (0.60 to 3.16)	2.11 (0.86 to 5.16)	1.74 (0.41 to 7.49)
Nausea and vomiting	1.0 (ref)	0.94 (0.44 to 2.05)	1.45 (0.69 to 3.04)	0.76 (0.13 to 4.28)
Urgent care within 30 days from PROMIS assessment[d]	1.0 (ref)	1.92* (1.04 to 3.61)	1.11 (0.49 to 2.39)	4.82*** (2.25 to 10.03)
Urgent care with admission[d]	1.0 (ref)	1.62 (0.76 to 3.55)	1.10 (0.41 to 2.74)	3.42* (1.19 to 8.80)

Abbreviations: H/L, Hispanic/Latinx; NHA, non-Hispanic Asian; NHW, non-Hispanic White; OTH, other racial/ethnic groups; PROMIS, Patient-Reported Outcomes Measurement Information System; ref, reference group.

[a]Differences across the racial/ethnic groups were tested using the chi-square test.

[b]Other primary cancers include peritoneal carcinomatosis, multiple myeloma, and acute myeloblastic leukemia.

[c]Generalized estimating equations with a sandwich variance estimator, binomial family, logit link function, and an exchangeable correlation matrix, adjusted for visit number (categorical). Effect size was presented as odds ratio.

[d]Poisson regression, with person-days as the offset variable. Effect size was presented as rate ratio.

*P < .05, **P < .01, ***P < .001.

TABLE 4. Comparison of Implementation Science Outcomes by Race/Ethnicity

Variables	NHW (n = 106)	H/L (n = 77)	NHA (n = 51)	OTH (n = 16)	*P*
No. of visits					>.05[a]
Total	223	184	122	35	
Median per patient (Q1, Q3)	2 (1, 3)	2 (2, 3)	2 (2, 3)	2 (1.75, 3)	
PROMIS duration (in minutes)					<.05[b]
Median per visit (Q1, Q3)	6 (5, 7)	8 (6, 12)	7 (5, 9)	7 (6, 11.25)	
Satisfaction with pharmacist's education, No. (%)					<.05 (NHW *v* OTH only)[c]
Very satisfied	170 (80.2)	122 (71.8)	90 (78.3)	19 (59.4)	
Satisfied	41 (19.3)	48 (28.2)	24 (20.9)	12 (37.5)	
Dissatisfied	1 (0.5)	0 (0.0)	0 (0.0)	1 (3.1)	
Very dissatisfied	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	

Abbreviations: H/L, Hispanic/Latinx; NHA, non-Hispanic Asian; NHW, non-Hispanic White; OR, odds rartio; OTH, other racial/ethnic groups; PROMIS, Patient-Reported Outcomes Measurement Information System; Q1, quartile 1; Q3, quartile 3.

[a]Poisson regression. There is no statistically significant difference when comparing the number of completed visits per patient of H/L ($P = .201$), NHA ($P = .254$), and OTH ($P = .830$) against NHW.

[b]Linear mixed modeling, adjusted for visit number (categorical) with random intercepts for individual participants. On average, compared with NHW, H/L, NHA, and OTH groups, respectively, spent 2.2 minutes (95% CI, 1.0 to 3.4, $P < .001$), 1.7 minutes (95% CI, 0.3 to 3.0, $P = .016$), and 2.7 minutes (95% CI, 0.5 to 4.8, $P = .017$) longer to complete the PROMIS tool.

[c]Generalized estimating equations with a sandwich variance estimator, binomial family, logit link function, and an exchangeable correlation matrix, adjusted for visit number (categorical). OTH participants were less likely to rate pharmacist's education as very satisfied compared with NHW participants (OR, 0.37 [95% CI, 0.14 to 0.98]; $P = .045$). No statistically significant association was observed for H/L ($P = .203$) or NHA ($P = .584$) participants when compared with NHW participants.

TABLE 5. Association of Mild to Severe Pain Interference and Nausea and Vomiting Among Racial/Ethnic Minorities Compared With Non-Hispanic White Participants, Analyzed Cross-Sectionally From Visit 1 to 3 With Logistic Regression

Variables	Visit 1 (N = 250)	Visit 2 (n = 193)	Visit 3 (n = 89)
Race/ethnicity, No. (%)			
NHW	106 (42.4)	77 (39.9)	31 (34.8)
H/L	77 (30.8)	63 (32.6)	30 (33.7)
NHA	51 (20.4)	41 (21.2)	22 (24.7)
OTH	16 (6.4)	12 (6.2)	6 (6.7)

Cross-Sectional Logistic Regression

Outcomes	OR (95% CI)	OR (95% CI)	OR (95% CI)
Mild to severe pain interference			
Race/ethnicity			
NHW	1.0 (ref)	1.0 (ref)	1.0 (ref)
H/L	2.28** (1.25 to 4.20)	2.09* (1.06 to 4.19)	1.21 (0.43 to 3.40)
NHA	1.41 (0.71 to 2.79)	1.87 (0.86 to 4.07)	1.32 (0.43 to 4.03)
OTH	2.98* (1.03 to 9.37)	3.92* (1.13 to 15.84)	1.58 (0.26 to 9.84)
Mild to severe nausea and vomiting			
Race/ethnicity			
NHW	1.0 (ref)	1.0 (ref)	1.0 (ref)
H/L	2.73** (1.30 to 5.89)	1.71 (0.86 to 3.44)	1.39 (0.51 to 3.85)
NHA	1.41 (0.55 to 3.47)	1.63 (0.74 to 3.56)	0.84 (0.27 to 2.54)
OTH	2.19 (0.55 to 7.35)	2.08 (0.60 to 7.29)	2.43 (0.41 to 19.44)

Abbreviations: H/L, Hispanic/Latinx; NHA, non-Hispanic Asian; NHW, non-Hispanic White; OTH, other racial/ethnic groups; OR, odds ratio; ref, reference group.

*$P < .05$, **$P < .01$.

CI, 1.13 to 3.30]; $P = .017$) and pain (OR, 1.79 [95% CI, 1.03 to 3.13]; $P = .041$) in H/L participants (Appendix Fig A2).

Across the four race/ethnicity groups, the number of completed pharmacist visits did not differ (median = 2 visits for all groups, $P > .05$ for all comparisons). Although we observed little to no dissatisfied or very dissatisfied responses across groups (Table 4), OTH participants were less likely to rate pharmacist's education as very satisfied compared with NHW participants (OR, 0.37 [95% CI, 0.14 to 0.98]; $P = .045$). No association was observed for H/L ($P = .203$) or NHA ($P = .584$) compared with NHW participants.

DISCUSSION

This is one of few studies that has implemented on-site ePRO-driven symptom management in an infusion center heavily serving REM patients. Our approach is innovative as we shift the current practice paradigm by elucidating allied health professionals' role in personalizing care by leveraging ePRO. Coupled with real-time assessments, availability of translated tools, and oncology pharmacists' interventions, assessing ePRO provided opportunities to intervene for various symptoms. Our multilevel approach was found to be satisfactory, and the length of assessments was acceptable. The majority of the unplanned hospitalization and urgent care visits were infection-related, which are unlikely to be preventable through ePRO assessments. By inviting all newly diagnosed patients at the infusion center to participate, we were able to enroll a sample that mimics the racial/ethnic distribution of our catchment area. Our analysis of ePRO assessment among different REM provides information on how to enhance ePRO-guided clinical care within a majority-minority population.

There are several implications of our findings. First, although it is well known that treatment could lead to worsening of symptoms, it is also possible that patients' symptoms may be inadequately managed before receiving treatment. In both cases, our program facilitated uncovering clinically significant symptoms that necessitated timely interventions by assessing physical and psychological symptoms commonly observed in patients receiving anticancer therapies. Furthermore, other treatment-related toxicities (ie, neuropathy, constipation, diarrhea) that were not preconfigured within our ePRO were also intervened as appropriate. Second, our program facilitated pharmacist-patient discussions to mutually agree on whether stable patients could be discharged from further ePRO assessments. This allowed pharmacists to prioritize care of patients who were having inadequate symptom control, preventing a higher patient load. Although innovative, our approach requires further refinement, including investigation into whether participants discharged early from our study may benefit from assessments for future symptoms.

Our intervention builds on the scientific framework backed by the National Institute on Minority Health and Health Disparities,[17] which advocates for a multidomain and multilevel approach to address health disparity. On the individual level, the incorporation of ePRO facilitated patients' active reporting of symptoms and hence symptom identification, allowing pharmacists to address variations in health-seeking behaviors. Similarly, the avail of translated tools reduced language barriers. On the interpersonal level, the use of ePRO improved pharmacist-patient communication, enhancing relevance and person-centricity,[18] in agreement with previous findings.[19-21] The potential of ePRO to facilitate patient-centered care is essential, considering that REM are routinely experiencing poorer quality person-centered care.[22,23] This adds to the findings suggesting that the incorporation of an ePRO tool can improve early identification of symptoms and thus address health issues among REM diagnosed with cancer.

Our implementation approach has also potentially addressed health disparity issues in several ways. First, our sample's racial/ethnic distribution matched the distribution of the county in which the study took place. Second, our approach was accepted by our participants, as evidenced by patients' willingness to continue with our study throughout multiple visits at a comparable rate across racial/ethnic groups. Moreover, our results show that REM patients were more likely to report certain symptoms compared with NHW, highlighting potential disparities in symptom severity and management. In response, pharmacists provided interventions at a greater propensity for REM patients. Although we were unable to evaluate the direct impact of ePRO assessments on unplanned urgent care utilization and hospitalization due to our study design, we observed that the majority of unplanned medical care were linked to acute infections, and as such would not be preventable with ePRO assessments alone. Relatedly, REM were more likely to receive urgent care compared with NHW despite being monitored using ePRO assessments. Moving forward, it is important to consider additional strategies, such as the use of navigation[24] or remote monitoring,[25] on top of on-site symptom assessments to identify REM patients at high risk of adverse events.

Although integration of ePRO in routine care seems promising, there are several foreseeable challenges. First, patients' and providers' perceptions of the process must be considered. As such, we evaluated process indicators (ie, acceptability of the tools and sessions). Relatedly, with near-identical t-scores obtained with PROMIS short forms and CAT, we chose to use CAT to reduce time burden for patients.[26] Likewise, we are currently evaluating provider burden in a qualitative study. Second, as our ePRO tools were only available to patients while at the infusion center, pharmacists manually documented results into EHR. We hope that, in the future, ePRO tools can be integrated into the EHR and patients can complete the instrument before their appointment. Finally, we observed that REM required additional time to complete the ePRO. Unfortunately, we did

not capture technological and health literacy levels; future studies should evaluate whether ePRO is tailored adequately for populations with poorer health literacy.

In conclusion, we have successfully developed and implemented a multilevel ePRO-driven intervention that allows oncology pharmacists to intervene on patients' symptoms. In the process, we found a higher prevalence of symptoms and urgent care visits during anticancer treatment among REM compared with NHW participants. Future studies should evaluate whether such monitoring systems can prevent morbidity and mortality in REM, as well as reduce unwanted health care utilization.

AFFILIATIONS

[1]School of Pharmacy & Pharmaceutical Sciences, University of California Irvine, Irvine, CA
[2]Department of Pharmacy, Chao Family Comprehensive Cancer Center, Orange, CA

CORRESPONDING AUTHOR

Alexandre Chan, PharmD, MPH, BCOP, FCCP; e-mail: a.chan@uci.edu.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/OP.24.00050.

AUTHOR CONTRIBUTIONS

Conception and design: Alexandre Chan, Ding Quan Ng, Daniel Hoang
Financial support: Alexandre Chan
Administrative support: Alexandre Chan, Daniel Hoang
Provision of study materials or patients: Alexandre Chan, Matthew Heshmatipour, Linda Van, Vuong Green
Collection and assembly of data: Alexandre Chan, Ding Quan Ng, Daniela Arcos, Matthew Heshmatipour, Alison Chen, Lan Duong, Linda Van, Thomas Nguyen, Vuong Green, Daniel Hoang
Data analysis and interpretation: Alexandre Chan, Ding Quan Ng, Matthew Heshmatipour, Benjamin J. Lee
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the Hematology Oncology Pharmacy Association (HOPA) for providing research funding for this study. In addition, we acknowledge Dr Kaleem Anwar, Ms Gretchen Avilar, Mr Ryan Baniel, Ms Daniella Chan, Ms Mary Dagsi, Dr Yu Ke, Ms Chelsea McKinney, Ms Reem Nasr, Ms Kayleen Ports, Ms Sara Sarpas, and Dr Lari Wenzel for their assistance with this study.

REFERENCES

1. Martinez KA, Snyder CF, Malin JL, et al: Is race/ethnicity related to the presence or severity of pain in colorectal and lung cancer? J Pain Symptom Manage 48:1050-1059, 2014
2. Wagner EH, Aiello Bowles EJ, Greene SM, et al: The quality of cancer patient experience: Perspectives of patients, family members, providers and experts. Qual Saf Health Care 19:484-489, 2010
3. Santos Salas A, Fuentes Contreras J, Armijo-Olivo S, et al: Non-pharmacological cancer pain interventions in populations with social disparities: A systematic review and meta-analysis. Support Care Cancer 24:985-1000, 2016
4. Holle LM, Bilse T, Alabelewe RM, et al: International Society of Oncology Pharmacy Practitioners (ISOPP) position statement: Role of the oncology pharmacy team in cancer care. J Oncol Pharm Pract 27:785-801, 2021
5. Crespo A, Tyszka M: Evaluating the patient-perceived impact of clinical pharmacy services and proactive follow-up care in an ambulatory chemotherapy unit. J Oncol Pharm Pract 23:243-248, 2017
6. McKee M, Frei BL, Garcia A, et al: Impact of clinical pharmacy services on patients in an outpatient chemotherapy academic clinic. J Oncol Pharm Pract 17:387-394, 2011
7. Periasamy U, Mohd Sidik S, Rampal L, et al: Effect of chemotherapy counseling by pharmacists on quality of life and psychological outcomes of oncology patients in Malaysia: A randomized control trial. Health Qual Life Outcomes 15:104, 2017
8. Dilworth TJ, Mott D, Young H: Pharmacists' communication with Spanish-speaking patients: A review of the literature to establish an agenda for future research. Res Social Adm Pharm 5:108-120, 2009
9. Mohammad A, Saini B, Chaar BB: Exploring culturally and linguistically diverse consumer needs in relation to medicines use and health information within the pharmacy setting. Res Social Adm Pharm 11:545-559, 2015
10. Hurley-Kim K, Unonu J, Wisseh C, et al: Health disparities in pharmacy practice within the community: Let's brainstorm for solutions. Front Public Health 10:847696, 2022
11. Curran GM, Bauer M, Mittman B, et al: Effectiveness-implementation hybrid designs: Combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 50:217-226, 2012
12. Catchment Area. 2023. https://cancer.uci.edu/about/catchment-area
13. PROMIS® Score Cut Points. Northwestern University, 2023. https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/promis-score-cut-points
14. Frawley HC, Lin KY, Granger CL, et al: An allied health rehabilitation program for patients following surgery for abdomino-pelvic cancer: A feasibility and pilot clinical study. Support Care Cancer 28: 1335-1350, 2020
15. Garratt AM, Helgeland J, Gulbrandsen P: Five-point scales outperform 10-point scales in a randomized comparison of item scaling for the Patient Experiences Questionnaire. J Clin Epidemiol 64: 200-207, 2011
16. Glasgow RE, Vogt TM, Boles SM: Evaluating the public health impact of health promotion interventions: The RE-AIM framework. Am J Public Health 89:1322-1327, 1999
17. Alvidrez J, Castille D, Laude-Sharp M, et al: The National Institute on Minority Health and health disparities research framework. Am J Public Health 109:S16-S20, 2019
18. Cheung YT, Chan A, Charalambous A, et al: The use of patient-reported outcomes in routine cancer care: Preliminary insights from a multinational scoping survey of oncology practitioners. Support Care Cancer 30:1427-1439, 2022
19. Basch E, Barbera L, Kerrigan CL, et al: Implementation of patient-reported outcomes in routine medical care. Am Soc Clin Oncol Educ Book 38:122-134, 2018
20. Kotronoulas G, Kearney N, Maguire R, et al: What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol 32:1480-1501, 2014
21. Velikova G, Booth L, Smith AB, et al: Measuring quality of life in routine oncology practice improves communication and patient well-being: A randomized controlled trial. J Clin Oncol 22:714-724, 2004
22. 2022 National Healthcare Quality and Disparities Report. https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/nhqrdr/2022qdr-final-es.pdf

23. Azad AD, Yilmaz M, Bozkurt S, et al: Diverse patient trajectories during cytotoxic chemotherapy: Capturing longitudinal patient-reported outcomes. Cancer Med 10:5783-5793, 2021
24. Chan RJ, Milch VE, Crawford-Williams F, et al: Patient navigation across the cancer care continuum: An overview of systematic reviews and emerging literature. CA Cancer J Clin 73:565-589, 2023
25. Daly B, Nicholas K, Flynn J, et al: Analysis of a remote monitoring program for symptoms among adults with cancer receiving antineoplastic therapy. JAMA Netw Open 5:e221078, 2022
26. Segawa E, Schalet B, Cella D: A comparison of computer adaptive tests (CATs) and short forms in terms of accuracy and number of items administrated using PROMIS profile. Qual Life Res 29: 213-221, 2020

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Electronic Patient-Reported Outcome-Driven Symptom Management by Oncology Pharmacists in a Majority-Minority Population: An Implementation Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/op/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Alexandre Chan
Consulting or Advisory Role: Blueprint Medicines, Lilly, Hengrui Medicine

Thomas Nguyen
Employment: University of California, Irvine

Vuong Green
Employment: UCI Health

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Implementation Science Outcomes Defined Following the RE-AIM Framework

RE-AIM Dimensions	Explanation	Outcomes
Reach	Concerns the characteristics of the patients who are willing to participate in the program (patients' completion of the ePRO tool and clinicians' intervening on them), as well as reasons (why or why not) patients would participate	Participation rate Documented reasons for not participating in the study Comparing characteristics between participants and nonparticipants Comparing distribution of race/ethnicity of participants with catchment area demographics
Effectiveness	Concerns the impact of the program on patients at the individual and broader level (includes quality of life and economic outcomes, among others), including potential negative effects	Participants' satisfaction regarding the pharmacists' counseling Interventions completed by pharmacists Counts and proportions of worsened and improved symptoms
Adoption	Concerns intervention agents (people who deliver the program) who are willing to administer ePRO and intervene on the scores, and why or why not	Characteristics of pharmacists who administered the program
Implementation	Concerns the fidelity to the various elements of functions or components of the program, including consistency of delivery as intended, time, and cost of the implementation. Includes adaptations made to interventions and implementation	Time taken to complete the ePRO tool Participants' acceptability of the length of the ePRO tool Rate of completing all seven symptom domains across all visits Rate of urgent care utilization within 30 days of visit
Maintenance	Concerns the extent to which the program becomes institutionalized or part of the routine clinical practices. Includes perceived long-term effects of the program on outcomes (eg, in patient care)	Participants' acceptability of the frequency of completing the ePRO tool

Abbreviation: ePRO, electronic patient-reported outcome.

TABLE A2. Effectiveness Outcomes Stratified by PROMIS Visits and Compared Across Racial/Ethnic Backgrounds

	Within V1 and V2	Within V3, V4, and V5
Outcome	Ratio (95% CI)	Ratio (95% CI)
Worsened pain interference[a]		
NHW	Reference	Reference
H/L	2.96* (1.26 to 6.97)	1.21 (0.40 to 3.64)
Non-Hispanic Asian	2.77* (1.08 to 7.14)	1.18 (0.37 to 3.79)
Others	3.35 (0.85 to 13.21)	0.79 (0.11 to 5.49)
Improved pain interference[a]		
NHW	Reference	Reference
H/L	2.65* (1.15 to 6.12)	2.07 (0.81 to 5.27)
Non-Hispanic Asian	1.94 (0.74 to 5.04)	1.74 (0.65 to 4.68)
Others	(no improvement observed)	2.95 (0.74 to 11.74)
Urgent care within 30 days from PROMIS assessment[b]		
NHW	Reference	Reference
H/L	2.50* (1.25 to 5.23)	0.96 (0.23 to 4.06)
Non-Hispanic Asian	1.55 (0.63 to 3.67)	1.39 (0.33 to 5.89)
Others	7.27*** (3.23 to 16.37)	4.09 (0.81 to 18.57)
Urgent care with admission[b]		
NHW	Reference	Reference
H/L	2.22 (0.97 to 5.33)	0.96 (0.18 to 5.18)
Non-Hispanic Asian	1.38 (0.46 to 3.83)	1.39 (0.26 to 7.52)
Others	4.85*** (1.63 to 13.45)	(no admissions recorded)

Abbreviations: H/L, Hispanic/Latinx; NHW, non-Hispanic White; PROMIS, Patient-Reported Outcomes Measurement Information System.
[a]Generalized estimating equations with a sandwich variance estimator, binomial family, logit link function, and an exchangeable correlation matrix, adjusted for visit number (categorical). Effect size was presented as odds ratio.
[b]Poisson regression, with person-days as the offset variable. Effect size was presented as rate ratio.
*P < .05, **P < .01, ***P < .001.

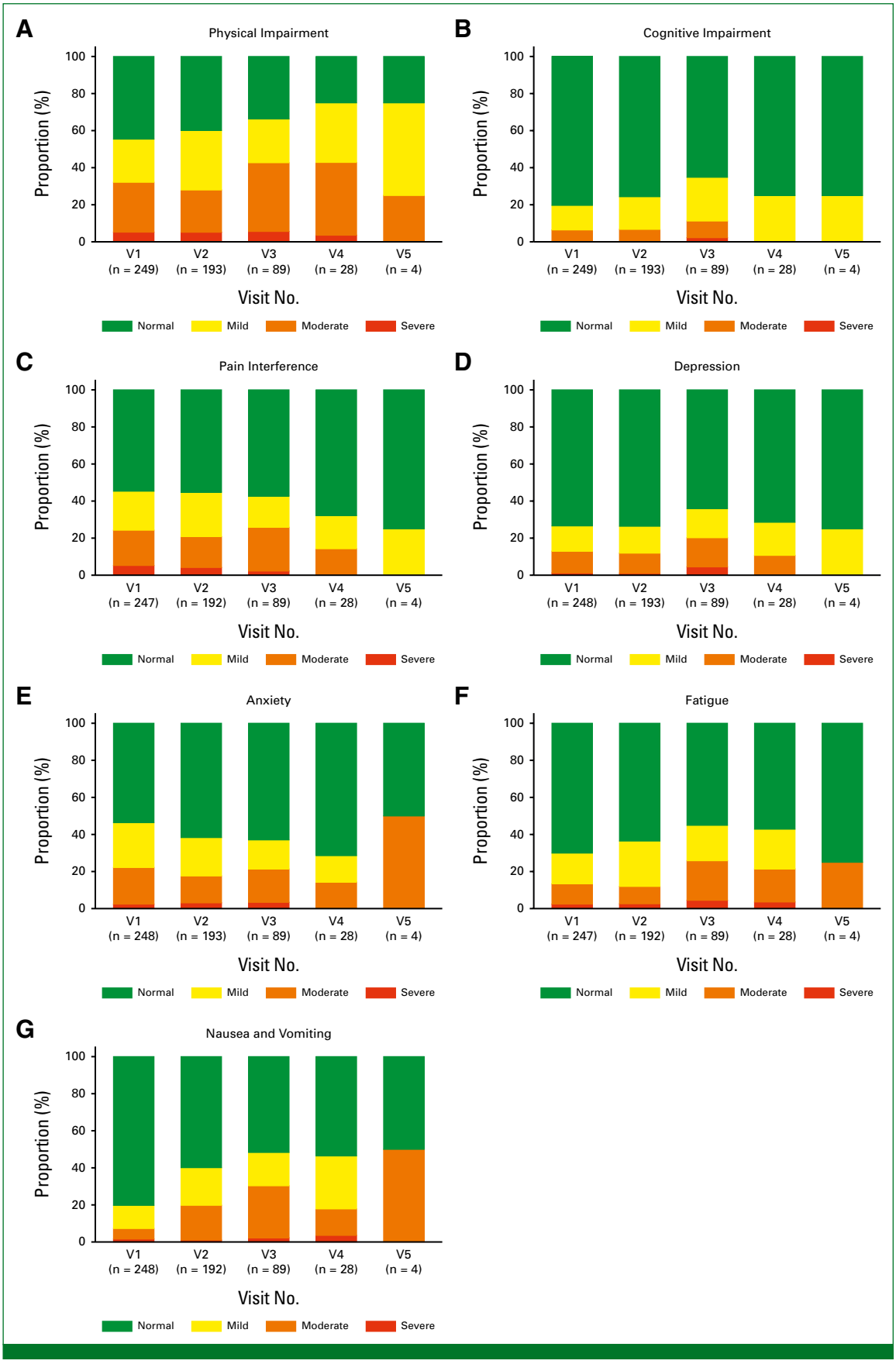

FIG A1. Symptom trajectories as captured by the PROMIS tool from visit 1 to 5 (V1-V5). PROMIS, Patient-Reported Outcomes Measurement Information System.

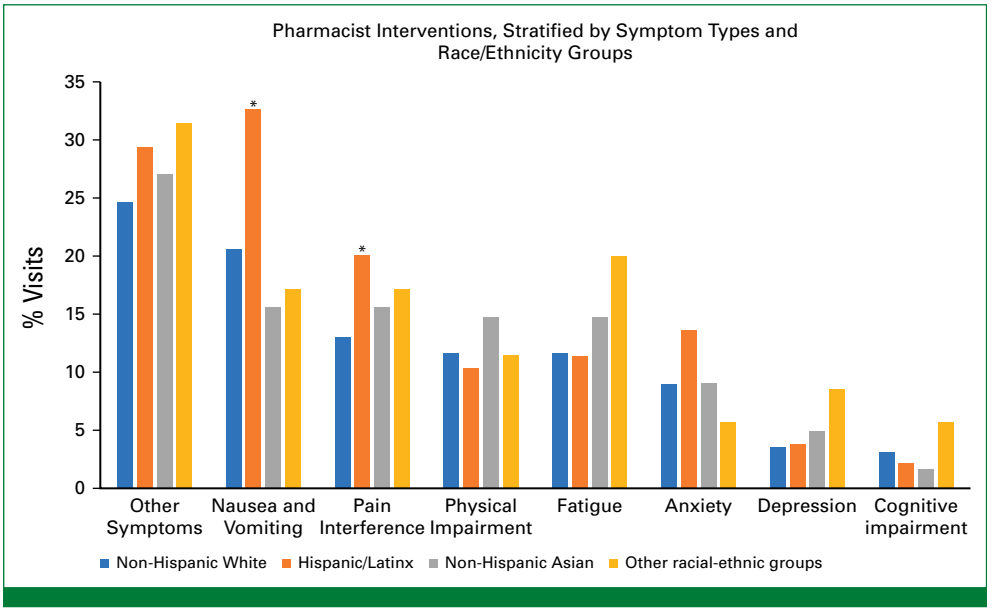

FIG A2. The proportion of visits intervened by pharmacists, stratified by symptom types and race/ethnicity groups. *P* values were calculated by testing for differences in the proportions across race/ethnicity groups (non-Hispanic White being the reference) using generalized estimating equations with a sandwich variance estimator, binomial family, logit link function, and an exchangeable correlation matrix, adjusted for visit number (categorical). *$P < .05$.

Chapter 6: Integrative Oncology as a Strategy to Improve Cancer Survivorship

6.1 Introductory Comments

Findings from Chapters 3 and 4 highlighted that physiological, emotional, and psychosocial symptoms are common among cancer survivors, especially when they are receiving treatment. Unfortunately, many of these toxicities, such as CRF and cancer-related cognitive changes, lack effective pharmacological and non-pharmacological treatment. (9) These toxicities may lead to unwanted treatment delay and/or early discontinuation, as well as reduction of patients' quality of care. TCM, one of the IO modalities, holds great promise to provide a holistic management of these symptoms in cancer survivors. To evaluate the effectiveness of TCM as an intervention, a randomized controlled trial was designed to address the efficacy of a TCM herbal regimen in managing survivors' symptoms while they are receiving chemotherapy.

6.2 Aim

To evaluate the efficacy of Xiang Bei Yang Rong Tang (XBYRT) in cancer survivors, a TCM concoction, on patients' QOL and CRF. Additionally, to evaluate the impact of XBYRT on physiological function, symptoms and safety, plasma biomarkers, and safety outcomes among cancer survivors.

6.3 Summary

Besides learning the role of XBYRT for managing CRF symptoms during cancer treatment, through this chapter we also gained several insights into how IO can enhance survivorship care. First, we demonstrated the feasibility of using an IO modality such as TCM to address unmet symptom needs in cancer survivors undergoing treatment. Second, our trial involved TCM physicians who provided ongoing monitoring for participating survivors. As highlighted by healthcare professionals in Chapter

2, the involvement of other healthcare professionals can significantly improve the conduct of survivorship trials. Third, this study shows that it is feasible to integrate innovative treatment modalities during chemotherapy, particularly when supported by a robust scientific methodology such as a randomized controlled trial (RCT). Lastly, although it was demonstrated in Chapter 5 that PRO tools can effectively capture clinically important symptoms directly from patients, the incorporation of biomarkers in randomized controlled trials can also provide objective evidence and perspectives for researchers and clinicians. The addition of objective assessment tools (such as neuropsychological assessments) may be considered in future studies, as it will also underscore the importance of integrating objective data to enhance the scientific rigor of supportive care research.

6.4 Publication

- **Chan A,** Chan D, Ng DQ, Zheng HF, Tan QM, Tan CJ, Toh JHM, Yap NY, Toh YL, Ke Y, Wang ECA, Lim QPN, Ho HK, Chew L, Tan TJ. HEalth-Related Quality of Life-Intervention in Survivors of Breast and Other Cancers Experiencing Cancer-Related Fatigue and Associated Cognitive Symptoms Using TraditionAL Chinese Medicine: The 'HERBAL' Trial. *Integr Cancer Ther* 2025 Jan-Dec;24:15347354251314514. doi: 10.1177/15347354251314514. PMID: 39840742.

6.5 Author's Contribution

- I conceived the research idea and obtained funding through the Ministry of Health grant call in 2018. I have also worked with my team to source for the appropriate investigational products (both TCM and matching placebo). In terms of the clinical trial, I have conceived the design of the trial, conducted the data analysis, manuscript writing, and editing of the publication. In addition, I supervised and trained my research team (undergraduate and postgraduate students, post-doctoral scientist and research coordinators) to coordinate the data collection and preparation of the intervention for the study.

Research Article

Integrative Cancer Therapies
Volume 24: 1–12

DOI: 10.1177/15347354251314514
journals.sagepub.com/home/ict
Sage

HEalth-Related Quality of Life-Intervention in Survivors of Breast and Other Cancers Experiencing Cancer-Related Fatigue and Associated Cognitive Symptoms Using TraditionAL Chinese Medicine: The 'HERBAL' Trial

Alexandre Chan, PharmD[1*], Daniella Chan, BS[1*], Ding Quan Ng, BSPharm[1*], Huang Fang Zheng, MD[2], Quan Ming Tan, MCM[2], Chia Jie Tan, PhD[3], Jolene Hui Min Toh, BS[4], Ning Yi Yap, PhD[5], Yi Long Toh, PhD[4], Yu Ke, PhD[6], Edmund Chun Ann Wang, BS[6], Queenie Pei Ni Lim, BSocSc[6], Han Kiat Ho, PhD[4], Lita Chew, MMS[4], and Tira J. Tan, MBBS[6]

Abstract

Introduction: As pharmacological strategies remain limited for relieving fatigue and associated cognitive symptoms, integrative modalities such as traditional Chinese medicine (TCM) could be explored as therapeutic strategies in cancer survivors. Here, we evaluate and report the efficacy and safety of a TCM concoction, modified Xiang Bei Yang Rong Tang (XBYRT), on quality of life (QOL), cancer-related fatigue (CRF), and cognitive symptoms, compared to placebo. **Methods:** In a single-centered, randomized, double-blinded, placebo-controlled pilot trial conducted from 2019 to 2022, fatigued cancer survivors ≥21 years old were recruited to receive the XBYRT intervention or placebo (5% diluted) once daily for the duration of 8 weeks. Patient-reported outcomes for QOL, CRF, cognition, blood samples for biomarker testing, and adverse events were collected at baseline (T0), 4 weeks (T1), 8 weeks (T2), and 10 weeks (T3) after baseline. Linear regression was performed to evaluate differences between groups at T2 and T3. **Results:** A total of 1502 patients were screened, with 672 patients considered eligible. Of the eligible, 15 XBYRT and 13 placebo subjects with similar mean ages (58.5 vs 58.4) were recruited. Both groups were predominantly Chinese (93% vs 62%), breast cancer patients (87% vs 62%), and diagnosed with stage 2 cancer (60% vs 46%). Although no significant difference was found in QOL between groups, the XBYRT group exhibited improved emotional fatigue at T3 ($P = .045$) and higher BDNF levels at T2 ($P = .047$) and T3 ($P = .029$). After baseline adjustment, XBYRT was associated with better perceived cognitive impairment at T2 ($P = .011$) and T3 ($P = .017$), as well as overall perceived cognitive function at T3 ($P = .028$). XBYRT is well tolerated, with grade 3 adverse events reported in three XBYRT (20%) and two placebo (15%) subjects. **Conclusion:** In this pilot study, XBYRT as an integrative therapy is safe and generates encouraging improvements in cognitive and fatigue symptoms. Difficulties with recruitment limited the generalizability of trial findings, thus findings should be verified through a larger, multi-centered trial.

Keywords

cancer-related fatigue, traditional Chinese medicine, Xiang Bei Yang Rong Tang, integrative oncology, cancer-related cognitive impairment, quality of life

Submitted August 12, 2024; revised December 10, 2024; accepted January 6, 2025

Introduction

Cancer patients are surviving longer due to advances in diagnosis and treatment. However, they are now faced with wide-ranging debilitating toxicities as a consequence of these treatments, some lasting years after treatment cessation. Cancer-related fatigue (CRF), occurring in up to 85% of cancer survivors,[1] is characterized by a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness that negatively impacts quality of life (QOL). The lasting impact of CRF was evident in up to 52% of cancer survivors 3-years post diagnosis,[1] and 42% of working cancer survivors.[2] Despite these consequences, there is limited understanding of the underlying pathogenesis and pharmacological treatments remain investigational with limited efficacy.

Consequently, many cancer survivors seek complementary and alternative medicine to address general health and symptoms that persist despite conventional treatments, of which traditional Chinese medicine (TCM) is commonly used in Asia.[3-5] We have designed a concoction in collaboration with certified TCM practitioners, namely Xiang Bei Yang Rong Tang (香贝养荣汤, XBYRT), which contains 15 herbal components (Table 1) aimed at improving patients' QOL and reducing CRF and associated symptoms. Notably, the concoction contains *Radix Astragali seu Hedysari and Rhizoma Atractylodis*,[6] which are known to improve fatigue, and C*odonopsis Pilosula*,[7] which is frequently used to ameliorate chronic fatigue syndrome. Other individual herbal components such as *Fructus Lycii*, *Fructus Ligustri Lucidi*, and *Fructus Alpinia*, have demonstrated neuroprotective effects by reducing the accumulation of reactive oxygen species, a known contributor to the pathogenesis of neurogenerative diseases.[8-10] Additionally, extracts of *Radix Polygalae*[11] show neuroprotective effects against oxidative stress and apoptosis, while also improving nerve growth, neuronal plasticity, neurotransmitter reuptake, and neurogenesis, likely by increasing brain-derived neurotrophic factor (BDNF) expression via regulation of the cyclic AMP-responsive element-binding protein (CREB)-dependent pathway.[12] In our in-vitro toxicology studies, XBYRT has a favorable toxicity profile and drug interaction profile.[13]

To evaluate the efficacy of XBYRT in cancer survivors, we have conducted a randomized controlled pilot trial on patients' QOL and CRF, with the goal to evaluate its role as an integrative oncology modality. Additionally, to evaluate its impact on physiological function, symptoms and safety, we also aim to compare the perceived cognitive function, plasma biomarkers and safety outcomes to comprehensively quantify the impact of XBYRT on cancer survivors.

Methods

This manuscript was prepared following the CONSORT 2010 statement (Supplemental Table S1).

Trial Design

The study was a randomized, double-blinded, placebo-controlled, parallel trial, conducted from October 2019 to October 2022 (ClinicalTrials.gov: NCT04104113, September 26, 2019). The study received SingHealth Centralized Institutional Review Board (IRB) approval (CIRB No.: 2019/2135) and the protocol was previously published.[14]

Participants

We recruited cancer survivors through oncologist referral at the National Cancer Centre Singapore (NCCS). Eligible participants were ≥21 years old, reported a fatigue screen score of ≥4 in the past 7 days (0, no fatigue; 10, worst fatigue) as recommended by ASCO cancer-related fatigue guidelines,[15] had completed surgery, chemotherapy, or radiotherapy and were not planned on receiving adjuvant therapy during the study period, except for aromatase inhibitors or ovarian suppression for breast cancer survivors. Patients with metastases, cancer recurrence, untreated fatigue-causing co-morbidities, on fatigue-inducing medications, taking warfarin, receiving or planning to receive TCM treatment, or breastfeeding or intending to conceive were excluded. Certified TCM physicians also screened the

[1]University of California Irvine, Irvine, CA, USA
[2]Singapore Thong Chai Medical Institution, Singapore, Singapore
[3]University of Utah, Salt Lake City, UT, USA
[4]National University of Singapore, Singapore, Singapore
[5]Subang Jaya Medical Centre, Subang Jaya, Malaysia
[6]National Cancer Centre Singapore, Singapore

*Co-first authors.

Corresponding Authors:
Alexandre Chan, School of Pharmacy and Pharmaceutical Sciences, University of California Irvine, 802 West Peltason Drive, Irvine, CA 92697-4625, USA.
Email: a.chan@uci.edu

Tira J. Tan, Division of Medical Oncology, National Cancer Centre, 30 Hospital Boulevard, Singapore 168583, Singapore.
Email: tira.tan.j.y@singhealth.com.sg

Table 1. Formula and Components of the Modified Xiang Bei Yang Rong Tang Decoction.

Chinese name	Chinese name (Pinyin)	Scientific name	Dosage (g)	Purported effect
黄芪	Huang Qi	*Radix Astragali seu Hedysari*	15	Augments Qi and raises Yang, augments defensive-Qi, consolidates the superficies, promotes drainage of pus and healing, facilitates water movement and reduces swelling
党参	Dang Shen	*Radix Codonopsis pilosulae*	15	Tonifies the middle-jiao, augments Qi and generates fluids and blood
白术	Bai zhu	*Rhizoma Atractylodis macrocephalae*	12	Augments Qi, strengthens the spleen, dries dampness, promotes diuresis, stops sweating
茯苓	Fu Ling	*Poria*	15	Drains water, dissipates dampness, strengthens the spleen and calms the mind
白芍	Bai shao	*Radix Paeoniae alba*	15	Nourishes blood, retains Yin, soothes the liver and relieves pain, and stops excessive perspiration
枸杞子	Guo Qi zi	*Fructus Lycii*	12	Nourishes the liver and kidney, clears the eyes and moistens the lung
女贞子	Nü Zhen Zi	*Fructus Ligustri lucidi*	12	Tonifies the liver and kidney, cools heat and clears the eye
车前子	Che Qian Zi	*Plantago asiatica*	12	Induces diuresis, drain dampness, improve vision and resolve phlegm
鸡内金	Ji Nei Jin	*Endothelium Corneum gigeriae Galli*	10	Promotes digestion and invigorate spleen, arrest seminal emission and relieve enuresis
生麦芽	Shen Mai Ya	*Hordeum vulgare L.*	15	Promotes digestion and invigorate spleen, stop lactation and release distension
益智仁	Yi Shin Ren	*Fructus Alpinia oxyphylla*	10	Tonifies kidney yang, secure essence and reduce urination, warm spleen yang, improve appetite and reduce salivation
香附	Xiang Fu	*Rhizoma Cyperi*	10	Unblocks the liver and regulates Qi, regulates menstruation and stops pain
远志	Yuan Zhi	*Radix Polygalae*	10	Stabilizes the heart and calms the mind, dissolves phlegm and opens orifices, and reduces abscesses and swelling
浙贝母	Zhe bei mu	*Bulbus Fritillariae thunbergii*	10	Clears heat and resolves phlegm, disperses masses/abnormal growth and promotes the healing of carbuncles
土茯苓	Tu Fu Ling	*Smilax glabra Roxb*	15	Removes toxicity, excrete dampness and ease joint movement

potential participants to ensure patient eligibility to receive the concoction based on the TCM syndrome differentiation. According to TCM principles, satisfaction of the TCM syndrome differentiation involves the deficiency of qi and blood by experiencing either: (1) two major symptoms with typical pulse and tongue conditions or (2) one major symptom and two possible symptoms with pulse and tongue conditions (Supplemental Table S2). The National Standard in People's Republic of China and the Clinical Practice Guidelines of Chinese Medicine in Oncology currently endorses this method of condition identification.[16]

Intervention

Study participants were randomized to either the XBYRT or placebo arms, and participants were given investigational products prepared as granules designed to be dissolved in hot water for once daily consumption for 8 weeks. In the XBYRT arm, participants received a 24 g daily dosage, selected based on the safety and efficacy guidelines from the *Pharmacopoeia of the People's Republic of China and Chinese Materia Medica Textbook for Higher Education*[17,18] (Table 1). The placebo granules comprised 5% of the herbal components, 95% maltodextrin, 0.002% denatonium benzoate as bitterant and colorant to ensure that its taste and smell is similar to XBYRT treatment while minimizing therapeutic effect. Participants were reminded to take their daily dosages and record missed dosages. The granules were manufactured by Kinhong Pte Ltd., Singapore, a Good Manufacturing Practices-certified manufacturer.

To advise on safe concomitant administration with medications, we had previously evaluated the potential interaction of XBYRT with the activities of CYP3A4 and CYP2D6 and found that the herbal components did not inhibit the CYP enzymes. Further, resulting liver cell viability demonstrated that XBYRT is not likely to cause hepatotoxicity.[13]

Assessments

Before treatment initiation, participants' demographics, cancer diagnosis, medical history, and concomitant medications

were recorded. Questionnaires, blood draws and safety monitoring were completed at four time points: baseline (T0) and 4 weeks (T1), 8 weeks (T2), and 10 weeks (T3) after baseline. Pulse conditions were also assessed at four time points to ensure patient safety. Due to the COVID-19 pandemic, subsequent pulse assessments were conducted through teleconsultations (phone or video call) or to be omitted. Based on Singapore's TCM Practitioners Board guidelines, while the first visit must be in person, follow ups can be virtual.

Quality of life (QOL). Health-related QOL was measured using the global health status (GHS) domain of the EORTC Core Quality of Life questionnaire (EORTC QLQ-C30) questionnaire. A higher score indicated higher QOL.

Cancer-related fatigue (CRF). The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) measures CRF across five subscales: general, physical, emotional fatigue, and mental fatigue, and vigor. Except for the vigor subscale, higher scores in each domain represented more fatigue. An overall score was obtained by combining subscale scores (subtracting vigor scores), with higher scores indicating worse fatigue symptoms. We have previously performed a study to evaluate the psychometric properties and measurement equivalence of the English and Chinese versions of MFSI-SF in breast cancer and lymphoma patients in Singapore.[19]

Perceived cognition. Perceived cognitive function was assessed using the FACT-Cog v3, which produced four subscales' scores: perceived cognitive impairment (CogPCI), perceived cognitive abilities (CogPCA), impact of perceived cognitive impairment on QOL (CogQOL), and comment from others on cognitive function (CogOTH). Totaling the subscale scores generated the total score, with better perceived cognition indicated by higher scores. We have previously evaluated the psychometric property and measurement equivalence of the English and Chinese versions of FACT-Cog v3 among breast cancer patients in Singapore.[20]

Safety monitoring. Safety was assessed through patient reports and blood tests evaluating toxicities to organ functions (eg, renal and liver function tests, full blood count, and electrolyte level). Adverse events (AEs) were recorded and graded by research nurses using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Blood plasma processing and storage. A 9 mL blood sample was collected in ethylenediaminetetraacetic acid tubes. Subsequently, it was then centrifuged for 10 minutes at $1069 \times g$ at 4ºC. Aliquots of plasma and buffy coat were stored at −80ºC until analysis.

Inflammatory cytokines. Plasma levels of interleukin (IL)-2, IL-4, IL-6, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, and tumor necrosis factor (TNF)-α, were quantified using 50 µL of each sample with a highly sensitive multiplex immunoassay (Bioplex Human Cytokine 9-Plex Panel, Bio-Rad, USA).

Plasma brain-derived neurotrophic factor (BDNF) levels. We quantified BDNF levels with an enzyme-linked immunosorbent assay (ELISA) kit (Biosensis BEK-2211-1P/2P, Australia) using 100 µL of sample diluted 100-fold.

BDNF Val66Met genotyping (rs6265). Genomic DNA was isolated from the buffy coat with QIAmp DNA Blood Mini Kit (Qiagen, Germany) and was polymerase chain reaction (PCR) amplified with forward primers (5′-GGACTCTGGAGAGCGTGAA-3′) and reverse primers (5′-CGTGTACAAGTCTGCGTCCT-3′). PCR products genotyping was completed by automated Sanger sequencing with a 3730xl DNA Analyzer (Applied Biosystems, USA).

Outcomes

Our primary endpoint was the difference of QOL scores between treatment and control groups, hence the primary analysis involved comparing the T2 and T3 GHS scores between the treatment and control groups. Secondary analyses included comparing MFSI-SF and FACT-Cog total and subscale scores, plasma BDNF and cytokine levels, at T2 and T3, as well as prevalence of AEs between the two arms. Exploratory outcomes included the association of the biomarkers with patient-reported outcomes (PROs).

Sample Size

To ensure an adequate sample size to inform a future phase III trial design, we aimed to recruit 80 subjects (40 per arm) as recommended by Teare et al.[21] after accounting for a 10% dropout rate.

Randomization

Block randomization with a block size of 10 was performed by a third-party clinical trial service provider using the sealed envelope method. The physicians, trial pharmacists, study team, and study participants were blinded to the block size, randomization sequence and treatment assignment.

Statistical Methods

Baseline characteristics were descriptively summarized using counts and percentages for categorical variables, and means and standard deviations (SD) for continuous variables. Differences in all outcomes were tested at T2

and T3 using linear regression with or without baseline adjustment. Further sensitivity analysis was performed for significant outcomes by adjusting for rs6265 genotypes which are known to influence patient outcomes.[22] All analyses were two-tailed, tested at 5% significance level, and conducted on R version 4.3.2.

Results

Participants

A total of 1502 cancer survivors were screened for eligibility between October 2019 to October 2022, of which 830 were ineligible as they were either not fatigued (n = 678) or met exclusion criteria (n = 152). Of the 672 that were eligible, 28 survivors entered the trial. The rest of the survivors did not enroll for the following reasons: not interested (n = 512), too busy or had procedure concerns (n = 87), were considering participation but did not get back to research personnel (n = 33), and other reasons (n = 12; Figure 1).

Fifteen XBYRT and 13 placebo subjects with comparable mean ages (58.5 vs 58.4) were recruited (Table 2). Both groups mainly consisted of Chinese (93% vs 62%), breast cancer patients (87% vs 62%) and stage II cancer diagnoses (60% vs 46%). Surgery, chemotherapy, and radiotherapy were the most common treatment modalities in both groups. There was a lower proportion of rs6265 Met carriers among the XBYRT arm compared to placebo (47% vs 77%). We observed no difference between the two groups for all PROs and continuous biomarkers at baseline (all $P > .05$, Supplemental Tables S3 and S5). Recruitment was hindered as the trial was conducted during the COVID-19 pandemic starting in 2020, resulting in delays, and ultimately had to close prior to achieving the planned sample size due to funding issues.

QOL, CRF, and Perceived Cognition

Descriptively, a widening gap between the XBYRT and placebo groups was observed for all PRO (Figure 2 and Supplemental Table S3) over the course of the trial. However, we found no difference in GHS scores (primary endpoint) at T2 and T3 between the groups (Supplemental Tables S3 and S4).

Regarding CRF, the XBYRT arm demonstrated better emotional fatigue symptoms at T3 ($P = .045$, $\beta = -3.82$, 95% CI = −7.53 to −0.10) (Supplemental Table S3). Statistical significance was not reached at other timepoints nor other MFSI-SF subscales.

Regarding perceived cognition, no difference was detected in the FACT-Cog subscales across all time points between the two groups. However, after adjusting for baseline, the XBYRT group exhibited better perceived cognitive function, represented by CogPCI, at T2 ($P = .011$, $\beta = 8.27$, 95% CI = 2.07 to 14.5) and T3 ($P = .017$, $\beta = 8.97$, 95% CI = 1.77 to 16.2) (Supplemental Table S4). Moreover, a better total FACT-Cog score at T3 ($P = .028$, $\beta = 15.4$, 95% CI = 1.86 to 29.0) was exhibited amongst the XBYRT group.

Biomarkers

The XBYRT group demonstrated significantly higher BDNF levels (in pg/mL) at T2 ($P = .047$, $\beta = 5598$, 95% CI = 94 to 11 103) and T3 ($P = .029$, $\beta = 4010$, 95% CI = 452 to 7570) (Supplemental Table S5), although statistical significance was not achieved after baseline adjustment. No statistical significance was found for other biomarkers (Supplemental Table S5 and S6).

Sensitivity Analysis: Adjusting for rs6265 Genotypes

In a sensitivity analysis adjusting for rs6265 genotypes (Val/Val vs Met carriers), FACT-Cog CogPCI and total scores at T3 (after baseline adjustment), and BDNF levels at T2 and T3 remained significantly higher among XBYRT ($P < .05$, data not reported). In these models, Met carriers scored significantly lower in FACT-Cog total scores at T3 ($P = .049$, $\beta = -14.9$, 95% CI = −29.7 to −0.04).

Safety

In the XBYRT arm, grade 3 adverse events were reported in three patients (20%): one experienced insomnia at T1; the second patient experienced insomnia and headache at T1; the third experienced headache at T2. In the placebo arm, two subjects (15%) experienced grade 3 adverse events: one experienced constipation at T1; the second patient experienced insomnia (T1 and T2), dry mouth (T2 and T3), and flushing (T2 and T3). Safety findings are summarized in Supplemental Table S7.

Exploratory Analysis: BDNF-PRO Spearman Correlation Analysis

Because XBYRT treatment appears to influence emotional fatigue, perceived cognition and BDNF levels, an exploratory Spearman correlation analysis was conducted to explore the relationship between BDNF and the various PROs. Within the XBYRT group, increase in BDNF levels is significantly associated with the increase in FACT-Cog CogPCI and total scores, from T0 to T3 ($P < .05$, Figure 3). No other statistically significant relationships were observed.

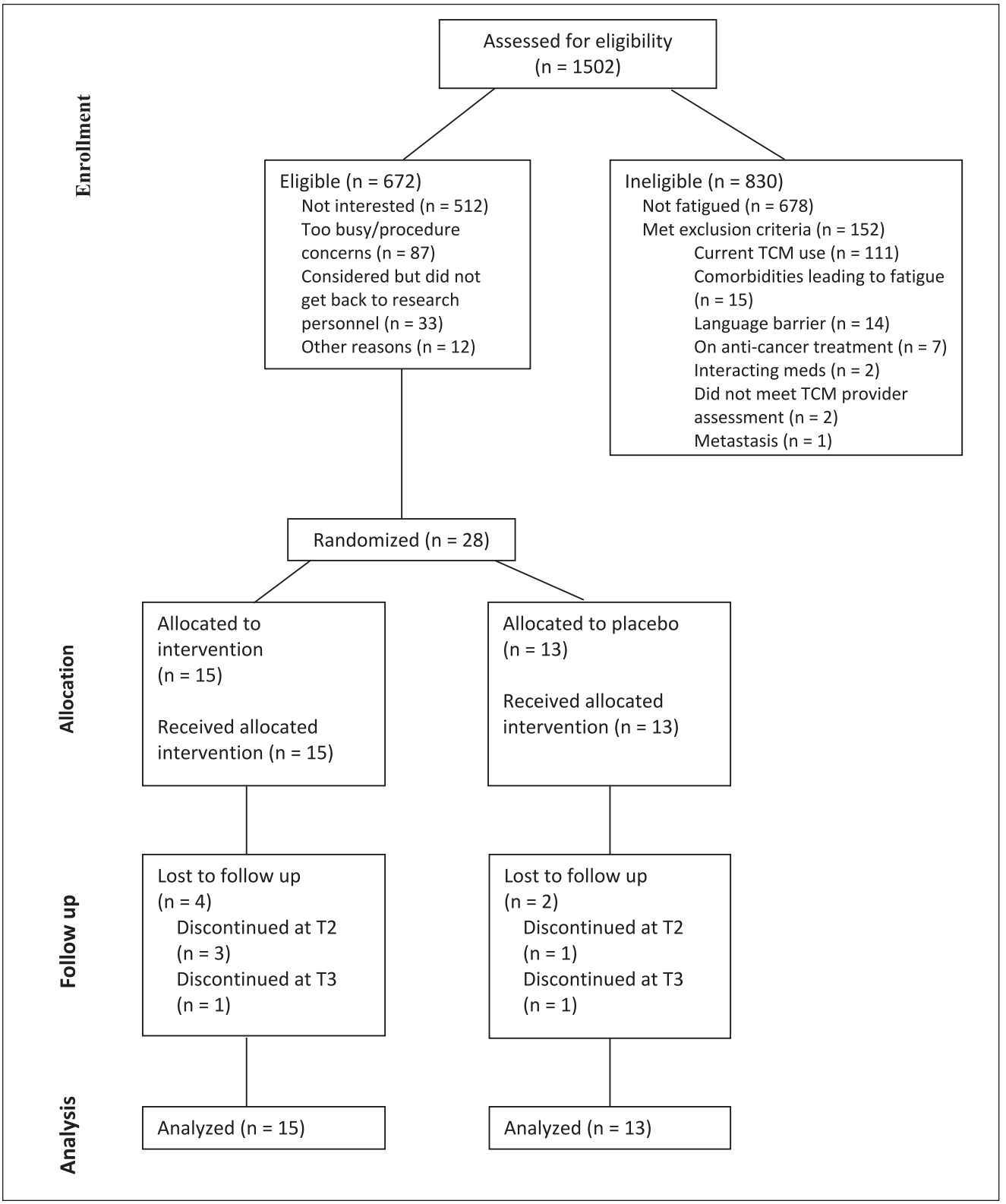

Figure 1. Subject CONSORT diagram.

Table 2. Baseline Characteristics of XBYRT and Placebo Groups.

Variables	XBYRT group (N = 15)	Placebo group (N = 13)
Age at survey		
Mean (SD)	58.5 (6.3)	58.4 (10.0)
Sex, n (%)		
Male	0 (0.0)	1 (7.7)
Female	15 (100.0)	12 (92.3)
Race/ethnicity, n (%)		
Chinese	14 (93.3)	8 (61.5)
Indian	0 (0.0)	2 (15.4)
Malay	0 (0.0)	1 (7.7)
Other	1 (6.7)	2 (15.4)
BMI		
Mean (SD)	25.4 (4.5)	25.8 (4.9)
Menopausal state, n (%)		
Pre-menopausal	1 (6.7)	2 (15.4)
Post-menopausal	14 (93.3)	10 (76.9)
Male	0 (0.0)	1 (7.7)
Cancer type, n (%)		
Breast	13 (86.7)	8 (61.5)
Lymphoma	0 (0.0)	2 (15.4)
Endometrial	1 (6.7)	0 (0.0)
Pancreatic	0 (0.0)	1 (7.7)
Ovarian	0 (0.0)	1 (7.7)
Lung	1 (6.7)	0 (0.0)
Uterine	0 (0.0)	1 (7.7)
Cancer stage, n (%)		
I	3 (20.0)	4 (30.8)
II	9 (60.0)	6 (46.2)
III	3 (20.0)	3 (23.1)
Education level, n (%)		
Primary	1 (6.7)	0 (0.0)
Secondary	6 (40.0)	6 (46.2)
Pre-university	1 (6.7)	1 (7.7)
Graduate/postgraduate	7 (46.7)	6 (46.2)
Employed, n (%)		
Yes	9 (60.0)	5 (38.5)
No	6 (40.0)	8 (61.5)
ECOG, n (%)		
0	15 (100.0)	11 (84.6)
1	0 (0.0)	2 (15.4)
Treatment received, n (%)		
Radiotherapy	10 (66.7)	7 (53.9)
Chemotherapy	9 (60.0)	13 (100.0)
Targeted therapy	3 (20.0)	4 (30.8)
Hormonal therapy (completed)	4 (26.7)	1 (7.7)
Hormonal therapy (ongoing)	4 (26.7)	4 (30.8)
Surgery	15 (100.0)	11 (84.6)
Comorbidities, n (%)		
Hyperlipidemia	3 (20.0)	3 (23.1)
Hypertension	2 (13.3)	3 (23.1)
Insomnia	2 (13.3)	2 (15.4)
Hyperthyroidism	1 (6.7)	0 (0.0)
Hypothyroidism	0 (0.0)	3 (23.1)
Diabetes	1 (6.7)	1 (7.7)
Depression	0 (0.0)	2 (15.4)
EORTC QLQ-C30, mean (SD)		
GHS score	53.3 (14.7)	51.3 (21.5)
MFSI-SF, mean (SD)		
General scale	12.4 (5.2)	11.2 (5.8)
Physical scale	10.2 (4.7)	8.8 (4.5)
Emotional scale	5.7 (4.5)	7.0 (3.9)
Mental scale	7.2 (5.1)	7.0 (3.9)
Vigor scale	10.0 (4.1)	10.1 (4.5)
Total score	25.5 (19.3)	23.9 (18.2)
FACT-Cog, mean (SD)		
Cog-PCI	50.4 (16.2)	52.9 (14.8)
Cog-QOL	10.2 (4.5)	8.8 (3.8)
Cog-Oth	14.5 (2.0)	14.8 (2.0)
Cog-PCA	16.7 (5.4)	15.8 (6.9)
Total score	94.4 (23.0)	92.2 (24.3)
BDNF SNP rs6265, n (%)		
Val/Val	7 (46.7)	3 (23.1)
Met carriers (Val/Met, Met/Met)	7 (46.7)	10 (76.9)
Unknown	1 (6.7)	0 (0.0)
Plasma biomarkers, mean (SD)		
BDNF (pg/mL)	5725.4 (7513.7)	2722.5 (4299.5)
IL-2 (pg/mL)	0.8 (0.9)	0.3 (0.4)
IL-4 (pg/mL)	0.1 (0.3)	0.0 (0.0)
IL-6, (pg/mL)	0.5 (0.3)	0.8 (1.2)
IL-8 (pg/mL)	3.05 (1.37)	2.95 (1.42)
IL-10 (pg/mL)	1.0 (0.5)	1.0 (0.4)
GMCSF (pg/mL)	0.0 (0.1)	0.0 (0.0)
IFNg (pg/mL)	0.9 (0.5)	0.9 (0.5)
TNFα (pg/mL)	10.8 (5.3)	12.9 (5.7)

Abbreviations: BDNF, brain-derived neurotrophic factor; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—C30; FACT-Cog, fatigue assessment of cancer therapy—cognitive function; GHS, global health score; GMCSF, granulocyte-macrophage colony-stimulating factor; IFNg, interferon gamma; IL, interleukin; MFSI-SF, multidimensional fatigue symptom inventory—short form; PCA, perceived cognitive abilities; PCI, perceived cognitive impairments; Q, quartile; QOL, quality of life; SD, standard deviation; SNP, single nucleotide polymorphism; T0, timepoint 0; T1, timepoint 1; T2, timepoint 2; T3, timepoint 3; TNFα, tumor necrosis factor alpha; XBYRT, Xiang Bei Yang Rong Tang.

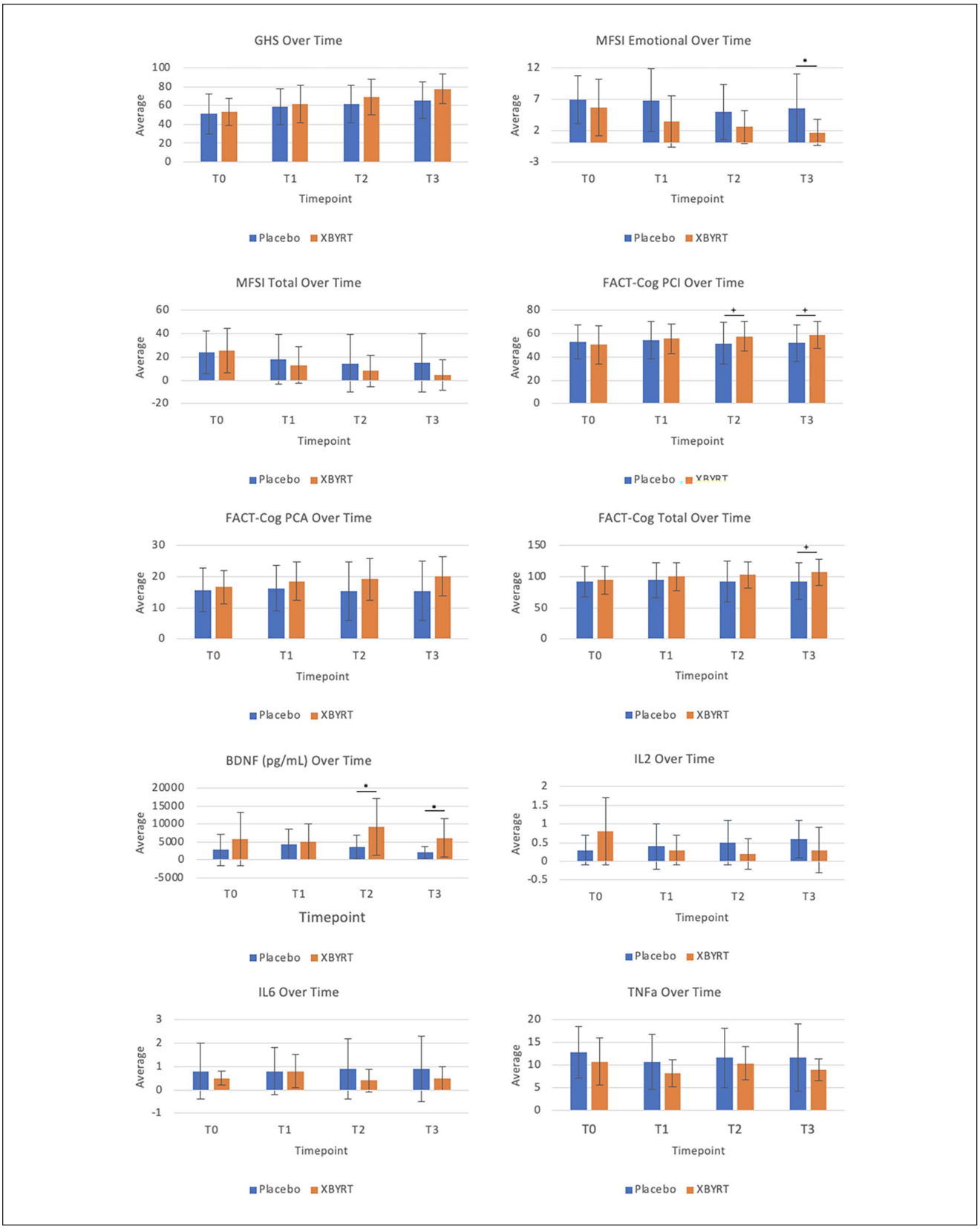

Figure 2. Assessment and biomarker measurements across all timepoints between the XBYRT and placebo groups.
*$P < .05$ without baseline adjustment. $^{+}P < .05$ with baseline adjustment.

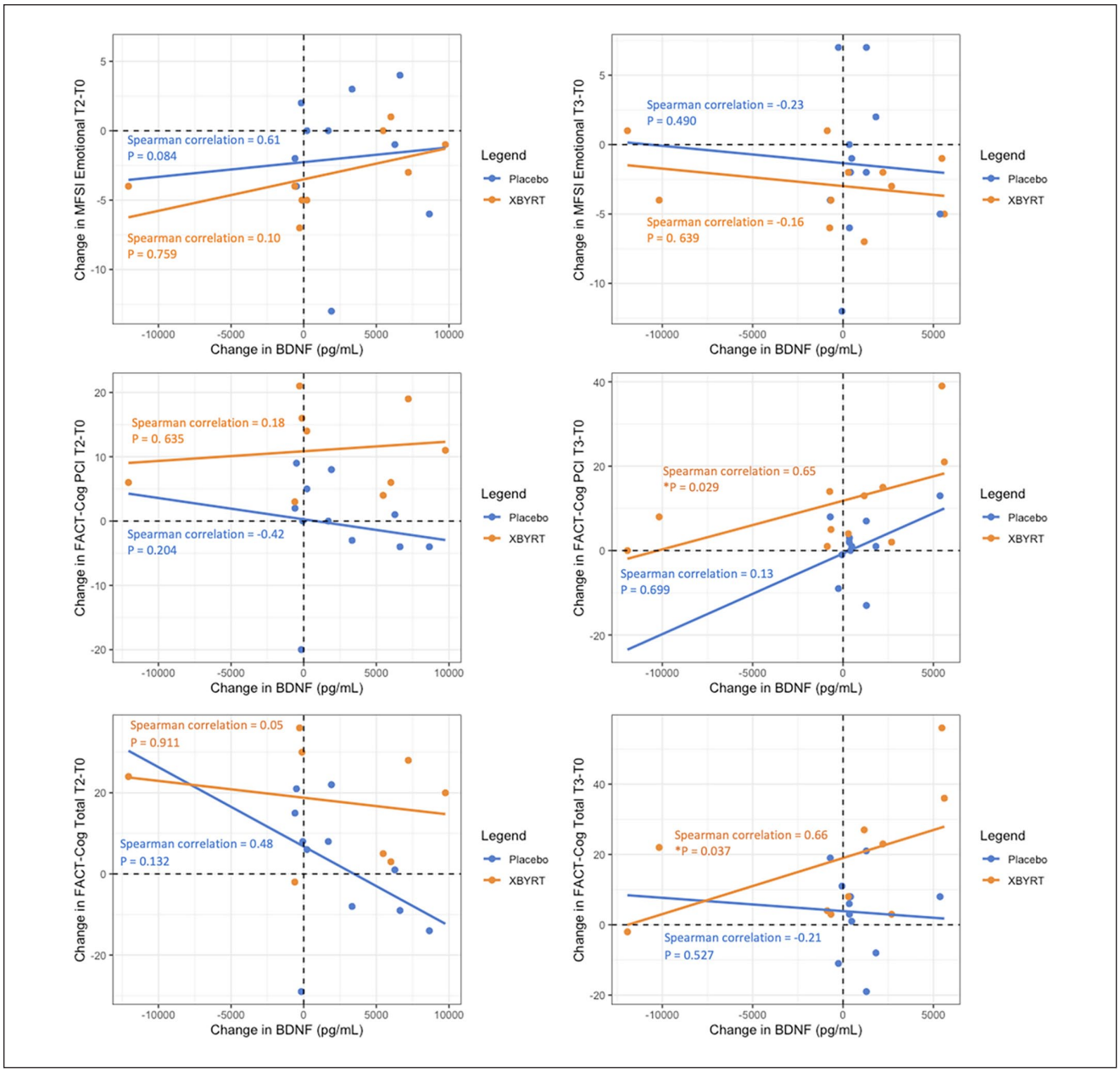

Figure 3. Spearman correlation coefficients for differences between T2 and baseline and T3 and baseline for PROs.
*$P < .05$.

Discussion

In this randomized controlled pilot trial of herbal medicine for CRF, we found an improvement of fatigue and cognitive symptoms among those treated with XBYRT compared to placebo. We observed a significant sustained improvement after treatment for both emotional fatigue and perceived cognition. Our analysis of plasma biomarkers reported significant upregulation in BDNF levels after 8 weeks of XBYRT, although this increase was not sustained after treatment cessation. This increase in BDNF levels was associated with improved cognitive function after cessation of XBYRT therapy. We did not observe any significant safety concerns with the concoction. Taken together, we conclude that the XBYRT treatment demonstrated encouraging efficacy and safety data that warrant further investigation as a potential clinically feasible treatment for CRF and cancer-related cognitive impairment (CRCI).

According to theories of TCM, CRF is characterized both by a deficiency in qi, the body's vital energy, and in

blood.[23,24] Chemotherapy and radiotherapy can result in impairment and consumption of Qi and blood, as these anticancer treatments suppress bone marrow, are cytotoxic, and result in fatigue, weakness, lack of energy or decline in physical functioning, causing the body to be in a deficiency state. It has been found that a qi deficiency correlated with CRF and worse QOL among cancer patients.[5] Although there was no impact in overall QOL in our study, we observed an improvement in emotional fatigue and perceived cognitive function in the intervention arm. These clinical outcomes are consistent with the therapeutic intent for individual ingredients of XBYRT, which includes *Radix Astragali seu Hedysari and Rhizoma Atractylodis macrocephalae.*[6] In a network pharmacology analysis, it was suggested that the mechanism of action of *Radix Astragali seu Hedysari* and *Rhizoma Atractylodis macrocephalae* on CRF mainly involved compounds, such as quercetin, kaempferol and luteolin, acting through multiple targets, such as protein kinase AKT1, tumor necrosis factor (TNF), and IL-6. Other individual herbal components such as *Fructus Lycii*, *Fructus Ligustri lucidi*, and *Fructus Alpinia oxyphylla*, have demonstrated neuroprotective effects. In the literature, *Fructus Ligustri lucidi* and *Fructus Alpinia oxyphylla* contain ethyl acetate extracts and sesquiterpenoids, respectively, which have shown to reduce the accumulation of reactive oxygen species, a known contributor to the pathogenesis of neurogenerative diseases.[9,10] However, we did not observe a statistically significant reduction in TNFα and IL-6 biomarkers in the XBYRT arm which may be attributed to the small study sample size. Moreover, studies have shown that oligosaccharide esters from *Radix Polygalae*, tenuifoliside, and 3,6′-disinapoylsucrose (DISS), increase BDNF expression via regulation of the CREB-dependent pathway.[12] These may explain the improvement of better perceived cognitive function and higher BDNF levels post XBYRT.

Interestingly, Met carriers of *BDNF* rs6265 single nucleotide polymorphism (SNP) were not as responsive to the treatment compared to participants who are homozygous for the wildtype (Val) allele. This illustrates the potential utility of the SNP to screen for Val/Val cancer survivors who may benefit most from receiving XBYRT. Correspondingly, these patients were also most in need of such interventions as they were predisposed with a higher risk of declines in cognition and BDNF downregulation after cancer treatment based on our previous longitudinal studies of breast and young adult cancer survivors from Singapore.[22,25-27] Findings in the literature, however, had not been consistent across studies conducted in other countries.[28] Inconsistent findings were similarly noted for rs6265 and CRF, with Met alleles showing a protective effect against fatigue symptoms in male[29] cancer survivors but posing a risk in females.[30] Differences in the relationship between rs6265 and CRF could be a function of gender, ethnicity, culture, and cancer type and should be investigated in a well-powered study.

There have been previous interventional studies which have evaluated various TCM concoctions containing multiple herbs in ameliorating CRF. For a study performed in Korea, 40 patients with CRF were randomized into either the control or intervention (Bu-Zhong-Yi-Qi-Tang [BZYQT]). The main ingredients of this decoction include *Radix Astragali*, *Radix* Ginseng, and *Atractylodis lanceae rhizome*. Statistically significant improvement in fatigue ($P < .05$) was found in patients receiving BZYQT for 2 weeks.[31] However, the short duration of the intervention poses a study limitation. In a single-arm study with the intent to correct qi deficiency, the efficacy of Ren Shen Yangrong Tang (RSYRT) was investigated among 33 cancer survivors who reported moderate to severe fatigue.[32] The formula includes ingredients such as *Radix Codonopsis*, *Rhizoma atractylodis macrocephalae* and *Radix rehmannia*. Patients were found to have a significant decrease fatigue severity after receiving the intervention for the course of 6 weeks. Moreover, in addition to all the patients experiencing subjective improvement within 4 weeks of the intervention, there was a statistically significant decrease in fatigue severity score using the MD Anderson Symptom Inventory-C ($P < .001$). However, these findings are likely biased by the lack of adequate blinding and control. In another double-blinded, placebo-controlled, randomized study of colon and breast cancer patients (n = 120), Chinese herbal medicine was given to manage nausea but not hematologic toxicity.[33] In this study, between baseline and each chemotherapy cycle, the score change for each EORTC-QLQ-C30 domain was compared. However, no statistically significant difference was found between the placebo and TCM groups.

Considering the shortcomings of these prior studies, our trial has taken multiple approaches, including a placebo-controlled randomized design to evaluate the efficacy of our concoction. The adoption of this trial design to generate evidence demonstrating efficacy of XBYRT was a major strength of our study. To establish the role of TCM as a viable option for supportive care in cancer, the same standards imposed on pharmacological trials should also apply. Our study incorporated several unique and essential features that future trials should consider when evaluating herbal concoctions. Firstly, given the variation in composition of herbal concoctions, we have previously conducted toxicology studies of XBYRT to identify potential pharmacokinetic interactions and ensure patients who were on medications at risk of interactions with XBYRT were excluded from the study.[13] Additionally, an active placebo at 5% strength of XBYRT was used. As the taste of herbal concoctions is widely known to be strong and typically bitter, the use of an active placebo was critical to prevent

participants from recognizing that they were on the placebo arm. Maintaining blinding of participants is especially crucial given the use of patient-reported tools in our study.

However, we encountered significant challenges with recruitment, achieving 35% of the recruitment target, due to a variety of reasons including COVID-19. Nearly half (45%) of the approached patients were deemed ineligible due to low or absent fatigue levels, 34% cited a lack of interest to participate due to concerns with TCM usage, and 7% were excluded due to current TCM use. To address similar recruitment challenges in future trials of TCM, the expected duration of recruitment should be adjusted based on the prevailing acceptability of TCM within the target population. Moreover, aligning trial recruitment with ongoing symptom monitoring activities presents a promising strategy to ensure that the trial can be suitably offered to patients with reported symptom(s) of interest, such as fatigue.

Conclusion

This randomized controlled pilot trial found XBYRT as a potentially safe integrative therapy that produced encouraging improvements in cognitive and fatigue symptoms. It is, however, necessary to keep in mind the potential challenge of applying standardized TCM decoctions to patients when designing studies in the future, as individualized decoctions may be more practical or optimal for treatment. To verify our findings, a larger, multi-centered trial will inform whether XBYRT is an appropriate intervention to manage and improve symptoms in cancer patients and survivors.

Acknowledgments

We thank the Singapore Ministry of Health for providing research funding for this study. In addition, we acknowledge Dr Raymond Ng, Dr Veronique Kak Mien Tan, Seng Kok Ricky Ang, Tze Kiat Tan, Yan Peng Leona Quek, Kok Keong Teo, Si Yu Ong, Koh Kong Tan and Wei Sheng Loo for their assistance with this study.

Authors Contributions

Conceptualization: TJT and AC. Methodology: TJT, HFZ, QMT, CJT, NYY, and AC. Investigation: TJT, HFZ, QMT, ECAW and QPNL. Acquired and analyzed data: DQN, DC, JHMT, and AC. Interpretated data: DQN, DC, and AC. Visualization: DC. Drafted the manuscript: DQN, DC, CJT, YK, and AC. Revised and approved final version of manuscript: All authors. Project administration: TJT, LC, and AC. Funding acquisition: TJT, HFZ, QMT, CJT, NYY, and AC.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This trial is funded by the Singapore Ministry of Health Traditional Chinese Medicine Research Grant (TCMRG-3-NUS-01).

Ethical Approval

Institutional Review Board (IRB) approval: CIRB No.: 2019/2135.

Trial Registration

ClinicalTrials.gov (NCT04104113).

ORCID iDs

Alexandre Chan https://orcid.org/0000-0003-4391-4219
Daniella Chan https://orcid.org/0009-0000-2323-5038
Ding Quan Ng https://orcid.org/0000-0002-0754-7901
Chia Jie Tan https://orcid.org/0000-0003-2452-0556

Supplemental Material

Supplemental material for this article is available online.

References

1. Thong MSY, van Noorden CJF, Steindorf K, Arndt V. Cancer-related fatigue: causes and current treatment options. *Curr Treat Options Oncol*. 2020;21:17. doi:10.1007/s11864-020-0707-5
2. Matsunaga M, He Y, Khine MT, et al. Prevalence, severity, and risk factors of cancer-related fatigue among working cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv Res Pract*. Published online February 28, 2024. doi:10.1007/s11764-024-01557-8
3. Shih V, Chiang JYL, Chan A. Complementary and alternative medicine (CAM) usage in Singaporean adult cancer patients. *Ann Oncol Off J Eur Soc Med Oncol*. 2009;20:752-757. doi:10.1093/annonc/mdn659
4. Carmady B, Smith CA. Use of Chinese medicine by cancer patients: a review of surveys. *Chin Med*. 2011;6:22. doi:10.1186/1749-8546-6-22
5. Hsu CH, Lee CJ, Chien TJ, et al. The relationship between Qi deficiency, cancer-related fatigue and quality of life in cancer patients. *J Tradit Complement Med*. 2012;2:129-135. doi:10.1016/s2225-4110(16)30086-4
6. Zhang C, Guo W, Yao X, et al. Database mining and animal experiment-based validation of the efficacy and mechanism of Radix Astragali (Huangqi) and Rhizoma Atractylodis Macrocephalae (Baizhu) as core drugs of traditional Chinese medicine in cancer-related fatigue. *J Ethnopharmacol*. 2022;285:114892. doi:10.1016/j.jep.2021.114892
7. Zhang Y, Jin F, Wei X, et al. Chinese herbal medicine for the treatment of chronic fatigue syndrome: a systematic review and meta-analysis. *Front Pharmacol*. 2022;13:958005. doi:10.3389/fphar.2022.958005
8. Guo J, Xu GX, Hou ZJ, Xu JB, Huang LY. Effect of Lycium barbarum polysaccharides on the retinal ultrastructure of

streptozocin-induced diabetic rats. *Chin J Integr Tradit West Med*. 2013;33:1404-1407.
9. Ju HY, Chen SC, Wu KJ, et al. Antioxidant phenolic profile from ethyl acetate fraction of Fructus Ligustri Lucidi with protection against hydrogen peroxide-induced oxidative damage in SH-SY5Y cells. *Food Chem Toxicol Int J Publ Br Ind Biol Res Assoc*. 2012;50:492-502. doi:10.1016/j.fct.2011.11.036
10. Qiu C, Mu L, Wang J, et al. Sesquiterpenoids from the fruits of Alpinia oxyphylla Miq. and their neuroprotective effect. *Phytochemistry*. 2023;211:113680. doi:10.1016/j.phytochem.2023.113680
11. Jiang N, Wei S, Zhang Y, et al. Protective effects and mechanism of radix polygalae against neurological diseases as well as effective substance. *Front Psychiatry*. 2021;12:688703. doi:10.3389/fpsyt.2021.688703
12. Liu X, Wang D, Zhao R, Dong X, Hu Y, Liu P. Synergistic neuroprotective effects of two herbal ingredients via CREB-dependent pathway. *Front Pharmacol*. 2016;7:337. doi:10.3389/fphar.2016.00337
13. Yap N, David S, Zheng H, et al. Evaluation of in vitro cytochrome P450 inhibition and hepatotoxicity potential of a herbal formula (Xiang Bei Yang Rong Tang) for treatment of cancer-related fatigue. *Pharmacogn Mag*. 2021;17:630-635. doi:10.4103/pm.pm_522_20
14. Yap NY, Loo WS, Zheng HF, et al. A study protocol for HEalth-Related quality of life-intervention in survivors of Breast and other cancers experiencing cancer-related fatigue using TraditionAL Chinese Medicine: the HERBAL trial. *Trials*. 2020;21:909. doi:10.1186/s13063-020-04810-4
15. Bower JE, Bak K, Berger A, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol Off J Am Soc Clin Oncol*. 2014;32:1840-1850. doi:10.1200/JCO.2013.53.4495
16. Lin HS. Breast cancer. In: Lin HS, ed. *Chinese Practice Guidelines of Chinese Medicine in Oncology*. People's Medica Publishing House; 2016:129-138.
17. Gao X. *General Eleventh Five-Year National Planning Textbook for Higher Education: Chinese Materia Medica*. China Press of Traditional Chinese Medicine; 2009.
18. China Pharmacopoeia Commission. *Pharmacopeia Commission of the Ministry of Health of the People's Republic of China: Pharmacopoeia of the People's Republic of China*. 10th ed. The Stationary Office, 2015.
19. Chan A, Lew C, Wang XJ, et al. Psychometric properties and measurement equivalence of the Multidimensional Fatigue Syndrome Inventory—Short Form (MFSI-SF) amongst breast cancer and lymphoma patients in Singapore. *Health Qual Life Outcomes*. 2018;16:20. doi:10.1186/s12955-018-0846-6
20. Cheung YT, Lim SR, Shwe M, Tan YP, Chan A. Psychometric properties and measurement equivalence of the English and Chinese versions of the functional assessment of cancer therapy-cognitive in Asian patients with breast cancer. *Value Health J Int Soc Pharmacoeconomics Outcomes Res*. 2013;16:1001-1013. doi:10.1016/j.jval.2013.06.017
21. Teare MD, Dimairo M, Shephard N, Hayman A, Whitehead A, Walters SJ. Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study. *Trials*. 2014;15:264. doi:10.1186/1745-6215-15-264
22. Tan CJ, Lim SWT, Toh YL, et al. Replication and meta-analysis of the association between BDNF Val66Met polymorphism and cognitive impairment in patients receiving chemotherapy. *Mol Neurobiol*. 2019;56:4741-4750. doi:10.1007/s12035-018-1410-4
23. Deng SM, Chiu AF, Wu SC, et al. Association between cancer-related fatigue and traditional Chinese medicine body constitution in female patients with breast cancer. *J Tradit Complement Med*. 2021;11:62-67. doi:10.1016/j.jtcme.2020.08.005
24. Yeh MH, Chao CH, Koo M, Chen CY, Yeh CC, Li TM. Association of traditional Chinese medicine body constitution and moderate-to-severe cancer-related fatigue in cancer patients. *Complement Ther Med*. 2019;43:44-48. doi:10.1016/j.ctim.2019.01.004
25. Ng T, Teo SM, Yeo HL, et al. Brain-derived neurotrophic factor genetic polymorphism (rs6265) is protective against chemotherapy-associated cognitive impairment in patients with early-stage breast cancer. *Neuro-Oncol*. 2016;18:244-251. doi:10.1093/neuonc/nov162
26. Ng DQ, Cheng I, Wang C, et al. Brain-derived neurotrophic factor as a biomarker in cancer-related cognitive impairment among adolescent and young adult cancer patients. *Sci Rep*. 2023;13:16298. doi:10.1038/s41598-023-43581-1
27. Yap NY, Tan NYT, Tan CJ, et al. Associations of plasma brain-derived neurotrophic factor (BDNF) and Val66Met polymorphism (rs6265) with long-term cancer-related cognitive impairment in survivors of breast cancer. *Breast Cancer Res Treat*. 2020;183:683-696. doi:10.1007/s10549-020-05807-y
28. Ng DQ, Chan D, Agrawal P, et al. Evidence of brain-derived neurotrophic factor in ameliorating cancer-related cognitive impairment: a systematic review of human studies. *Crit Rev Oncol Hematol*. 2022;176:103748. doi:10.1016/j.critrevonc.2022.103748
29. Feng LR, Juneau P, Regan JM, et al. Brain-derived neurotrophic factor polymorphism Val66Met protects against cancer-related fatigue. *Transl Psychiatry*. 2020;10:302. doi:10.1038/s41398-020-00990-4
30. Goto T, Von Ah D, Li X, et al. Brain-derived neurotrophic factor rs6265 polymorphism is associated with severe cancer-related fatigue and neuropathic pain in female cancer survivors. *J Cancer Surviv Res Pract*. Published online July 18, 2023. doi:10.1007/s11764-023-01426-w
31. Jeong JS, Ryu BH, Kim JS, Park JW, Choi WC, Yoon SW. Bojungikki-Tang for cancer-related fatigue: a pilot randomized clinical trial. *Integr Cancer Ther*. 2010;9:331-338. doi:10.1177/1534735410383170
32. Xu Y, Chen Y, Li P, Wang XS. Ren Shen Yangrong Tang for fatigue in cancer survivors: a phase I/II open-label study. *J Altern Complement Med*. 2015;21:281. doi:10.1089/acm.2014.0211
33. Mok TSK, Yeo W, Johnson PJ, et al. A double-blind placebo-controlled randomized study of Chinese herbal medicine as complementary therapy for reduction of chemotherapy-induced toxicity. *Ann Oncol*. 2007;18:768-774. doi:10.1093/annonc/mdl465

Chapter 7: Psychoeducation Group Intervention as a Strategy to improve Survivorship Care in Breast Cancer Survivors

7.1 Introductory Comments

In the previous chapters, I successfully developed and implemented interventions that would benefit survivors initiating therapy (Chapter 5) and during treatment (Chapter 6) within the cancer center. However, it is understood that BCS are very eager to reengage in their normal life and manage toxicities in the community setting based on our conversations with the survivors (Chapter 2), and it is unknown what is the most effective and patient-friendly mode to deliver post-treatment survivorship care, especially when patients transition from active treatment to post-treatment. Using an RCT approach, as outlined in Chapter 3, the goal is to evaluate the effectiveness of a multidisciplinary, multi-intervention in addressing survivors' post-treatment needs in the community.

7.2 Aim

To evaluate the effectiveness of a PEG intervention program compared with usual care to reduce distress for physical symptoms and psychological aspects in early-stage BCS who have completed adjuvant chemotherapy.

7.3 Summary

Through this RCT, the PEG intervention program was found to be effective in reducing symptom burden in early-stage BCS, particularly in terms of the severity of physical symptoms as reflected by the decrease in severity scores. Specifically, a significant reduction in physical symptom distress and fatigue level was observed among patients receiving the PEG intervention program compared with those in the control group. Although a statistically significant reduction in

psychological distress was not observed over time, a trend towards less psychological distress and anxiety was observed in both study arms. Our findings are also congruent with findings in the literature. One meta-analysis (159) suggested that psychooncologic group interventions including individual psychotherapy, group psychotherapy, psychoeducation, and relaxation training, can produce positive effects on emotional distress, anxiety, and depression, and health-related quality of life. It is important to note that most of the studies included in the meta-analysis were conducted in Western countries; as emphasized in the literature review (Chapter 1) and observational study (Chapter 3) chapters, cultural adaptation is critical to ensure that participants find the content of the training to be relatable and helpful.(160)

All the responding patients agreed that they were satisfied with the program, with attendance of 80% by the cohort. The results were very encouraging as participants found this program acceptable. This chapter has demonstrated the feasibility of developing and implementing a group-based intervention for cancer survivors who have completed treatment. Using a pragmatic approach, the intervention is grounded in the United States IOM framework (Chapter 2, Table 2.1), which addresses the key domains of post-treatment survivorship. In addition, cultural elements and unmet needs identified by BCS, as discussed in earlier sections (Chapters 2 and 3) of this thesis, were incorporated into the program design. The workshop was also delivered by a multidisciplinary team of allied health professionals, including a dietitian, social worker, pharmacist, physiotherapist, and psychologist, and the training sessions were conducted in community settings, in order to transition survivors out of the traditional healthcare environment. This approach aligns with findings from BCS that cancer survivors prefer receiving follow-up care in the community.

7.4 Publication

- **Chan A**, Gan YX, Oh SK, Ng T, Shwe M, Chan R, Ng R, Goh B, Tan YP, Fan G. A Culturally Adapted Survivorship Program for Asian Early-Stage Breast Cancer Patients in Singapore: A

Randomized, Controlled Trial. *Psychooncology* 2017;26(10):1654-1659. (Reprinted with permission from John Wiley and Sons)

7.5 Author's Contribution

- I conceived the research idea and obtained funding through the National Cancer Centre Community Cancer Fund Grant Call and Pretty in Pink 2014 event. I conceived the research idea, worked with the Department of Psychosocial Oncology to develop the intervention, participated in data collection, led the data analysis, writing, and editing of the publication. In addition, I have supervised my research team (consisted of undergraduate and postgraduate students, research coordinators) to coordinate the intervention of the study, which involves the invitation of trainers and participants and promotion of the event.

Received: 12 October 2016 | Revised: 16 December 2016 | Accepted: 22 December 2016

DOI 10.1002/pon.4357

WILEY

PAPER

A culturally adapted survivorship programme for Asian early stage breast cancer patients in Singapore: A randomized, controlled trial

Alexandre Chan[1,2,3*] | Yan Xiang Gan[2*] | Suan Kai Oh[1] | Terence Ng[1,2] | Maung Shwe[1,2] | Raymond Chan[4,5] | Raymond Ng[3,6] | Brandon Goh[7] | Yee Pin Tan[7] | Gilbert Fan[7]

[1] Department of Pharmacy, National University of Singapore, Singapore

[2] Department of Pharmacy, National Cancer Centre Singapore, Singapore

[3] Duke-NUS Medical School Singapore, Singapore

[4] Queensland University of Technology, Brisbane, Queensland, Australia

[5] Royal Brisbane and Women's Hospital, Herston, Queensland, Australia

[6] Division of Medical Oncology, National Cancer Centre Singapore, Singapore

[7] Department of Psychosocial Oncology, National Cancer Centre Singapore, Singapore

Correspondence
Dr Alexandre Chan, Department of Pharmacy, Faculty of Science, National University of Singapore, Block S4, 18 Science Drive 4, 117543 Singapore.
Email: phaac@nus.edu.sg

Abstract

Background As cancer mortality rates improve in Singapore, there is an increasing need to improve the transition to posttreatment survivorship care. This study aimed to evaluate the effectiveness of a psychoeducation group (PEG) intervention program compared with usual care to reduce distress for physical symptom and psychological aspects in Asian breast cancer survivors who have completed adjuvant chemotherapy.

Methods This was a randomized, controlled trial comprising 72 Asian early stage breast cancer survivors who were randomized into the PEG (n = 34) or the control (n = 38) arm. The participants in the PEG arm underwent a weekly multidisciplinary PEG program delivered in a group format over 3 weeks coupled with cultural adaptation. Both arms were assessed at baseline and 2 months after intervention using the Rotterdam Symptom Checklist, Beck Anxiety Inventory, and EORTC QLQ-C30. A satisfaction questionnaire was also conducted among those survivors who have participated in the PEG program. Effective sizes were calculated using Cohen *d*.

Results The mean age ± *SD* of all participants was 53.0 ± 8.9 years, with the majority being Chinese (84.7%) and Malay (6.9%), and clinical characteristics were well balanced in both arms. Compared to the control arm, the PEG arm showed a significantly greater reduction in physical symptom distress (d = 0.76, P = .01) and fatigue (d = 0.49, P = .04). The 82.4% of the participants in the intervention group responded to the satisfaction questionnaire, and the majority (92.9%) agreed that the overall duration of the PEG intervention program was appropriate.

Conclusions A culturally adapted PEG program was effective in reducing physical symptom distress in Asian breast cancer survivors. (ClinicalTrials.gov: NCT02600299)

KEYWORDS

cancer, cancer survivors, oncology, physical symptom distress, psychoeducation group, psychological distress, survivorship

1 | BACKGROUND

With advancements in anticancer treatments, the global survival rates of early stage breast cancer patients have greatly improved, and the number of cancer survivors is projected to further increase in the coming years, including Singapore.[1] Although treatments have significantly reduced mortality rates, these treatments have impinged upon the individual's immediate and long-term quality of life (QOL). Early stage breast cancer survivorship issues are often multidimensional.[2,3] Adjusting back to normal life may take longer if cancer survivorship issues are severe. These issues are often co-related and often occur together, which is commonly described as symptom clustering in the literature.[4] For example, physical symptoms and psychological distress such as anxiety, fatigue, and cognitive impairment

*Alexandre Chan and Yan Xiang Gan contributed equally on this study.

are often known to cluster.[5] Thus, effective interventions to alleviate symptoms and improve QOL throughout the survivorship journey are essential in breast cancer survivors (BCS).

Despite the wealth of knowledge on cancer survivorship in the western culture, culturally appropriate, standardized survivorship programs are lacking in Singapore. Singapore is a multiethnic Asian society consisted of mostly Chinese, Malay, and Indians. To first address the problem, our research group has conducted a survey among Asian oncology practitioners in 2013 and the results revealed that practitioners prioritise their follow-up care on treatment-related adverse effects and noncancer medical history rather than postchemotherapy or postsurgical psychosocial issues.[6] This indicates that certain cancer survivorship issues, such as psychological distress, are not adequately addressed; and specific interventions for clinically significant psychological distress like posttreatment anxiety and depression are lacking. There are also significant barriers for Asian BCS to seek posttreatment medical intervention. Asian practitioners surveyed indicated that financial constraints, patients' lack of awareness, and unwillingness to discuss sensitive issues are significant patient-related barriers. Another study evaluating mental health literacy in Asian BCS suggests that Asian patients significantly lack knowledge in identifying symptoms for cognitive disturbances, anxiety, and depression, which may prevent survivors from proactively seeking medical attention.[7] In summary, the lack of holistic follow-up care by practitioners, together with patient factors that deter patients from seeking professional help for survivorship concerns, result a major unmet needs in the current practice.

Current literature on group intervention programs addressing cancer survivorship issues came to conflicting conclusions on its effectiveness. In 1 study, a 10-week long group–counselling program resulted in better psychosocial adaptation and abilities to cope with breast cancer among survivors.[8] However, another study involving 8-week long group psychotherapy concluded that there was no improvement in psychosocial outcomes for BCS.[9] This suggests that intervention programs with various content and outcomes are implemented and effectiveness varies. The effectiveness of these programmes could also be affected by cultural differences. Asians may have unmet cancer survivorship needs and these needs are influenced by cultural, educational, and lifestyle beliefs,[10] hence may influence their way of coping with stress and needs. The guideline for quality cancer survivorship care, published by the United States of America Institute of Medicine (IOM), suggested that intervention should be customised to patient needs and values.[2]

Because of the lack of survivorship programme utilizing standardized approaches in Singapore, a team of multidisciplinary health care professionals gathered and developed a psychoeducation group (PEG) intervention programme, with the goal to standardize the approach to deliver posttreatment survivorship care. The main aim is to develop an intervention programme that could utilize the group cognitive behavioral therapy (CBT) approach to encourage BCS to practice newly learned skills to self-manage their adverse effects at home.

To ensure that this programme is effective to reduce physical symptom and psychological distress in participants, a study was conducted to evaluate its feasibility and effectiveness to address survivorship issues in early stage BCS. We hypothesize that Asian BCS who have undergone the PEG programme will experience a greater reduction in distress for both physical symptom and psychological aspects as compared to Asian BCS who were receiving usual care. We hope that through this novel approach, we can facilitate the transition of patient to survivors and ultimately improve the QOL of Asian BCS.

2 | METHODS

2.1 | Study design

This single-center, prospective, randomized, and controlled study was conducted at the National Cancer Centre Singapore between August 2015 and January 2016. The SingHealth Institutional Review Board approved this study prior to its implementation, and this trial is registered with ClinicalTrials.gov: NCT02600299.

2.2 | Study population

Eligible patients were women 21 years and older who were diagnosed as having stages I to III breast cancer, had no known psychiatric diagnosis, and could read and comprehend English. Recruited patients must have completed their adjuvant chemotherapy. Patients requiring adjuvant radiation, adjuvant targeted therapy (such as trastuzumab), and/or endocrine therapies (such as tamoxifen and aromatase inhibitors) are allowed to participate in this study. Eligible patients were referred by their medical oncologists, and written informed consent was obtained from all patients.

2.3 | Randomization

Patients were enrolled by a research assistant and were randomly allocated to 1 of 2 groups: the intervention group (PEG intervention programme) or control group (usual care). The research assistant completed the random assignment using the randomization function of the Statistical Package for the Social Sciences program version 23. Other details on randomization are included in the Supplementary Methods.

2.4 | Intervention

2.4.1 | Psychoeducation group intervention programme

A multidisciplinary PEG intervention programme was developed by the investigators to address and alleviate survivorship issues that BCS encounter after treatment. Patients in the intervention group participated in 3 educational sessions of the PEG intervention programme. Each session was 4.5 hours long, and each patient participated in 3 sessions. The sessions were conducted in a meeting room at the cancer center on 3 different Saturdays. Each educational session covered 3 different segments that consisted of 3 different topics. (Supplementary Table S1) The program length was decided to not exceed 4.5 hours, to assure that survivors do not suffer from fatigue due to long sessions. A group approach was taken to deliver the programme. In the literature, group interventions have been shown with greater ease in simulating social situations in role plays and getting mutual support from group

members.[11] Besides, the group approach makes the intervention more feasible to sustain outside of the study setting.

For the education segments, health care professionals from various specialties led and shared their knowledge and experiences on specific concerns that were endorsed in the guidelines for quality cancer survivorship care published by the IOM.[2] This programme was conducted based on the principles of cognitive behavioral therapy.[12,13] Trainer for each session focused on the impact of the specific problems on the BCS and on the patients' coping strategies.

On the basis of the guidelines provided by the IOM, we have culturally adapted their recommendations. The cultural adaptation of the intervention programme was highly important in this study. Having knowledge on the cultural context and lifestyle preferences of a local population allows health care professionals to provide recommendations that can be easily incorporated into the participants' daily activities. For example, in the session conducted by the oncology pharmacist, the appropriate use of traditional Chinese medication (TCM) was addressed because many Asian patients use TCM as complementary treatment. By addressing this cultural practice, patients are educated on the suitability of TCM and the period during which TCM should be avoided to minimize potential drug-drug interactions. The dietician also provided practical recommendations in the session that discusses the nutritional aspect of living as cancer survivors. With the knowledge of Asian food preferences, the dietician in the programme recommended food that can fulfil nutritional requirements while catering to these preferences, thus improving the acceptability of the recommendations. Depending on the format of each session, participants were given sufficient time to practice the skills that were taught. Notes from all educational sessions were also provided for the BCS, to ensure that they are able to reinforce these skills at home.

At the end of each segment, the BCS were given time to ask questions specific to their personal experiences and issues. These queries were addressed by the health care professional, and when necessary, individual follow-up deemed was conducted after the session. A focus group session was also integrated into this programme to identify problems BCS face during the survivorship journey. The qualitative data obtained from this focus group was reported in a separate report.[14]

2.4.2 | Control group

Patients in the control group received usual care, whereby patients are provided with an information booklet on self-management of cancer- and treatment-related symptoms, which is routinely provided by the National Cancer Centre Singapore after cancer diagnosis.

2.5 | Assessments and outcome measure

The data for both the intervention and control groups were measured at 2 time points, 1 month before intervention (baseline) and within 2 months after intervention when the patients returned during follow-up appointments (Figure 1). To avoid possible interviewer bias, different research assistants were involved in collecting baseline and postintervention measures. At each session, 4 measurement tools (Rotterdam Symptom Checklist (RSCL), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), Beck Anxiety Inventory (BAI), and Satisfaction questionnaire) were used to assess patient outcomes. Details of these measurements tools were described in Supplementary Methods.

2.6 | Endpoints

The primary endpoints measured in this study were the mean change in both the RSCL physical symptom distress scores and psychological distress scores for each group (intervention and control groups). Secondary endpoints included mean change in the total BAI score; mean change in the EORTC QLQ-C30 functional scale scores and descriptive responses from the patient satisfaction questionnaire.

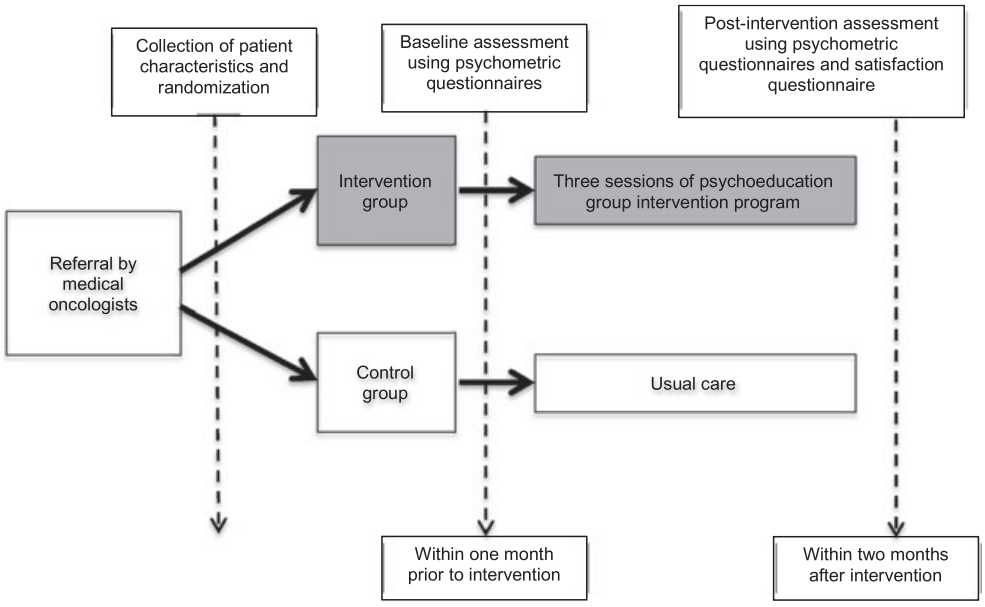

FIGURE 1 Flowchart showing the implementation process of this study

2.7 | Statistical analyses

Baseline characteristics are reported using frequency distributions and descriptive statistics including the mean and standard deviation. Differences in the baseline characteristics between groups were compared using the 2-sample *t* test for continuous variables and the chi-square test for categorical variables. A normality test was conducted prior to the analysis of main effect, and the data obtained from both groups followed a normal distribution. The main effect, which is the change in RSCL scores for both physical symptoms and psychological distress across the groups, was analyzed using the 2-sample *t* test. In this study, effect sizes for variables with a *P*-value <.2 were computed. A cutoff *P*-value <.2 was selected because these variables approach statistical significance, which would provide additional opportunities to investigate the magnitude of the benefits that the intervention could bring to patients. Pair-wise *t* tests within each group were also conducted to detect any changes within groups over time. Secondary outcome measures including the EORTC QLQ-C30 subdomain scores and BAI scores were analyzed using the same approach as the primary measure. An intention-to-treat approach was undertaken in this study.

In terms of sample size calculation, a meta-analysis reported moderate effect size (Cohen *d* = 0.7) for functional adjustments in studies investigating the effectiveness of psychosocial interventions.[15] On the basis of this effect size, we estimated that 64 patients were required to detect a difference in the mean changes of physical symptom and psychological distress between the intervention group and control group, assuming a 2-tailed α of 0.05 and a power of 0.80. The initial estimation of the sample size was 80, which accounted for the possibility of attrition in participation.

3 | RESULTS

3.1 | Study population

We identified 88 patients as being eligible for the study between August 2015 and January 2016. The PEG intervention program was implemented twice, in September 2015 and in November 2015. Overall, of the 43 patients randomized to the control group and the 45 patients randomized to the intervention group, 38 and 34 patients completed the study, respectively. (Figure S1). There were no statistically significant differences detected between any of the characteristics reported (all *P* > .05). (Table S2)

3.2 | Effects on physical symptom and psychological distress

In general, patients in the intervention group had a greater reduction in physical symptom distress than patients in the control group (Table 1). Patients in the intervention group reported a greater reduction of physical symptom distress over time than patients in the control group (−2.1 ± 7.4 vs −8.2 ± 9.4 points; *P* < .01), with the Cohen *d* effect size being 0.72. On the other hand, the change of psychological distress was similar between the 2 groups (−1.6 ± 15.6 vs −4.0 ± 18.8 points; *P* = .55). Patients in the intervention group (0.4 ± 1.0 points; *P* = .03) and control group (0.3 ± 1.0 points; *P* = .05) had an improved overall valuation of life over time; however, changes in scores between the intervention and control groups were not significantly different.

3.3 | Effects on secondary measures

The QLQ-C30 scores for both groups showed an increasing trend for the functional scale scores and global health status scores and a decreasing trend for symptom scale scores and single-item scores over time (Table S3). Statistically significant differences between the intervention and control groups were not observed for any of the scales and items, with the exception of the fatigue symptom scale. Patients in the intervention group experienced less fatigue over time than the patients in the control group (−6.5 ± 17.5 vs 3.5 ± 23.0 points; *P* = .04), with the Cohen *d* effect size being 0.49.

There was a general decrease in BAI scores over time for both the intervention and control groups. This trend indicates that there was a reduction of anxiety over time for the patients in both groups. Changes in the BAI score and the subscales were not statistically significant between groups.

Twenty-eight patients (82.4%) in the intervention group responded to the satisfaction questionnaire. The responding patients were satisfied with all aspects of the PEG intervention programme surveyed. All patients agreed that the content taught in the programme had addressed their needs and aided them in dealing with their survivorship issues more effectively and that they were comfortable with the facilities and the instructors who conducted the sessions. The

TABLE 1 Baseline and follow-up scores of the Rotterdam Symptom Checklist (RSCL)

	Control Group (n = 38)		Intervention Group (n = 34)			
	Mean Change Over Time, mean ± *SD*	Paired Comparison between Baseline and Follow-up, *P*-Value	Mean Change Over Time, mean ± *SD*	Paired Comparison between Baseline and Follow-up, *P*-Value	Cohen *d*	Comparison between Groups, *P*-Value
Physical symptom distress level[a]	−2.1 ± 7.4	.08	−8.2 ± 9.4	**<.01**	0.72	**<.01**
Psychological distress level[a]	−1.6 ± 15.6	.52	−4.0 ± 18.8	.22		.55
Activity level impairment#	0.3 ± 3.1	.50	−0.8 ± 2.9	.15	0.37	.14
Overall valuation of life[b]	0.3 ± 1	**.05**	0.4 ± 1	**.03**		.78

P-values less than or equal to 0.05 are denoted in bold.

[a]For physical symptom and psychological distress levels, a negative mean change score signifies a reduction of symptoms over time, whereas a physical score signifies an increase of symptoms over time;

[b]For activity level impairment and overall valuation of life, a positive mean change score signifies an improvement of activity level and overall evaluation of life over time, whereas a negative score signifies a reduction of activity level and overall evaluation of life over time.

majority (92.9%) agreed that the overall duration of the PEG intervention programme was appropriate.

4 | DISCUSSION

Results from this study suggest that the PEG intervention programme may be effective in reducing symptom burden in early stage BCS, particularly in terms of the severity of physical symptoms as reflected by the decrease in severity scores. The results are very encouraging because the acceptability of this effective programme is substantiated by the results of the satisfaction questionnaire, whereby all of the responding patients agreed that they were satisfied with the programme. A meta-analysis of the attrition rate of randomized, controlled trials in supportive care and palliative oncology found the average end rate of study attrition for these trials to be 44%.[16] All in all, the potential effects, acceptability, and the attrition rate from this study suggest that the PEG intervention programme is highly feasible for implementation on a larger scale.

We found a significant reduction in physical symptom distress and fatigue level in the patients attending the PEG intervention programme in comparison with those in the control group. We attribute this finding to a number of components with the PEG intervention programme that addressed the techniques to mitigate physical symptom distress and fatigue, which included the exercise session conducted by the physiotherapist as well as the management of long-term toxicities associated with survivorship conducted by the oncology pharmacist. Other studies with physical exercises as the major component of a psychosocial intervention programme also showed promising results of reducing physical symptom burden.[17] Most of these interventions provided similar type of psychoeducation, which included self-management and coping techniques as fatigue, as well as learned activity management. This indicates that offering interventions that address physical symptoms is essential for improving the physical well being of BCS. Another important difference is the shorter overall duration of the PEG intervention programme compared to the programmes in the other studies.[11,17] A follow-up study is needed to confirm the sustainability of the effects of PEG intervention.

Although the reduction in psychological distress was not statistically significant for either the RSCL or the BAI scale, there was a general trend of improvement over time, with the participants reporting less psychological distress and anxiety in both study arms. Other studies with interventions addressing psychological distress in BCS have inconsistent results. In a pilot study exploring the effectiveness of a retreat-based, weeklong intervention in addressing psychological distress in BCS, significant reductions in psychological distress were detected.[18] However, another study with a 10-week psychosocial intervention programme did not report any significant improvement in psychological outcomes.[9] Our outcome for psychological distress is in line with inconsistencies and can be explained by 2 reasons. First, patients in both study groups had very low-baseline BAI scores, which indicate that our BCS population does not suffer from significant anxiety. This may have caused a floor effect in which patients may not have sufficient distress to show a significant effect of our intervention.[19] Second, the psychosocial content of this programme may not be comprehensive enough to address all the issues that the survivors were experiencing. Future studies are required to evaluate whether it is necessary to increase the coverage and duration of psychosocial content.

The cultural adaptation of the intervention program through the IOM guidelines was highly crucial in this study. As Asians are generally influenced by culture and beliefs, it is important to ensure that the content of our programme suits the needs of Asian BCS. This is quite evident from findings of our other preliminary studies.[7,14] For example, we learned that BCS utilize traditional Chinese medicine and meditation to improve their memory and related adverse effects. We also learned that BCS in Singapore had few avenues to seek help, particularly during the survivorship phase of their cancer treatment journey. Hence, the cultural adaptation allows participants of the PEG to truly adopt the skills and knowledge that they have acquired from the programme into their daily lives.

This study has several strengths. First, it is a randomized, controlled trial, which allows us to compare the specified outcomes between the PEG intervention programme and the severity of symptom burden. Second, the PEG intervention programme was developed on the basis of specific issues identified in previous studies done in our patient population, such as cognitive disturbances and anxiety.[5,20] Third, the recruited patients were relatively homogenous (age and education level), which reduces the effects of any potential confounders. Fourth, this study is powered for its sample size. Finally, the measurement tools used are psychometrically sound and have been used in other studies to assess outcomes of Asian cancer patients in Singapore.[21–23]

4.1 | Study limitations

This study also has several limitations. First, as a single-center trial in South East Asia, the outcomes of this study may not be generalizable to other settings. However, the ethnic makeup is representative of most South East Asians, as we have included patients of Chinese, Malay, and Indian ethnic. Such ethnic diversity observed in this study is also consistent with the ethnic makeup of breast cancer patients in Singapore. Second, approximately 18% of the patients in the intervention group did not complete the satisfaction survey. We acknowledge that it is still possible that a small percentage of the nonrespondents did not find the PEG programme satisfactory.

4.2 | Clinical implications

To date, most studies evaluating the effectiveness of intervention programmes were conducted in Western population. There is insufficient research evaluating these programmes within the Asian population. This study, which is conducted in BCS residing in Singapore, revealed that a culturally adapted, multidisciplinary psychoeducation programme is effective in reducing physical symptom distress and fatigue experienced by these survivors.

5 | CONCLUSION

Results of this randomized, controlled study suggest that the culturally adapted PEG intervention programme delivered by a multidisciplinary

team holds promise, with significant reductions seen in physical symptom distress. Overall, this study demonstrated the feasibility and potential effectiveness of the PEG intervention programme and that the integration of this programme into the care of early stage BCS can be considered to reduce physical symptom distress of these patients. Further study should evaluate the long-term effectiveness and cost-effectiveness of the PEG programme for BCS, as well as subgroups that will best benefit from the programme.

ACKNOWLEDGMENTS

This study is supported by the National Cancer Centre Community Cancer Fund Grant Call (COMCF-YR2014-NOV-SD3) and Pretty in Pink 2014 event.

CONFLICT OF INTEREST

The authors have no conflicts of interest that are directly relevant to the content of this study. This work was presented as poster presentation at the American Society of Clinical Oncology Annual Meeting in 2016, USA.

REFERENCES

1. Lee HP, Chew L, Chow KY, et al. Singapore cancer registry interim annual report. Trends in Cancer Incidence in Singapore 2010-2014. In. Health Promotion Board2015
2. Maria H, Sheldon G, Ellen S. *From Cancer Patient to Cancer Survivor: Lost in transition*. The National Academies of Sciences, Engineering and Medicine. Washington DC: National Academy of Sciences; 2006.
3. Fallowfield L, Jenkins V. Psychosocial/survivorship issues in breast cancer: are we doing better? *J Natl Cancer Inst*. 2015;107:335
4. Kim HJ, Barsevick AM, Tulman L. Predictors of the intensity of symptoms in a cluster in patients with breast cancer. *J Nurs Scholarsh*. 2009;41:158–165.
5. Cheung YT, Shwe M, Chui WK, et al. Effects of chemotherapy and psychosocial distress on perceived cognitive disturbances in Asian breast cancer patients. *Ann Pharmacother*. 2012;46:1645–1655.
6. Ng T, Toh MR, Cheung YT, Chan A. Follow-up care practices and barriers to breast cancer survivorship: perspectives from Asian oncology practitioners. *Support Care Cancer*. 2015;23:3193–3200.
7. Cheung YT, Ong YY, Ng T, et al. Assessment of mental health literacy in patients with breast cancer. *J Oncol Pharm Pract*. 2015;22:437–447.
8. Oz F, Dil S, Inci F, Kamisli S. Evaluation of group counseling for women with breast cancer in Turkey. *Cancer Nurs*. 2012;35:E27–E34.
9. Boesen EH, Karlsen R, Christensen J, et al. Psychosocial group intervention for patients with primary breast cancer: a randomised trial. *Eur J Cancer*. 2011;47:1363–1372.
10. Wen KY, Fang CY, Ma GX. Breast cancer experience and survivorship among Asian Americans: a systematic review. *J Cancer Surviv*. 2014;8:94–107.
11. Sherman KA, Heard G, Cavanagh KL. Psychological effects and mediators of a group multi-component program for breast cancer survivors. *J Behav Med*. 2010;33:378–391.
12. Greer S, Moorey S, Baruch JD, et al. Adjuvant psychological therapy for patients with cancer: a prospective randomised trial. *BMJ*. 1992;304(6828):675–680.
13. Kissane DW, Bloch S, Miach P, et al. Cognitive-existential group therapy for patients with primary breast cancer—techniques and themes. *Psychooncology*. 1997;6:25–33.
14. Chan A, Lum ZK, Ng T, et al. Perceptions and barriers of survivorship care in Asia: perceptions from Asian breast cancer survivors. *J Glob Oncol*. 2016;
15. Rehse B, Pukrop R. Effects of psychosocial interventions on quality of life in adult cancer patients: meta analysis of 37 published controlled outcome studies. *Patient Educ Couns*. 2003;50:179–186.
16. Hui D, Glitza I, Chisholm G, et al. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. *Cancer*. 2013;119:1098–1105.
17. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. *Cochrane Database Syst Rev*. 2009;CD006953
18. Vella EJ, Budd M. Pilot study: retreat intervention predicts improved quality of life and reduced psychological distress among breast cancer patients. *Complement Ther Clin Pract*. 2011;17:209–214.
19. Breakwell GM, Hammond S, Fife-Schaw C, Smith JA. *Research Methods in Psychology*. 3rd ed. London, UK: SAGE Publications; 2006.
20. Cheung YT, Lee HH, Chan A. Exploring clinical determinants and anxiety symptom domains among Asian breast cancer patients. *Support Care Cancer*. 2013;21:2185–2194.
21. Chan A, Lim E, Ng T, et al. Symptom burden and medication use in adult sarcoma patients. *Support Care Cancer*. 2015;23:1709–1717.
22. Ke Y, Ng T, Yeo HL, et al. Psychometric properties and measurement equivalence of the English and Chinese versions of the Beck Anxiety Inventory in patients with breast cancer. *Support Care Cancer*. 2016;
23. Luo N, Fones CS, Lim SE, et al. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30): validation of English version in Singapore. *Qual Life Res*. 2005;14:1181–1186.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Chan A, Gan YX, Oh SK, Ng T, ShweM, Chan R, Ng R, Goh B, Tan YP, Fan G. A culturally adapted survivorship programme for Asian early stage breast cancer patients in Singapore: A randomized, controlled trial. *Psycho-Oncology*. 2017. doi: 10.1002/pon.4357

Chapter 8: Introducing Cancer Survivorship to Undergraduate Students

8.1 Introductory Comments

Although we recognize cancer survivorship is an important issue that impacts many cancer survivors who are cured of their malignancies, cancer survivorship is certainly not a routine topic that is introduced to young adults, especially within undergraduate education. There are numerous studies documenting the benefits of introducing clinical oncology and related topics in undergraduate medical education. Our survivors' concerns (Chapters 3 and 4) and novel strategies in managing symptoms (Chapters 5, 6, and 7) provide a good basis for the topics that should be introduced to students. This study provides an opportunity to evaluate whether it is feasible to translate research findings that we learn from our patients into the classroom setting.

8.2 Aim

To examine the impact on students who have taken the "Life After Cancer" course using the knowledge, attitude, and perception framework.

8.3 Summary

This study was conducted to evaluate the pre- and post-course changes in knowledge, attitude, and perceptions of cancer survivors among undergraduate students who have undergone a seminar course on cancer survivorship. In summary, there was a modest improvement in students' perception and awareness towards cancer survivorship after taking the course. These improvements were possibly a result of the various discussions and activities conducted during the course.

This chapter is a significant component of the thesis, as it demonstrates the feasibility of integrating newly generated scientific knowledge into the undergraduate curriculum. It begins by

outlining key concepts related to the unmet needs in cancer survivorship, as identified by cancer survivors themselves. Through topic discussions, the course explored recent advancements aimed at addressing these needs across various stages of the treatment continuum. Additionally, students were introduced to strategies for overcoming barriers to conducting survivorship trials.

While the seminar-style format of the course successfully enhanced students' perceptions and awareness of survivorship-related issues, it did not lead to improvements in two critical areas: knowledge and attitudes toward caring for cancer survivors. Some knowledge items may have been inherently complex or controversial—for example, whether cancer survivors should receive vaccinations following chemotherapy—which could pose challenges for students without a healthcare background. Furthermore, certain concepts, such as the transition of cancer survivors from primary to specialty care settings, may not have been covered in sufficient depth during class discussions, potentially affecting students' understanding and response accuracy. In this study, although we set the stage to translate research findings into education enhancement within the undergraduate curriculum, the translation of survivorship research findings can also be extended to other members of the healthcare team who provide routine survivorship services.

8.4 Publications

- **Chan A.** Implementing a cancer survivorship seminar course to non-healthcare professional undergraduate students. *Support Care Cancer* **32**, 227 (2024). https://doi.org/10.1007/s00520-024-08426-1

8.5 Author's Contribution

- As the sole author and investigator on this project, I conceived the idea, ran the course for 3 years, coordinated all research activities, wrote the manuscript, and submitted it for publication.

Supportive Care in Cancer (2024) 32:227
https://doi.org/10.1007/s00520-024-08426-1

RESEARCH

Implementing a cancer survivorship seminar course to non-healthcare professional undergraduate students

Alexandre Chan[1]

Received: 28 January 2024 / Accepted: 7 March 2024

Abstract

Background At University of California, Irvine (UCI), a seminar course focused on cancer survivorship was developed and offered to non-healthcare professional undergraduate students. Utilizing the knowledge, attitude, and perception (KAP) framework, this study was designed to examine the impact on students who have taken this course, and to clarify the value of this course for undergraduate students.

Methods This was a cross-sectional survey. Undergraduate students enrolled in the Life After Cancer Freshmen Seminar course (Uni Stu 3) at UCI between 2021 and 2023 were invited to participate. The survey consisted of 4 main sections: (1) demographics, (2) knowledge of cancer survivorship, (3) attitude towards cancer survivorship, and (4) perception and awareness of cancer survivorship. The survey was administered prior to the implementation of the course, and the same survey was administered at the end of the course.

Results A total of 33 students completed the pre-implementation survey and 30 students completed the post-implementation survey. Comparing pre- and post-course implementation, there was an increase of perception and awareness of (i) resources and guidelines for cancer survivors (pre, 9.1% vs. post, 36.7%), (ii) mental health complications among cancer survivors (pre, 36.4% vs. post, 56.7%), (iii) benefits of cancer survivorship care (pre, 15.2% vs. post, 40%), latest research in cancer survivorship (pre, 0% vs. post, 23.3%), and (iv) tailoring survivors' needs according to their age groups (pre, 24.2% vs. post, 66.7%). Knowledge and attitude towards caring of cancer survivors were similar comparing pre- and post-course implementation.

Conclusion In an undergraduate seminar course focused on cancer survivorship, we observed an improvement of non-healthcare students' perception and awareness of cancer survivorship-related issues, advocating the value on introducing highly prevalent cancer survivorship topics early to both undergraduate STEM and non-STEM students.

Keywords Undergraduate · Cancer education · Cancer survivorship · KAP

Background

As of 2022, it is estimated that there are 18.1 million cancer survivors in the United States of America. This represents approximately 5.4% of the population. The number of cancer survivors is expected to increase to 22.5 million by 2032 [1]. The drastic increase of cancer survivors is primarily driven by the advancement of cancer diagnostics, cancer therapeutics, and earlier screening and detection of cancers. With such a growing number of people living with cancer, cancer is evolving into a chronic disease which causes a longer and deeper impact not only on patients but also to caregivers and families.

In view that cancer is more likely to affect older individuals, most young adults do not have extensive experience in interacting with cancer patients or managing complications associated with cancer. Within the United States, much of the cancer education within higher education is focused on prevention of skin cancer [2, 3] or human papillomavirus [4, 5]. Currently, didactic education on cancer is also primarily focused on healthcare students, with most educational program designed for medical [6–9] and nursing students [10–13]. These educational programs are mostly introduced as part of the undergraduate medical and nursing curriculums, and these programs are located outside of the United

✉ Alexandre Chan
a.chan@uci.edu

[1] Department of Clinical Pharmacy Practice, School of Pharmacy & Pharmaceutical Sciences, University of California, Irvine, 802 W Peltason Drive, Berk Hall, Irvine, CA 92697-4625, USA

Published online: 13 March 2024

States. Most of these courses aim to equip the workforce about cancer care. In summary, general concepts on cancer care are not routinely taught within an undergraduate curriculum in the United States.

Currently, there is literature to show the value of teaching science and healthcare topics to non-healthcare professional undergraduates [14–17]. However, it is unknown how undergraduate students perceive a didactic course that is dedicated to cancer survivorship. There is also a lack of literature on the perception of cancer survivorship and its education among undergraduate students.

At University of California, Irvine (UCI), an undergraduate seminar course focused on cancer survivorship was developed and offered annually between 2021 and 2023. Utilizing the knowledge, attitude, and practice/perception (KAP) framework [18], this study was designed to examine the impact of this course on undergraduate students. This study was also designed to clarify the value of such a course offered to undergraduate students.

Methods

Study design and setting

This was a cross-sectional survey conducted between 2021 and 2023 at UCI. Founded in 1965, UCI was ranked among the United States' top 10 public universities by U.S. News & World Report [19]. With close to 30,000 undergraduates enrolled, UCI was designated as an Asian American and Native American Pacific Islander-serving institution. This study was exempted by UCI Investigational Review Board, and a waiver of informed consent to participate was obtained for this study.

Inclusion/exclusion criteria

Undergraduate students enrolled in the Life After Cancer Freshmen Seminar course (Uni Stu 3) at UCI between 2021 and 2023 were invited to participate in this study.

Teaching pedagogy behind the freshmen seminars series and Life After Cancer

At UCI, the Freshman Seminar Series is designed to bring a high-impact learning experience to undergraduate students in their first year of study. In a small class environment, students can explore and learn about a special theme or topic by engaging with their peers and the faculty instructor. These seminars are typically scheduled for 1 h a week per quarter, with stimulating discussions and critical thinking being the primary goals. Most seminars are open to all interested students, with no pre-requisites and with enrollment preference given to freshmen. Each seminar course is designed as a one-unit small group seminar enrolling 15 students. Students normally took this course for a letter grade, though students may elect the pass/not pass option.

Designed as one of Freshmen Seminar Series by the principal investigator of this study, Life After Cancer was a 1-unit weekly seminar series designed to introduce concepts of cancer survivorship to undergraduate students. Through a total of 11 weeks of seminars, discussions, and group presentations, students learned how cancer has become a chronic condition in many survivors, especially among those who are cured. Students learned about the long-term complications of cancer treatments, as well as the cutting-edge research that is currently undertaking around the globe to mitigate these complications. The specific learning objectives of the seminar course were to:

1. Understand the definition and issues surrounding cancer survivorship.
2. Identify common toxicities and complications that are affecting various groups of cancer survivors.
3. Appreciate the disease trajectory of common cancers, from diagnosis to survivorship.
4. Discuss management strategies that are commonly employed to manage complications of cancer during survivorship.
5. Discuss the impact of cancer survivorship on the health care system.
6. Discuss the research directions that are taken to address the concerns related to cancer survivorship.

In this course, a number of topics were taught including the following: (1) an orientation of cancer management and cancer survivorship; (2) trajectory of cancer treatment from diagnosis to cancer survivorship; (3) survivorship in the elderly; (4) survivorship in pediatric, adolescent, and young adults; (5) survivorship in stem cell transplant patients; (6) model of survivorship care and rehabilitation technology.

When the course was offered in 2021, there were two assignments for this course, which included a group presentation and a term paper. However, the assignment was reduced to the group presentation only in 2022 and 2023.

- For the group presentation, students were assigned in groups to present a 15-min PowerPoint presentation with 10 min Q&A on the management of a toxicity that is commonly faced by cancer survivors. Two students were randomly paired to present on one of the following issues: cardiotoxicity, cognitive impairment, fatigue, financial toxicity, infertility, pain, and peripheral neuropathy. Students were required to use evidence-based information to introduce the management strategies.
- For the term paper, each student was assigned to write a 1500-word research paper on an assigned survivorship-related topic.

The seminar course was offered and taught for three consecutive years between 2021 and 2023. When the course first launched in January 2021, the course was taught virtually in view of the COVID-19 pandemic. The course was then subsequently taught fully in person in April 2022 and April 2023.

Data collection

During the first 2 weeks of the course, a pre-implementation survey was administered to the students. The survey was administered electronically using Qualtrics® in 2021 as the course was taught virtually, while the survey was administered on paper in 2022 and 2023. At the end of the course, the same survey was administered to the students before the end of the course.

Survey instrument

In view of the lack of a validated tool available for this study, a survey instrument was designed by the principal investigator (A.C.) of the study after conducting an extensive literature search on the impact of medical education on undergraduate students [3, 4, 7–13, 15]. As part of the survey development process, a panel of experts in cancer survivorship (R.C., Y.K., C.J.T., Y.L.T., D.Q.N.) reviewed the survey and provided feedback on the user-friendliness and appropriateness of the questions to the principal investigator. The survey instrument consisted of 4 main sections: (1) demographics, (2) knowledge of cancer survivorship, (3) attitude towards cancer survivorship, and (4) perception and awareness of cancer survivorship.

Knowledge items

Respondents were asked to determine whether each of the 10 items was true or false. Three items were related to general understanding of cancer survivorship, five items focused on outcomes/toxicities issues among cancer survivors, and two items focused on lifestyle issues in cancer survivorship. These knowledge items were derived from learning objectives of each weekly seminar.

Attitude items

Respondents were asked to rate each statement using a 4-level Likert scale (strongly disagree, disagree, agree, and strongly agree). Three items focused on respondents' comfort level in listening and responding to concerns of a cancer survivor, as well as looking after own family member who is a cancer survivor. Three items focused on respondents' attitude on education, whether it was appropriate to offer the course to college freshmen, respondents' understanding of cancer as a chronic disease, and respondents' interest in pursuing a healthcare profession (general vs cancer specialist).

Perception items

Respondents were asked to rate each statement using a 4-level Likert scale (strongly disagree, disagree, agree, and strongly agree). Six items focused on their awareness of current resources, mental health complications, benefits, research, personalization of cancer survivorship, and conceptualizing cancer as a chronic disease.

Statistical analysis

Descriptive statistics were used to summarize responses to each item. The chi-square test or Student's *t*-test was conducted for cross-sectional analyses to determine whether demographics were different before and after course implementation, with a two-sided p value < 0.05 considered statistically significant. Paired analysis was not conducted in view a few respondents dropped out during the course. All statistical analyses were conducted using SPSS version 28.

Results

Demographics

A total of 33 students completed the pre-implementation survey and 30 students completed the post-implementation survey. Ten students enrolled in 2021, 11 in 2022, and 12 in 2023. In the pre-implementation survey, majority of the respondents were female (69.7%), with a mean ($\pm$SD) age of 20 ± 1.7 years old. Seventeen respondents (51.5%) were majoring in STEM subjects, with biological sciences (24.2%), undecided (21.2%), and pharmaceutical sciences (15.2%) being the top 3 majors among the respondents. Demographics of respondents during the post-implementation survey were similar to those in the pre-implementation survey (Table 1).

Knowledge regarding cancer survivorship

Respondents' accuracy for each item ranged from 21.2 to 97.0% in the pre-implementation survey. The top 3 items that were most likely to be answered correctly were as follows: "Elderly cancer survivors are at higher risks for heart problems after chemotherapy." (97.0%), "Chemobrain tends to co-exist with cancer-related fatigue" (90.9%), and "Smoking cessation and weight management are common lifestyle management strategies in cancer survivors." (90.9%) (Table 2).

Table 1 Demographics of students responded pre- ($n=33$) and post- ($n=30$) course implementation

	Pre-implementation	Post-implementation	*p* value
Completed survey (*n*)	33	30	
Gender (*n*, %)			0.75
Male	10, 30.3%	8, 26.7%	
Female	23, 69.7%	22, 73.3%	
Mean age (SD)	20 (1.7)	20 (1.1)	0.40
Mean units (SD)	15 (2.9)	15 (2.5)	0.87
Majors (*n*, %)			0.92
STEM majors	17, 51.5%	17, 56.7%	
Anthropology	1, 3%	1, 3.3%	
Biological Sciences	8, 24.2%	7, 23.3%	
Biomedical Engineering	2, 6.1%	1, 3.3%	
Business Administration	3, 9.1%	3, 10%	
Criminology, Law & Society	0, 0%	1, 3.3%	
Economics	1, 3%	0, 0%	
Environmental Science and Policy	1, 3%	0, 0%	
History	1, 3%	0, 0%	
International Studies	1, 3%	0, 0%	
Mechanical Engineering	1, 3%	2, 6.7%	
Performance Arts	1, 3%	2, 6.7%	
Pharmaceutical Sciences	5, 15.2%	5, 16.7%	
Psychology	0, 0%	1, 3.3%	
Public Health Policy	1, 3%	1, 3.3%	
Sociology	0, 0%	1, 3.3%	
Undecided	7, 21.2%	5, 16.7%	

Table 2 Comparing respondents' true/false responses on knowledge statements pre-implementation versus post-implementation

	Statement	Answer	Category	Pre-implementation, answered correctly (*n*, %)	Post-implementation, answered correctly (*n*, %)
1	Breast cancer is largely incurable, with over half of the patients initially diagnosed as late stage	False	Disease	26, 78.8%	26, 86.7%
2	Survivorship care plan should be implemented 5 years after cancer diagnosis	False	General concept	22, 66.7%	21, 70%
3	Smoking cessation and weight management are common lifestyle management strategies in cancer survivors	True	Lifestyle	30, 90.9%	27, 90%
4	More than half of the young cancer survivors are able to resume schooling without problems after their cancer treatment	False	Outcomes/toxicities	17, 51.5%	17, 56.7%
5	Bone health should be monitored in the care of prostate and breast cancer survivors	True	Outcomes/toxicities	27, 81.8%	24, 80%
6	Cancer survivors should not receive vaccinations immediately after their chemotherapy because of their elevated risk for infections	False	Lifestyle	7, 21.2%	9, 30%
7	Elderly cancer survivors are at higher risks for heart problems after chemotherapy	True	Outcomes/toxicities	32, 97.0%	25, 83.3%
8	Fear of cancer recurrence is uncommon among cancer survivors	False	Outcomes/toxicities	29, 87.9%	25, 83.3%
9	"Chemobrain" tends to co-exist with cancer-related fatigue	True	Outcomes/toxicities	30, 90.9%	29, 96.7%
10	Current research focuses on the transition of cancer survivors from primary care settings to specialty care settings	False	General concept	8, 24.2%	6, 20%

Respondents' accuracy for each item ranged from 20.0 to 96.7% in the post-implementation survey. The top 3 items that were most likely to be answered correctly were as follows: "Chemobrain tends to co-exist with cancer-related fatigue" (96.7%), "Smoking cessation and weight management are common lifestyle management strategies in cancer survivors." (90%), and "Breast cancer is largely incurable, with over half of the patients initially diagnosed as late stage." (86.7%) (Table 2).

Attitude towards cancer survivorship

Most respondents indicated that they were most comfortable listening to cancer survivors' needs (strongly agree, 81.8%), followed by responding to survivors' concerns (strongly agree, 57.6%) as well as looking after a family member who is a cancer survivor (strongly agree, 54.5%). (Figure 1) Similar results were observed after implementation of the seminar, with most respondents indicated that they were most comfortable listening to survivors' needs (strongly agree: 76.7%), responding to their concerns (strongly agree, 53.3%) and looking after a family member who is a cancer survivor (strongly agree, 56.7%).

In terms of whether it was appropriate to educate cancer survivorship concepts to freshmen, more respondents strongly agreed after implementation (pre, 42.4% vs. post, 60.0%). Similarly, slightly more respondents strongly agreed that they were interested in pursuing a healthcare profession after their bachelor's degree (pre, 36.4% vs. post, 43.3%), as well as pursuing a healthcare profession and specialized in taking care of patients diagnosed with cancer (pre, 15.2% vs. post, 23.3%) (Fig. 2).

Perception towards cancer survivorship

Comparing respondents' perception and awareness before and after course implementation, an increase of strong agreement was observed regarding awareness of resources and guidelines available for cancer survivors to seek for information (pre, 9.1% vs. post, 36.7%), mental health complications among cancer survivors (pre, 36.4% vs. post, 56.7%), benefits of cancer survivorship care (pre, 15.2% vs. post, 40%), latest research in cancer survivorship (pre, 0% vs. 23.3%), and tailoring cancer survivors' needs according to their age groups (pre, 24.2% vs. post, 66.7%) (Fig. 3).

Discussion

In this study, we have successfully evaluated the impact of an undergraduate seminar course that was developed to teach basic concepts of cancer survivorship. Using the KAP framework, we have observed a modest improvement in students' perception and awareness towards cancer survivorship. This study is innovative because currently there is a lack of studies evaluating the impact of such clinically focused courses being taught to non-healthcare professional undergraduates. As cancer survivors become more prevalent in our society [20], there is a growing need to provide a broad overview on cancer management to young adults

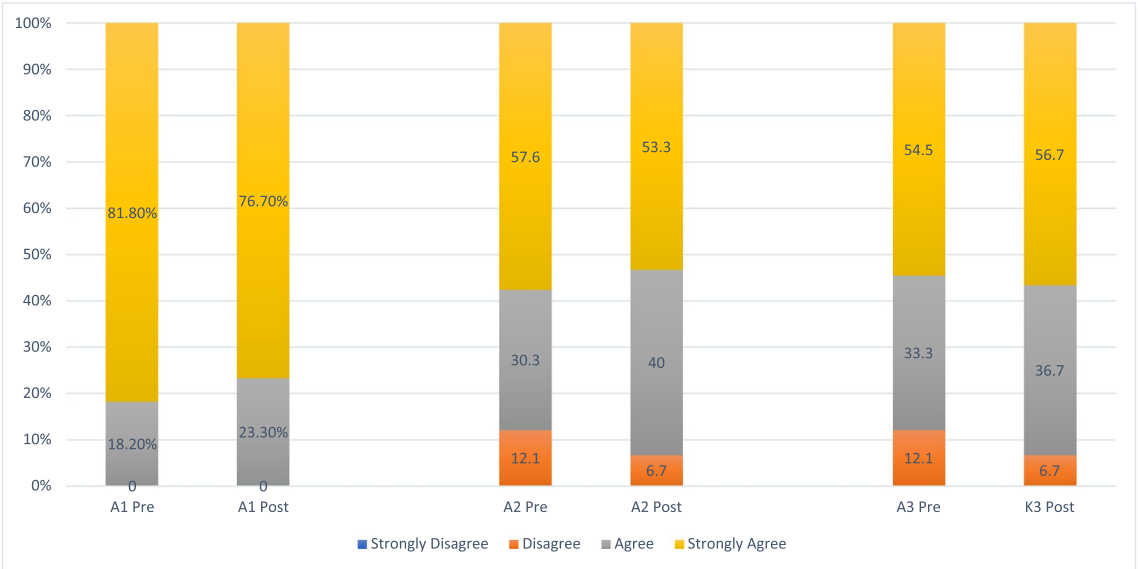

Fig. 1 Comparing respondents' responses pre-implementation ($n=33$) versus post-implementation ($n=30$) on attitude for caring cancer survivors. (A1) I am comfortable in listening to the concerns of a cancer survivor; (A2) I am comfortable in responding to the concerns of a cancer survivor; (A3) I am comfortable in looking after my own family member who is a cancer survivor

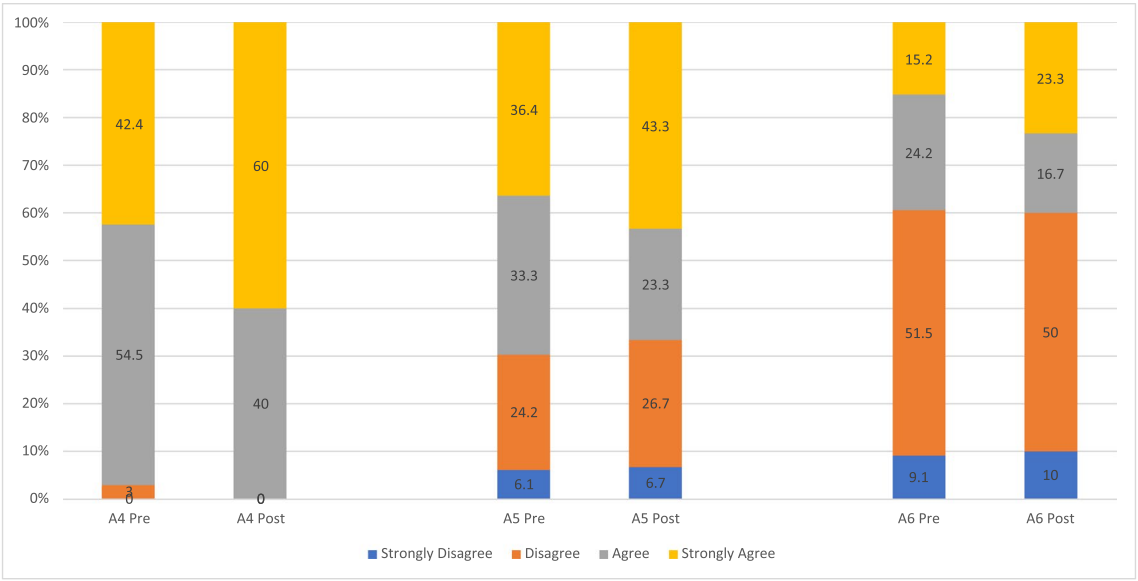

Fig. 2 Comparing respondents' responses pre-implementation ($n=33$) versus post-implementation ($n=30$) on education perspectives related to cancer survivorship. (A4) It is appropriate timing to educate concepts of cancer survivorship to university freshmen; (A5) I am interested in pursuing a healthcare profession after my bachelor's degree; (A6) I am interested in pursuing a healthcare profession after my bachelor's degree and specialized in taking care of patients diagnosed with cancer

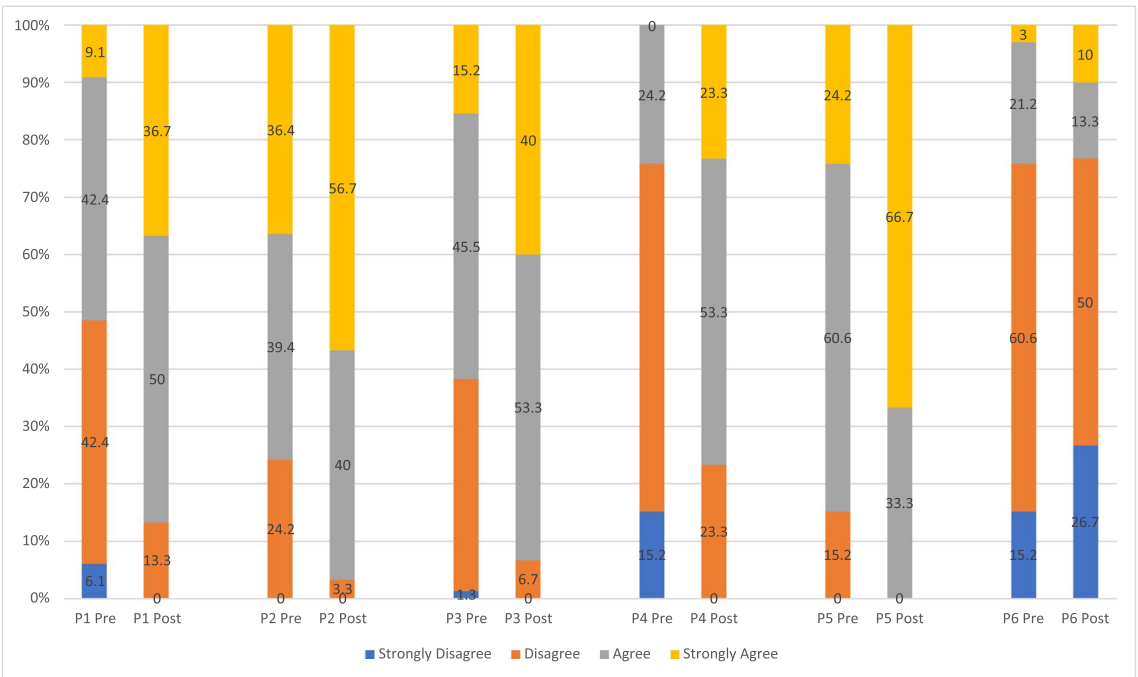

Fig. 3 Comparing respondents' responses pre-implementation ($n=33$) versus post-implementation ($n=30$) on their perceptions and awareness related to cancer survivorship. (P1) I am aware of the resources and guidelines available for cancer survivors to seek for information; (P2) I am aware of the mental health complications among cancer survivors; (P3) I am aware of the benefits of cancer survivorship care; (P4) I am aware of the latest research areas in cancer survivorship; (P5) I am aware that the caring of cancer survivors needs to be tailored according to their age groups; (P6) I find it difficult to conceptualize cancer as a chronic disease

who are undergoing tertiary education. This study provides insights to the education community on the value to offer clinically inclined courses in the earlier part of undergraduate non-healthcare professional education.

Most notably, positive improvements related to the perception and awareness of cancer survivorship were observed. We speculated that these improvements were likely contributed by the various discussions and activities conducted during the course. For example, the group assignment on management of cancer-related toxicities required students to actively look up clinical trials and guidelines on cancer survivorship, as well as the latest areas in cancer survivorship research. Several seminars were devoted to describing the different challenges encountered by various age groups of cancer survivors (pediatrics vs. adolescent and young adults [21] vs. elderly [22]), which has likely increased awareness of the issues and complications faced by survivors of different age groups and potential disparities [23]. The discussions on physical and psychosocial impacts frequently faced by cancer survivors might have also increased students' understanding of the mental health complications, as well as the benefit of cancer survivorship care. Overall, the course has successfully increased and improved the perception and awareness of cancer survivorship issues among students. The required assignments have also exposed the students to evidence-based healthcare literature, which may improve student empowerment within the learning process [24].

Although the seminar nature of the course has improved perceptions and awareness of cancer survivorships-related issues, two other aspects were not improved among students enrolled in the course: knowledge and attitude towards caring of cancer survivors. Regarding knowledge level, we did not observe any dramatic changes over time. One may argue that students answered certain knowledge items correctly prior to the course because undergraduate students in general have good test-taking skills and perhaps have intuitive knowledge. For example, most students likely found it sensible for cancer survivors to engage smoking cessation and weight management, hence explaining the high accuracy rates observed. Certain knowledge items, however, may be controversial (e.g., whether cancer survivors should receive vaccinations post-chemotherapy) which could be challenging for non-healthcare professional students to provide accurate responses. Lastly, concepts may not have been discussed in detail in class (e.g., transition of cancer survivors from primary care settings to specialty care settings), hence affecting the accuracy rate.

Additionally, we did not observe a change to the students' interest to provide care to people diagnosed with cancer before and after the implementation of the course. We observed that students were more comfortable with listening to the concerns of cancer survivors (all agreed), with a small proportion of students disagreed that they were comfortable responding and listening to the specific concerns from cancer survivors (including family members). As this course was designed to introduce concepts of cancer survivorship, including practical and research concepts, the course was not designed to provide empathy training which is an important to trait for anyone to provide survivorship care. Studies have shown that empathy-training is very specific which requires specific training activities [25]. It is also unknown what is the most optimal approach to motivate undergraduate non-healthcare students wanting to provide care to cancer patients. In the nursing literature, it was shown that experiential learning is most crucial to increase confidence and reduce fears among undergraduates nurses to provide care to cancer patients [26]. This is a difficult gap to bridge solely through a seminar course, considering the lack of a dedicated experiential component of the students' training, needless to say that these students also lacked professional identity. Future courses may want to consider incorporating an experiential component, such as interviewing a cancer survivor, in order to provide students opportunity to reflect and create relevance to the topic.

Designed as an introductory course on cancer survivorship to non-healthcare professional undergraduate students, the course has taken an innovative approach to introduce survivorship concepts. Nonetheless, there were challenges associated with the administration of the course. Firstly, with the limited time given (1 h per week for 11 weeks), it was very ambitious to introduce all vital concepts in detail. At UCI, a 1-unit course is roughly equivalent to 3 h of work per week by the students. Additionally, the course was enrolled by students with very diverse, including non-STEM backgrounds (> 40%) which may require extra effort to fully comprehend some of the topics. These students were also carrying a heavy workload (an average of 15 units per quarter). With these considerations in mind, one may question whether an introductory course on cancer survivorship was appropriate to be offered to undergraduate non-healthcare professional students. Despite these limitations, the course was very successful and well-liked by enrolled students. This course was designed to provide a sufficiently broad overview of the topics, with the aim to help students overcoming the fears to learn about a medical topic. Lastly, the course was also designed to introduce the latest research related to cancer survivorship, with the aim to inspire students to consider future graduate studies in healthcare-related subjects.

There were multiple strengths with our study. Data from three separate cohorts were included, as well as pre- and post-assessments, which allowed the comparison of outcomes over time. The study has also evaluated a

few dimensions through our surveys, which provided us with information on which domain student had the most benefit from with our approach. There were also several limitations. In view that a few students dropped the course after completing the pre-implementation survey, it was not possible to have the same number of completed questionnaires for pre- and post-implementation. Additionally, the survey results were anonymized, hence it was not possible to evaluate the paired outcomes. The survey primarily captured quantitative results using the KAP approach, hence it did not capture students' motivations and feelings on this course. Future studies may consider incorporating qualitative approaches (through focus groups or 1-on-1 interviews) to capture responses from enrolled students.

Conclusions

In an undergraduate seminar course focused on cancer survivorship, an improvement of students' perceptions and awareness of cancer survivorship-related issues was observed, advocating the value on introducing highly prevalent cancer survivorship topics early to both undergraduate STEM and non-STEM students. Future studies should evaluate whether incorporating experiential learning and additional information would improve knowledge and attitude of cancer survivorship among undergraduates.

Acknowledgements The author gratefully acknowledges the support of the students who have enrolled in the course (Uni Stu 3) and participated in the study, Sara Sarpas for providing support, and the expert panel (Raymond Chan, Yu Ke, Ding Quan Ng, Chia Jie Tan, and Yi Long Toh) for providing feedback on the survey instrument.

Author contribution A.C. wrote the main manuscript text, prepared figures, and reviewed the manuscript.

Data availability Data is available upon request.

Declarations

Ethics approval and consent to participate Not applicable.

Competing interests The author has declared no competing interest.

References

1. American Cancer Society (2022) Cancer treatment & survivorship facts & figures 2022–2024. Atlanta: American Cancer Society
2. Brady HL, Hamilton JG, Kaphingst KA et al (2022) 'I had a bigger cancer risk than I thought...': the experience of receiving personalized risk information as part of a skin cancer prevention intervention in the college setting. Health Expect 25:2937–2949
3. Lamanna LM (2004) College students' knowledge and attitudes about cancer and perceived risks of developing skin cancer. Dermatol Nurs 16(161–4):175–176
4. Goldfarb JA, Comber JD (2022) Human papillomavirus (HPV) infection and vaccination: a cross-sectional study of college students' knowledge, awareness, and attitudes in Villanova, PA. Vaccine X 10:100141
5. Klasko-Foster LB, Przybyla S, Orom H et al (2020) The influence of affect on HPV vaccine decision making in an HPV vaccine naive college student population. Prev Med Rep 20:101195
6. Moncaliano MC, Mahadevan A, Liu JC et al (2023) A virtual curriculum to increase exposure to oncologic subspecialties for undergraduate medical students. J Cancer Educ 38:985–990
7. Oskvarek J, Braunstein S, Farnan J et al (2016) Medical student knowledge of oncology and related disciplines: a targeted needs assessment. J Cancer Educ 31:529–532
8. Uijtdehaage S, Hauer KE, Stuber M et al (2009) A framework for developing, implementing, and evaluating a cancer survivorship curriculum for medical students. J Gen Intern Med 24(Suppl 2):S491–S494
9. Uijtdehaage S, Hauer KE, Stuber M et al (2009) Preparedness for caring of cancer survivors: a multi-institutional study of medical students and oncology fellows. J Cancer Educ 24:28–32
10. Altre R, Chou FY (2022) Nursing students' knowledge and attitude toward cancer survivorship. J Cancer Educ 37:1312–1321
11. Dietmann ME (2017) Nurse faculty beliefs and teaching practices for the care of the cancer survivor in undergraduate nursing curricula. J Cancer Educ 32:764–770
12 Edwards D, Anstey S, Kelly D et al (2016) An innovation in curriculum content and delivery of cancer education within undergraduate nurse training in the UK. What impact does this have on the knowledge, attitudes and confidence in delivering cancer care? Eur J Oncol Nurs 21:8–16
13. Fitch M, McAndrew A, Turner F et al (2011) Survivors teaching students: increasing awareness about ovarian cancer. Can Oncol Nurs J 21:16–26
14. Edirippulige S, Samanta M, Armfield NR (2018) Assessment of self-perceived knowledge in e-health among undergraduate students. Telemed J E Health 24:139–144
15. O'Brocta R (2024) Description and student perceptions of a medications dosing calculations course for non-healthcare majors. Int J Pharm Pract 32(1):104–106
16. Bradforth SE, Miller ER, Dichtel WR et al (2015) University learning: improve undergraduate science education. Nature 523:282–284
17. Wrighting DM, Dombach J, Walker M et al (2021) Teaching undergraduates to communicate science, cultivate mentoring relationships, and navigate science culture. CBE Life Sci Educ 20:31

18. Andrade C, Menon V, Ameen S et al (2020) Designing and conducting knowledge, attitude, and practice surveys in psychiatry: practical guidance. Indian J Psychol Med 42:478–481
19. UCI News (2023) UCI is ranked among nation's top 10 public universities for ninth year in a row. https://news.uci.edu/2023/09/18/uc-irvine-is-ranked-among-nations-top-10-public-universities-for-ninth-year-in-a-row/.
20. Miller KD, Nogueira L, Devasia T et al (2022) Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin 72:409–436
21. Chan A, Ports K, Ng DQ, et al (2023) Unmet needs, barriers, and facilitators for conducting adolescent and young adult cancer survivorship research in Southern California: a Delphi survey. J Adolesc Young Adult Oncol 12(5):765–772
22. Bluethmann SM, Mariotto AB, Rowland JH (2016) Anticipating the "silver tsunami": prevalence trajectories and comorbidity burden among older cancer survivors in the United States. Cancer Epidemiol Biomarkers Prev 25:1029–1036
23. National Cancer Institute (2024) Cancer Disparities. https://www.cancer.gov/about-cancer/understanding/disparities.
24. Russell JS, Martin L, Curtin D et al (2004) Non-science majors gain valuable insight studying clinical trials literature: an evidence-based medicine library assignment. Adv Physiol Educ 28:188–194
25. Numanee IZ, Zafar N, Karim A et al (2020) Developing empathy among first-year university undergraduates through English language course: a phenomenological study. Heliyon 6:e04021
26. Cannity KM, Banerjee SC, Hichenberg S et al (2021) Acceptability and efficacy of a communication skills training for nursing students: building empathy and discussing complex situations. Nurse Educ Pract 50:102928

Chapter 9: Discussion and conclusion

9.1 Introduction

This chapter summarizes and discusses the key findings and implications from the published papers presented in Chapters 3 to 8, with a focus on the three main aims of the thesis. Firstly, findings related to understanding cancer survivorship needs are considered. This is followed by the learnings from three studies to design and test novel, multidisciplinary interventions at different points along the cancer care continuum, taking into account factors such as health equity and cultural adaptation. Finally transferable lessons from a study to embed research findings into education are discussed, including implications for future research translation initiatives. The chapter concludes with reflections on the limitations of the thesis and recommendations for continuing and future research.

9.2 Discussion and Implication of Findings

Throughout this thesis, a range of approaches has been employed to address the evolving unmet needs experienced by cancer patients and survivors across different phases of the cancer care continuum. Given the dynamic nature of physical and psychological symptoms over time, the findings reinforce the importance of implementing tailored interventions at appropriate stages of survivorship. This work also highlights the interdisciplinary and patient-centered nature of survivorship care, emphasizing a holistic approach through the engagement of diverse healthcare professionals. (Figure 9.1) The interventions developed in this thesis primarily incorporate three key strategies: (i) leveraging multidisciplinary teams, (ii) applying multilevel intervention designs, and (iii) utilizing culturally appropriate approaches to deliver survivorship care. Additionally, this thesis extends its scope by translating foundational concepts of cancer survivorship into undergraduate education through a dedicated course, aiming to assess its impact on students' knowledge, attitudes, and perceptions of survivorship issues.

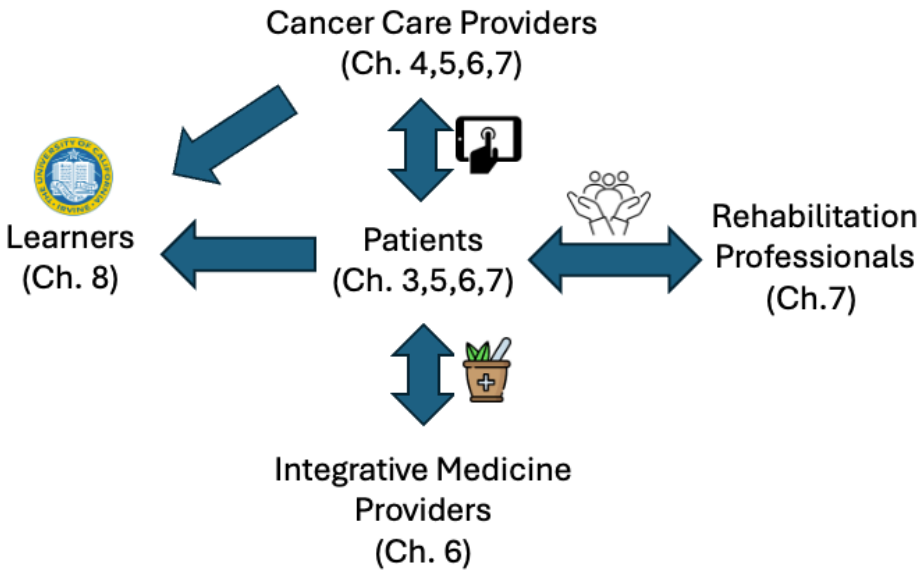

Figure 9.1. Interactions among various stakeholders within each chapter of the thesis.

It is important to consider different types of modalities to identify and manage patients' problems within the overall treatment continuum. For example, for patients who are newly diagnosed with cancer and initiating cancer treatment, the use of a PRO tool can help with monitoring symptoms, allowing personalized and rapid, targeted management. For patients who are actively receiving treatment and experiencing side effects that are difficult to treat, integrative modalities may provide relief to patients; however, the importance of standardization of these approaches is needed. Lastly, community survivors may benefit from educational programs, such as a group-based approach, which is outpatient-based and, at the same time, allows survivors to build up their confidence and self-efficacy.

In the following sections, I will discuss the findings that are specific to each aim of the thesis, and their implications in survivorship care and future research.

Specific Aim 1: To investigate the unmet needs and symptoms of cancer survivors among relevant stakeholders.

As we evaluate and compare the top unmet needs that were observed in BCS and AYA cancer survivors, consistent themes surfaced, which included mental health issues, strategies to improve neurocognitive disorders and related school/occupational performance, and fatigue symptoms, and these problems could occur throughout the cancer continuum. Our findings align with existing literature regarding the prevalence and patterns of neuropsychiatric conditions among AYA cancer survivors. For instance, a real-world study conducted approximately nine years post-diagnosis found that conditions such as neuropathy, memory loss, and epilepsy were significantly more common among AYA cancer survivors compared to matched non-cancer controls. (161) Similarly, a multi-country study examining quality of life and symptom burden among Australian and Asian cancer survivors reported high prevalence of neuropsychiatric symptoms—including fatigue, pain, and insomnia—with minimal differences observed between high- and low-income countries. (162) These findings, along with findings from this study aim, underscore the ongoing need for standardized assessment approaches and tailored evaluation tools to address unmet psychosocial needs. (163) Current literature strongly advocates for the integration of mental health services into routine cancer care, irrespective of geographical or socioeconomic context, to mitigate emotional distress and enhance overall patient well-being. (32) In the Asian context, strategic action plans are essential to reduce disparities in care, including the exploration of cost-effective strategies and the development of localized guidelines to improve the delivery of psychosocial care for cancer survivors.

Specific Aim 2: To experiment with novel, multidisciplinary interventions and implement them in the routine care of cancer survivors.

To address the unmet needs that were uncovered from our survivors in Aim 1, I pragmatically designed and experimented with three different interventions to improve various survivorship issues that were identified among them. These interventions were also strategically employed within the different trajectories as patients go through the different phases of the cancer continuum: from the point of diagnosis, while they were undergoing treatment, and at completion of their treatment. The findings of these interventions have also addressed a number of unmet needs that were raised in Chapter 1, and I will discuss the implications further below:

9.2.2.1. Multilevel interventions improve cancer survivorship and reduce health disparities

Studies in this aim have demonstrated that multilevel interventions can effectively address individual symptoms among cancer survivors, while also enhancing survivorship care through broader systemic approaches. As discussed in Chapter 2, beyond the improvement of clinical outcomes that we would observe on the individual level, interventions involving communication with healthcare providers (as discussed in Chapters 5 and 6) and community-level engagement (Chapter 7) have consistently been shown to improve the overall provision of care. Multilevel strategies are particularly valuable in cancer care, as survivors often transition through different phases of treatment and recovery, requiring coordinated support across various levels of influence. (164) Evidence from a recent clinical trial comparing health coach-led multilevel interventions to clinician-directed care in advanced cancer patients revealed improved utilization of hospice and palliative services. (165) Similarly, a recently conducted qualitative study involving metastatic BCS highlights the capacity of multilevel interventions to address the complex and multifaceted needs of this population. (166) Importantly, these approaches not only enhance clinical outcomes within individual survivors as we have observed in these interventional studies, but more importantly these approaches have also improved service-

related outcomes such as patient satisfaction, by fostering communication and collaboration among patients, caregivers, clinicians, and allied health professionals. (167)

Studies in this aim have also highlighted how a multilevel approach can help address health disparities that impact equitable access to supportive care interventions for cancer survivors. The use of ePRO, as discussed in Chapter 5, enabled timely identification of symptoms and facilitated appropriate therapeutic responses. Additionally, the group-based intervention described in Chapter 7 ensured that survivors in the community settings received essential post-treatment care that might otherwise have been overlooked. These findings emphasize the importance of integrating healthcare interventions at strategic points along the cancer care continuum to mitigate disparities and enhance the quality and accessibility of survivorship care.

9.2.2.2 Incorporation of multidisciplinary care within cancer survivorship helps to address the lack input from patients

Findings under this study aim have also underscored the value of multidisciplinary collaboration in enhancing cancer survivorship care. Strategic integration of allied health professionals has demonstrated tangible health benefits across various interventions. In Chapter 5, the involvement of oncology pharmacists facilitated timely symptom management by enabling early identification and evidence-based treatment of patient-reported issues. Chapter 6 highlighted the role of traditional Chinese medicine physicians in conducting syndrome differentiation assessments, ensuring the safe and effective delivery of integrative oncology care. Chapter 7 illustrated how community-based group interventions, led by allied health providers such as physical therapists and psychologists, contributed to improved physical health outcomes through survivorship education. These findings align with a recent survey of 384 survivorship programs across the United States, which revealed that nurses, social workers, occupational therapists, and physical therapists are commonly engaged in survivorship care within multidisciplinary care teams. (168)

By incorporating a broader range of healthcare professionals, our approach also addresses longstanding challenges in specialist-driven models—such as limited time for survivorship discussions and gaps in supportive care expertise among oncologists. (169) This is particularly critical for the effective delivery of self-management strategies, which play a vital role in promoting and sustaining long-term wellness among cancer survivors. (170) Nevertheless, the optimal timing and cost-effectiveness of engaging these professionals remain areas for future research to ensure sustainable and impactful survivorship care delivery.

9.2.2.3 Culturally appropriate care improves survivorship outcomes and helps reducing disparities of care

A distinctive feature across the interventions presented under this aim is the incorporation of culturally appropriate care, which was operationalized in various ways to enhance relevance and accessibility for diverse survivor populations. In Chapter 5, ethnic minority participants were provided with language-specific ePRO tools to facilitate accurate symptom identification and timely management. Chapter 6 involved the use of a TCM formulation for survivors experiencing CRF during chemotherapy, with a matching placebo designed to replicate the taste and smell of the intervention, ensuring cultural sensitivity and methodological rigor. In Chapter 7, allied health professionals employed culturally relevant strategies—such as using mahjong to support cognitive function and Tai Chi exercises to alleviate fatigue and other symptoms—within a community-based group intervention. These approaches reflect findings from a recent systematic review, which noted that most culturally tailored survivorship interventions for racial and ethnic minorities primarily address sociocultural and linguistic barriers, often structural in nature and likely to influence intervention uptake. (171) Notably, none of the interventions presented in this thesis employed a behavioral framework, such as social cognitive theory, in their cultural adaptation strategies. This observation reflects a broader trend identified in recent literature, which indicates that most culturally

appropriate survivorship interventions targeting racial and ethnic minority populations primarily focus on sociocultural and linguistic adaptations. While these approaches help address structural barriers to intervention uptake, the lack of behavioral frameworks suggests a need for more sophisticated strategies in future research. (172) Incorporating such frameworks may enhance the internalization of health benefits and promote sustained engagement with survivorship interventions among racially and ethnically diverse populations.

Specific Aim 3: To develop and evaluate an education-focused translational intervention embedding contemporary principles and research evidence on survivorship care.

As an extension of the survivorship intervention studies presented in this thesis, a pedagogical approach was adopted to enhance translational science strategies and solutions. This specific aim was designed to improve awareness and understanding of cancer survivorship among undergraduate students, particularly those from non-healthcare backgrounds. Notably, the intervention led to improved perceptions and heightened awareness of survivorship-related issues, underscoring the value of integrating foundational and practical cancer survivorship content into undergraduate education. However, improvements in knowledge acquisition were not evident at the conclusion of the intervention, a finding consistent with previous studies evaluating similar educational efforts in undergraduates. (173) Several factors may explain this outcome. First, students may have lacked the necessary scientific foundation to fully comprehend the material presented, limiting their ability to retain and apply the knowledge. Second, the seminar-style format may not have encouraged sufficient engagement or study outside of class, resulting in poor retention. Third, the assessment tools used to evaluate knowledge may have been too advanced for non-healthcare students, suggesting a need for better alignment between instructional content and evaluation methods. Nonetheless, this study fulfilled its original objective of exploring the translational potential of cancer survivorship research and concepts through the implementation of a dedicated undergraduate course.

There is much potential for the translation of research knowledge into future cancer care courses. With the rise of artificial intelligence (AI) as well as biomedical engineering techniques, follow-up courses can be designed to educate undergraduate students on how advanced technologies can play a role in the rehabilitation process of cancer survivorship. This includes the use of virtual technology to improve the delivery of exercises and physical therapy sessions, as well as the use of AI to optimize the identification of patients who are at risks for cancer-related toxicities. These courses may stimulate innovativeness among trainees, which may lead to the creation of novel interventions that would help to address unmet needs within the survivorship community.

9.3 Thesis limitations and challenges

This thesis adopts a pragmatic approach to identifying the survivorship challenges faced by cancer survivors and designing targeted interventions to address their unmet needs across the cancer care continuum.

Although we have observed real-world findings that can address survivorship care needs, it is important to acknowledge limitations, as studies were conducted in specific patient populations that may not be representative of all cancer survivors. The patient groups selected in the reported studies were identified because they represented priority groups for the cancer center where I was employed and conducted the study. However, the findings relating to survivor needs and interventions to address identified needs may not all be generalizable to the cancer survivorship population as a whole. Despite this limitation, findings related to the interventions, such as the use of ePRO tools and the use of integrative oncology approaches should have wider transferability, as these interventions have demonstrated in other similar studies that they are effective for managing cancer-related symptoms.

Furthermore, despite the fact that I have mostly used PRO tools to evaluate the change of clinical outcomes in enrolled patients, at times it might be beneficial to incorporate objective

measures that can provide another dimension of clinical efficacy improvement. Biomarkers can provide us with mechanistic insights into the symptom changes as objective assessments, which can certainly provide additional evidence regarding patients' symptom improvement. The objective results would also allow us to evaluate the outcomes without running into the risk of placebo (174) and Hawthorne effects (175). For example, in our clinical trial, we were using self-reported questionnaires to evaluate the change in cognitive symptoms. However, it would also be prudent to incorporate objective neuropsychological assessments that would complement the self-reported findings from patients, in order to provide a full picture of both subjective and objective responses for evaluation. Additionally, the use of more robust designs (such as RCT) may allow us to eliminate potential placebo effects (in the case of the IO interventional trial). However, this strategy may not be feasible in all study designs, such as our ePRO implementation pilot study. Future studies should consider employing more robust research designs, such as stepped wedge or cluster randomized trials, which may offer greater methodological rigor and be better suited to evaluating complex interventions in cancer survivorship care.

9.4 Recommendations for future studies

In summary, this thesis proposes a comprehensive approach to cancer survivorship care that leverages a multidisciplinary team to deliver multilevel, culturally sensitive interventions aimed at alleviating survivorship-related symptoms. Building upon the findings of this thesis, I propose several avenues for future research that can further advance the field of cancer survivorship.

While this thesis focused on the role of TCM as an intervention in symptom management (Chapter 6), it is important to acknowledge that other integrative modalities—such as acupuncture and Tai Chi—remain underexplored and warrant further investigation, especially in the area of CRF. (176) These therapies show promise in addressing CRF and other survivorship issues, including peripheral neuropathy and vasomotor symptoms such as anxiety, depression and pain, which are

prevalent among cancer survivors.(146, 177) Given the growing body of evidence and emerging clinical guidelines supporting these interventions, future research should not only evaluate their efficacy but also address barriers to access. These barriers may be educational, structural, or systemic, and overcoming them will require targeted interventions to reduce disparities in survivorship care.

Second, the integration of advanced technologies into survivorship care strategies is increasingly critical. Findings from the practitioner survey (Chapter 3) highlight workforce limitations as a significant challenge in engaging survivors in research and care. Although this thesis did not directly assess technological solutions, innovations such as telehealth have gained momentum, particularly in the post-COVID-19 era. (178) Telehealth can reduce the burden of in-person visits, facilitate triage of treatment-related toxicities, and enable coordinated care from multidisciplinary teams. Additionally, emerging technologies like AI offer potential for enhancing survivorship care through tools such as ePROs. (179, 180) AI-driven analysis of ePRO data may help identify high-risk patients who require timely intervention, thereby improving clinical outcomes. As mentioned earlier, translated research from these advanced technology interventions may also further improve education outcomes in learning curriculums.

Third, while this thesis primarily focuses on the various treatment phases of the cancer continuum, future research should explore the potential of prehabilitation strategies to proactively mitigate survivorship symptoms. (181, 182) Evidence is accumulating around the benefits of exercise-based prehabilitation in newly diagnosed lung cancer patients, particularly in improving pulmonary function and related outcomes. (183) Similarly, dietary interventions are crucial for gastrointestinal cancer survivors and may help reduce the risk of comorbidities. (184) Investigating whether multidisciplinary, culturally tailored prehabilitation programs can enhance survivorship outcomes is a promising avenue. Such proactive approaches may prevent unnecessary physical and psychological distress, ultimately contributing to more holistic and effective survivorship care.

Lastly, although culturally appropriate care might help to reduce health disparities and inequalities of care, other strategies beyond addressing linguistic barriers (such as employing social cognitive theory) should be considered. Future RCTs could evaluate whether a combination of various strategies may further reduce health disparities. Furthermore, this thesis has employed multilevel interventions to influence health disparities on the individual, interpersonal, and community levels (Chapter 2, Figure 2). Future studies should evaluate how to engage societal influence, likely through health policies, to address health disparities in cancer survivorship care.

9.5 Reflections on the PhD journey

As a clinician scientist who is routinely providing care to cancer survivors, working on this thesis has enabled me to rethink the possibilities of how to evolve survivorship care, as well as to challenge the status quo of the way survivorship care is currently provided. Within the complex and changing landscape of the treatment continuum, there is a need to develop innovative strategies to monitor patients' status by embracing new technologies. Hence, I have started capturing PROs monitoring using telemedicine strategies in my new projects.

Building on the success of the group-based intervention for cancer survivors as well as the increasing acceptance of evidence-based integrative oncology, I am currently exploring how other forms of integrative therapies, such as acupuncture, can be offered as group interventions in the community setting to further improve patients' access to these interventions. There is an increasing amount of data suggesting acupuncture is effective in addressing pain symptoms in cancer survivors, and there is a need to conduct further studies to evaluate how these interventions can be effectively implemented in the community setting.

Finally, given early screening as well as improvement of disease awareness, we will continue to observe an increase in the prevalence of cancer in our society. No one should be left behind to learn about the concepts of cancer survivorship and the fundamentals of the management of this debilitating disease. This thesis underscores the growing importance of integrating healthcare topics into tertiary education, given their potential to positively influence attitudes and health beliefs. Such educational initiatives play a vital role in promoting preventive health measures and enhancing overall physical and mental well-being across society.

9.6 Summary

This chapter concludes this thesis by drawing together the findings across the six studies that have been presented. A central theme that emerges is the critical importance of implementing innovative, patient-centered interventions to address the diverse challenges faced by cancer survivors across the treatment continuum—from diagnosis through active treatment and into post-treatment care. For these strategies to be effective, they must be multidisciplinary, multilevel, and culturally responsive. The thesis also demonstrates the feasibility of translating survivorship research into education within tertiary academic settings, showing positive shifts in learners' attitudes and perceptions toward survivorship care. Overall, this thesis underscores the value of conducting pragmatic research to meet the evolving needs of cancer survivors.

Bibliography

1. National Cancer Institute Division of Cancer Control & Population Sciences. Statistics and Graphs 2025. Available from: https://cancercontrol.cancer.gov/ocs/statistics.

2. Shapiro CL. Cancer Survivorship. The New England journal of medicine. 2018;379(25):2438-50.

3. Filho AM, Laversanne M, Ferlay J, Colombet M, Pineros M, Znaor A, et al. The GLOBOCAN 2022 cancer estimates: Data sources, methods, and a snapshot of the cancer burden worldwide. Int J Cancer. 2024.

4. Ehlers DK, Weaver N, Ma J, Mama SK, Page LL, Rowland J, et al. Functional limitations among adult cancer survivors in the United States. J Cancer Surviv. 2024.

5. Lee EM, Jimenez-Fonseca P, Galan-Moral R, Coca-Membribes S, Fernandez-Montes A, Sorribes E, et al. Toxicities and Quality of Life during Cancer Treatment in Advanced Solid Tumors. Curr Oncol. 2023;30(10):9205-16.

6. Baltussen JC, de Glas NA, van Holstein Y, van der Elst M, Trompet S, Uit den Boogaard A, et al. Chemotherapy-Related Toxic Effects and Quality of Life and Physical Functioning in Older Patients. JAMA Netw Open. 2023;6(10):e2339116.

7. Ng T, Chan M, Khor CC, Ho HK, Chan A. The genetic variants underlying breast cancer treatment-induced chronic and late toxicities: a systematic review. Cancer Treat Rev. 2014;40(10):1199-214.

8. Kuderer NM, Desai A, Lustberg MB, Lyman GH. Mitigating acute chemotherapy-associated adverse events in patients with cancer. Nature reviews Clinical oncology. 2022;19(11):681-97.

9. Lustberg MB, Kuderer NM, Desai A, Bergerot C, Lyman GH. Mitigating long-term and delayed adverse events associated with cancer treatment: implications for survivorship. Nature reviews Clinical oncology. 2023;20(8):527-42.

10. Jordan K, Chan A, Gralla RJ, Jahn F, Rapoport B, Ruhlmann CH, et al. Emetic risk classification and evaluation of the emetogenicity of antineoplastic agents-updated MASCC/ESMO consensus recommendation. Support Care Cancer. 2023;32(1):53.

11. Larkin PJ, Cherny NI, La Carpia D, Guglielmo M, Ostgathe C, Scotte F, et al. Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29(Suppl 4):iv111-iv25.

12. Bossi P, Antonuzzo A, Cherny NI, Rosengarten O, Pernot S, Trippa F, et al. Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29(Suppl 4):iv126-iv42.

13. Wikramanayake TC, Haberland NI, Akhundlu A, Laboy Nieves A, Miteva M. Prevention and Treatment of Chemotherapy-Induced Alopecia: What Is Available and What Is Coming? Curr Oncol. 2023;30(4):3609-26.

14. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33(28):3199-212.

15. Barroso A, Estevinho F, Hespanhol V, Teixeira E, Ramalho-Carvalho J, Araujo A. Management of infusion-related reactions in cancer therapy: strategies and challenges. ESMO Open. 2024;9(3):102922.

16. Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29(Suppl 4):iv166-iv91.

17. Pentheroudakis G, Orecchia R, Hoekstra HJ, Pavlidis N, Group EGW. Cancer, fertility and pregnancy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v266-73.

18. Chan A, Hertz DL, Morales M, Adams EJ, Gordon S, Tan CJ, et al. Biological predictors of chemotherapy-induced peripheral neuropathy (CIPN): MASCC neurological complications working group overview. Support Care Cancer. 2019;27(10):3729-37.

19. Tel H, Tel H, Doğan S. Fatigue, anxiety and depression in cancer patients. Neurology, Psychiatry and Brain Research. 2011;17(2):42-5.

20. Carroll JE, Small BJ, Tometich DB, Zhai W, Zhou X, Luta G, et al. Sleep disturbance and neurocognitive outcomes in older patients with breast cancer: Interaction with genotype. Cancer. 2019;125(24):4516-24.

21. Carter J, Lacchetti C, Andersen BL, Barton DL, Bolte S, Damast S, et al. Interventions to Address Sexual Problems in People With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Adaptation of Cancer Care Ontario Guideline. J Clin Oncol. 2018;36(5):492-511.

22. Cheung YT, Chui WK, Chan A. Neuro-cognitive impairment in breast cancer patients: pharmacological considerations. Crit Rev Oncol Hematol. 2012;83(1):99-111.

23. Alexandre J, Cautela J, Ederhy S, Damaj GL, Salem JE, Barlesi F, et al. Cardiovascular Toxicity Related to Cancer Treatment: A Pragmatic Approach to the American and European Cardio-Oncology Guidelines. J Am Heart Assoc. 2020;9(18):e018403.

24. Dhamija E, Meena P, Ramalingam V, Sahoo R, Rastogi S, Thulkar S. Chemotherapy-induced pulmonary complications in cancer: Significance of clinicoradiological correlation. Indian J Radiol Imaging. 2020;30(1):20-6.

25. Wood ME, Vogel V, Ng A, Foxhall L, Goodwin P, Travis LB. Second malignant neoplasms: assessment and strategies for risk reduction. J Clin Oncol. 2012;30(30):3734-45.

26. Berman R, Davies A, Cooksley T, Gralla R, Carter L, Darlington E, et al. Supportive Care: An Indispensable Component of Modern Oncology. Clin Oncol (R Coll Radiol). 2020;32(11):781-8.

27. Multinational Association of Supportive Care in Cancer (MASCC). What is Supportive Care? (para 2) 2025. Available from: https://mascc.org/what-is-supportive-care/.

28. Scotte F, Taylor A, Davies A. Supportive Care: The "Keystone" of Modern Oncology Practice. Cancers (Basel). 2023;15(15).

29. Ozdemir BC, Gerard CL, Espinosa da Silva C. Sex and Gender Differences in Anticancer Treatment Toxicity: A Call for Revisiting Drug Dosing in Oncology. Endocrinology. 2022;163(6).

30. Bellizzi KM, Mustian KM, Palesh OG, Diefenbach M. Cancer survivorship and aging : moving the science forward. Cancer. 2008;113(12 Suppl):3530-9.

31. Pisu M, Martin MY. Financial toxicity: a common problem affecting patient care and health. Nat Rev Dis Primers. 2022;8(1):7.

32. Chan A, Eng L, Jiang C, Dagsi M, Ke Y, Tanay M, et al. Global disparities in cancer supportive care: An international survey. Cancer medicine. 2024;13(17):e70234.

33. Penedo FJ, Natori A, Fleszar-Pavlovic SE, Sookdeo VD, MacIntyre J, Medina H, et al. Factors Associated With Unmet Supportive Care Needs and Emergency Department Visits and Hospitalizations in Ambulatory Oncology. JAMA Netw Open. 2023;6(6):e2319352.

34. Mayer DK, Alfano CM. Personalized Risk-Stratified Cancer Follow-Up Care: Its Potential for Healthier Survivors, Happier Clinicians, and Lower Costs. J Natl Cancer Inst. 2019;111(5):442-8.

35. Watson EK, Rose PW, Neal RD, Hulbert-Williams N, Donnelly P, Hubbard G, et al. Personalised cancer follow-up: risk stratification, needs assessment or both? British journal of cancer. 2012;106(1):1-5.

36. Hui D, Hannon BL, Zimmermann C, Bruera E. Improving patient and caregiver outcomes in oncology: Team-based, timely, and targeted palliative care. CA Cancer J Clin. 2018;68(5):356-76.

37. Lubejko BG, Wilson BJ. Oncology nursing scope and standards of practice: Oncology Nursing Society2019.

38. Suzuki S, Chan A, Nomura H, Johnson PE, Endo K, Saito S. Chemotherapy regimen checks performed by pharmacists contribute to safe administration of chemotherapy. J Oncol Pharm Pract. 2017;23(1):18-25.

39. Yap KY, Low HX, Koh KS, Un M, Shih V, Chan A. Feasibility and acceptance of a pharmacist-run tele-oncology service for chemotherapy-induced nausea and vomiting in ambulatory cancer patients. Telemed J E Health. 2013;19(5):387-95.

40. Schoeman J, Kellerman IM, Ladas EJ, Ndlovu S, Rogers PC, du Plessis J, et al. Implemented nutritional intervention algorithm in pediatric oncology compared to standard nutritional supportive care outcomes. Clin Nutr ESPEN. 2024;63:870-7.

41. Horne B, Gilleece M, Jackson G, Snowden JA, Liebersbach S, Velikova G, et al. Psychosocial supportive care services for haematopoietic stem cell transplant patients; a service evaluation of three UK transplant centres. Eur J Cancer Care (Engl). 2014;23(3):349-62.

42. Hannon B, Swami N, Pope A, Rodin G, Dougherty E, Mak E, et al. The oncology palliative care clinic at the Princess Margaret Cancer Centre: an early intervention model for patients with advanced cancer. Support Care Cancer. 2015;23(4):1073-80.

43. Ben-Arye E, Samuels N, Daher M, Turker I, Nimri O, Rassouli M, et al. Integrating Complementary and Traditional Practices in Middle-Eastern Supportive Cancer Care. Journal of the National Cancer Institute Monographs. 2017;2017(52).

44. Hui D, Hoge G, Bruera E. Models of supportive care in oncology. Curr Opin Oncol. 2021;33(4):259-66.

45. Alfieri S, Brunelli C, Borreani C, Capri G, Angi M, Bianchi GV, et al. Characterizing Different Multidisciplinary Team Models Implemented Within One Comprehensive Cancer Center. J Multidiscip Healthc. 2023;16:1845-55.

46. Coyle N. Supportive care program, pain service, Memorial Sloan-Kettering Cancer Center. Support Care Cancer. 1995;3(3):161-3.

47. Hui D, Cherny N, Latino N, Strasser F. The 'critical mass' survey of palliative care programme at ESMO designated centres of integrated oncology and palliative care. Ann Oncol. 2017;28(9):2057-66.

48. Ke Y, Neo PSH, Yang GM, Neo SH, Tan YY, Tan YP, et al. Impact of a Multidisciplinary Supportive Care Model Using Distress Screening at an Asian Ambulatory Cancer Center: A Cluster Randomized Controlled Trial. JCO Oncol Pract. 2024;20(9):1207-18.

49. Viklund P, Wengstrom Y, Lagergren J. Supportive care for patients with oesophageal and other upper gastrointestinal cancers: The role of a specialist nurse in the team. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2006;10(5):353-63.

50. Sherman AC, Coleman EA, Griffith K, Simonton S, Hine RJ, Cromer J, et al. Use of a supportive care team for screening and preemptive intervention among multiple myeloma patients receiving stem cell transplantation. Support Care Cancer. 2003;11(9):568-74.

51. Evans Webb M, Murray E, Younger ZW, Goodfellow H, Ross J. The Supportive Care Needs of Cancer Patients: a Systematic Review. J Cancer Educ. 2021;36(5):899-908.

52. So WKW, Wong CL, Choi KC, Chan CWH, Chan JCY, Law BMH, et al. A Mixed-Methods Study of Unmet Supportive Care Needs Among Head and Neck Cancer Survivors. Cancer Nurs. 2019;42(1):67-78.

53. Cheng KKF, Cheng HL, Wong WH, Koh C. A mixed-methods study to explore the supportive care needs of breast cancer survivors. Psychooncology. 2018;27(1):265-71.

54. Hendriks MJ, Hartmann N, Harju E, Roser K, Michel G. "I don't take for granted that I am doing well today": a mixed methods study on well-being, impact of cancer, and supportive needs in long-term childhood cancer survivors. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2022;31(5):1483-97.

55. Kim W, Shin C, Larkey L, Jo S, James D. Supportive Care Needs: Perspectives of Cancer Patients and Healthcare Providers. Clin Nurs Res. 2022;31(6):1033-41.

56. Khan NN, Maharaj A, Evans S, Pilgrim C, Zalcberg J, Brown W, et al. A qualitative investigation of the supportive care experiences of people living with pancreatic and oesophagogastric cancer. BMC Health Serv Res. 2022;22(1):213.

57. Dhakal K, Wang P, Mboineki JF, Getu MA, Chen C, Shrestha DL. The distinct experience of supportive care needs among cervical cancer patients: A qualitative study. Tumori. 2023;109(4):394-405.

58. Chan RJ, Knowles R, Ashbury FD, Bowen J, Chan A, Chin M, et al. Supportive care 2030 movement: towards unifying ambitions for global excellence in supportive cancer care-an international Delphi study. EClinicalMedicine. 2024;76:102825.

59. Balitsky AK, Rayner D, Britto J, Lionel AC, Ginsberg L, Cho W, et al. Patient-Reported Outcome Measures in Cancer Care: An Updated Systematic Review and Meta-Analysis. JAMA Netw Open. 2024;7(8):e2424793.

60. Cella D, Choi S, Garcia S, Cook KF, Rosenbloom S, Lai JS, et al. Setting standards for severity of common symptoms in oncology using the PROMIS item banks and expert judgment. Qual Life Res. 2014;23(10):2651-61.

61. Jensen RE, Potosky AL, Reeve BB, Hahn E, Cella D, Fries J, et al. Validation of the PROMIS physical function measures in a diverse US population-based cohort of cancer patients. Qual Life Res. 2015;24(10):2333-44.

62. Wagner LI, Schink J, Bass M, Patel S, Diaz MV, Rothrock N, et al. Bringing PROMIS to practice: brief and precise symptom screening in ambulatory cancer care. Cancer. 2015;121(6):927-34.

63. Cessna JM, Jim HS, Sutton SK, Asvat Y, Small BJ, Salsman JM, et al. Evaluation of the psychometric properties of the PROMIS Cancer Fatigue Short Form with cancer patients. J Psychosom Res. 2016;81:9-13.

64. Flynn KE, Reeve BB, Lin L, Cyranowski JM, Bruner DW, Weinfurt KP. Construct validity of the PROMIS® sexual function and satisfaction measures in patients with cancer. Health Qual Life Outcomes. 2013;11:40.

65. Schick-Makaroff K, Molzahn AE. Evaluation of real-time use of electronic patient-reported outcome data by nurses with patients in home dialysis clinics. BMC Health Serv Res. 2017;17(1):439.

66. Absolom K, Warrington L, Hudson E, Hewison J, Morris C, Holch P, et al. Phase III Randomized Controlled Trial of eRAPID: eHealth Intervention During Chemotherapy. J Clin Oncol. 2021;39(7):734-47.

67. Moore EM, King TA, Wood EM, Ruseckaite R, Klarica D, Spencer A, et al. Patient-reported outcome measures in multiple myeloma: Real-time reporting to improve care (My-PROMPT) - a pilot randomized controlled trial. Am J Hematol. 2020;95(7):E178-E81.

68. Lu SC, Porter I, Valderas JM, Harrison CJ, Sidey-Gibbons C. Effectiveness of routine provision of feedback from patient-reported outcome measurements for cancer care improvement: a systematic review and meta-analysis. J Patient Rep Outcomes. 2023;7(1):54.

69. Howell D, Molloy S, Wilkinson K, Green E, Orchard K, Wang K, et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. Annals of Oncology. 2015;26(9):1846-58.

70. Chan A, Ng DQ, Arcos D, Heshmatipour M, Lee B, Chen A, et al. Electronic Patient-Reported Outcomes (ePRO)-driven Symptom Management by Oncology Pharmacists in a Majority-Minority Population: An Implementation Study. JCO Oncology Practice. 2024.

71. Lin A, Giuliano CJ, Palladino A, John KM, Abramowicz C, Yuan ML, et al. Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials. Sci Transl Med. 2019;11(509).

72. Rapp SR, Dressler EV, Brown WM, Wade JL, 3rd, Le-Lindqwister N, King D, et al. Phase III Randomized, Placebo-Controlled Clinical Trial of Donepezil for Treatment of Cognitive Impairment in Breast Cancer Survivors After Adjuvant Chemotherapy (WF-97116). J Clin Oncol. 2024;42(21):2546-57.

73. Miladi N, Dossa R, Dogba MJ, Cleophat-Jolicoeur MIF, Gagnon B. Psychostimulants for cancer-related cognitive impairment in adult cancer survivors: a systematic review and meta-analysis. Support Care Cancer. 2019;27(10):3717-27.

74. Vollert J, Cook NR, Kaptchuk TJ, Sehra ST, Tobias DK, Hall KT. Assessment of Placebo Response in Objective and Subjective Outcome Measures in Rheumatoid Arthritis Clinical Trials. JAMA Netw Open. 2020;3(9):e2013196.

75. Islami F, Baeker Bispo J, Lee H, Wiese D, Yabroff KR, Bandi P, et al. American Cancer Society's report on the status of cancer disparities in the United States, 2023. CA Cancer J Clin. 2023.

76. Dos-Santos-Silva I, Gupta S, Orem J, Shulman LN. Global disparities in access to cancer care. Commun Med (Lond). 2022;2:31.

77. John DA, Kawachi I, Lathan CS, Ayanian JZ. Disparities in perceived unmet need for supportive services among patients with lung cancer in the Cancer Care Outcomes Research and Surveillance Consortium. Cancer. 2014;120(20):3178-91.

78. Mazor MB, Li L, Morillo J, Allen OS, Wisnivesky JP, Smith CB. Disparities in Supportive Care Needs Over Time Between Racial and Ethnic Minority and Non-Minority Patients With Advanced Lung Cancer. J Pain Symptom Manage. 2022;63(4):563-71.

79. Hess E, Anandan A, Osman F, Lee-Miller C, Parkes A. Disparities in Treatment Satisfaction and Supportive Care Receipt for Young Adult Oncology Patients on the Basis of Residential Location. JCO Oncol Pract. 2022;18(9):e1542-e52.

80. Cardone C, Arnold D. The Cancer Treatment Gap in Lower- to Middle-Income Countries. Oncology. 2023;101 Suppl 1(1):2-4.

81. Barcellini A, Dal Mas F, Paoloni P, Loap P, Cobianchi L, Locati L, et al. Please mind the gap-about equity and access to care in oncology. ESMO Open. 2021;6(6):100335.

82. Uijtdehaage S, Hauer KE, Stuber M, Go VL, Rajagopalan S, Wilkerson L. Preparedness for caring of cancer survivors: a multi-institutional study of medical students and oncology fellows. J Cancer Educ. 2009;24(1):28-32.

83. Uijtdehaage S, Hauer KE, Stuber M, Rajagopalan S, Go VL, Wilkerson L. A framework for developing, implementing, and evaluating a cancer survivorship curriculum for medical students. J Gen Intern Med. 2009;24 Suppl 2(Suppl 2):S491-4.

84. Brady HL, Hamilton JG, Kaphingst KA, Jensen JD, Kohlmann W, Parsons BG, et al. 'I had a bigger cancer risk than I thought...': The experience of receiving personalized risk information as part of a skin cancer prevention intervention in the college setting. Health Expect. 2022;25(6):2937-49.

85. Lamanna LM. College students' knowledge and attitudes about cancer and perceived risks of developing skin cancer. Dermatol Nurs. 2004;16(2):161-4, 75-6.

86. Goldfarb JA, Comber JD. Human papillomavirus (HPV) infection and vaccination: A cross-sectional study of college students' knowledge, awareness, and attitudes in Villanova, PA. Vaccine X. 2022;10:100141.

87. Klasko-Foster LB, Przybyla S, Orom H, Gage-Bouchard E, Kiviniemi MT. The influence of affect on HPV vaccine decision making in an HPV vaccine naive college student population. Prev Med Rep. 2020;20:101195.

88. Williams A, Williams M. An Undergraduate Health Care Experience Course Increases Confidence and Improves Student Understanding of Health Care Careers. CBE Life Sci Educ. 2024;23(2):ar21.

89. Allemang B, Sitter K, Dimitropoulos G. Pragmatism as a paradigm for patient-oriented research. Health Expect. 2022;25(1):38-47.

90. Kaushik V, Walsh CA. Pragmatism as a Research Paradigm and Its Implications for Social Work Research. Social Sciences. 2019;8(9):255.

91. Lincoln YS, Denzin NK. The Sage handbook of qualitative research: Sage Publications; 2011.

92. Hothersall SJ. Epistemology and social work: enhancing the integration of theory, practice and research through philosophical pragmatism. Eur J Soc Work. 2019;22:860-70.

93. Johnson RB, Onwuegbuzie AJ. Mixed Methods Research: A Research Paradigm Whose Time Has Come. Educational Researcher. 2004;33(7):14-26.

94. Cornish F, Gillespie A. A pragmatist approach to the problem of knowledge in health psychology. J Health Psychol. 2009;14(6):800-9.

95. Hall JN. Pragmatism, evidence, and mixed methods evaluation. New directions for evaluation. 2013;2013(138):15-26.

96. Tashakkori A, Teddlie C. Sage handbook of mixed methods in social & behavioral research: sage; 2010.

97. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63.

98. National Comprehensive Cancer Network. Breast Cancer [Version 1.2025:[

99. Vaz-Luis I, Di Meglio A, Havas J, El-Mouhebb M, Lapidari P, Presti D, et al. Long-Term Longitudinal Patterns of Patient-Reported Fatigue After Breast Cancer: A Group-Based Trajectory Analysis. J Clin Oncol. 2022;40(19):2148-62.

100. Loh KY, Ng T, Lee CP, Ng R, Chan A. Medication use by early-stage breast cancer survivors: a 1-year longitudinal study. Support Care Cancer. 2016;24(4):1639-47.

101. Cheung YT, Shwe M, Chui WK, Chay WY, Ang SF, Dent RA, et al. Effects of chemotherapy and psychosocial distress on perceived cognitive disturbances in Asian breast cancer patients. Ann Pharmacother. 2012;46(12):1645-55.

102. Chan A, Soh D, Ko Y, Huang YC, Chiang J. Characteristics of unplanned hospital admissions due to drug-related problems in cancer patients. Support Care Cancer. 2014;22(7):1875-81.

103. Ko Y, Gwee YS, Huang YC, Chiang J, Chan A. Costs and length of stay of drug-related hospital admissions in cancer patients. Clin Ther. 2014;36(4):588-92.

104. Chan A, Low XH, Yap KY. Assessment of the relationship between adherence with antiemetic drug therapy and control of nausea and vomiting in breast cancer patients receiving anthracycline-based chemotherapy. J Manag Care Pharm. 2012;18(5):385-94.

105. Hertz DL, Tofthagen C, Rossi E, Bernasconi DP, Lim J, Carlson M, et al. Patient perceptions of altering chemotherapy treatment due to peripheral neuropathy. Support Care Cancer. 2023;32(1):48.

106. Molassiotis A, Cheng HL, Leung KT, Li YC, Wong KH, Au JSK, et al. Risk factors for chemotherapy-induced peripheral neuropathy in patients receiving taxane- and platinum-based chemotherapy. Brain Behav. 2019;9(6):e01312.

107. Pachman DR, Watson JC, Lustberg MB, Wagner-Johnston ND, Chan A, Broadfield L, et al. Management options for established chemotherapy-induced peripheral neuropathy. Support Care Cancer. 2014;22(8):2281-95.

108. Chan RJ, McCarthy AL, Devenish J, Sullivan KA, Chan A. Systematic review of pharmacologic and non-pharmacologic interventions to manage cognitive alterations after chemotherapy for breast cancer. Eur J Cancer. 2015;51(4):437-50.

109. Cheung YT, Lim SR, Ho HK, Chan A. Cytokines as mediators of chemotherapy-associated cognitive changes: current evidence, limitations and directions for future research. PLoS One. 2013;8(12):e81234.

110. Cheung YT, Ng T, Shwe M, Ho HK, Foo KM, Cham MT, et al. Association of proinflammatory cytokines and chemotherapy-associated cognitive impairment in breast cancer patients: a multi-centered, prospective, cohort study. Ann Oncol. 2015;26(7):1446-51.

111. Li W, Liang H, Wang W, Liu J, Liu X, Lao S, et al. Global cancer statistics for adolescents and young adults: population based study. J Hematol Oncol. 2024;17(1):99.

112. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. CA Cancer J Clin. 2020;70(6):443-59.

113. Page LL, Devasia TP, Mariotto A, Gallicchio L, Mollica MA, Tonorezos E. Prevalence of cancer survivors diagnosed during adolescence and young adulthood in the United States. J Natl Cancer Inst. 2024.

114. Nathan PC, Hayes-Lattin B, Sisler JJ, Hudson MM. Critical issues in transition and survivorship for adolescents and young adults with cancers. Cancer. 2011;117(10 Suppl):2335-41.

115. Woldehaimanot TE, Lin Goh W, Poon E, Fan Kam Tong G, Neo Soek Hui P, Quek R, et al. 498PD_PR Prevalence and types of distress among Adult and Young Adolescent (AYA) newly diagnosed with cancer in Singapore. Annals of Oncology. 2016;27(suppl_9).

116. Bellizzi KM, Smith A, Schmidt S, Keegan TH, Zebrack B, Lynch CF, et al. Positive and negative psychosocial impact of being diagnosed with cancer as an adolescent or young adult. Cancer. 2012;118(20):5155-62.

117. Husson O, Zebrack B, Block R, Embry L, Aguilar C, Hayes-Lattin B, et al. Personality Traits and Health-Related Quality of Life Among Adolescent and Young Adult Cancer Patients: The Role of Psychological Distress. Journal of adolescent and young adult oncology. 2017;6(2):358-62.

118. Soliman H, Agresta SV. Current issues in adolescent and young adult cancer survivorship. Cancer control : journal of the Moffitt Cancer Center. 2008;15(1):55-62.

119. Kent EE, Parry C, Montoya MJ, Sender LS, Morris RA, Anton-Culver H. "You're too young for this": adolescent and young adults' perspectives on cancer survivorship. J Psychosoc Oncol. 2012;30(2):260-79.

120. Chan A, Poon E, Goh WL, Gan Y, Tan CJ, Yeo K, et al. Assessment of psychological distress among Asian adolescents and young adults (AYA) cancer patients using the distress thermometer: a prospective, longitudinal study. Support Care Cancer. 2018;26(9):3257-66.

121. Group AS. Health-related quality of life and psychological distress among cancer survivors in Southeast Asia: results from a longitudinal study in eight low- and middle-income countries. BMC Med. 2017;15(1):10.

122. Lim CC, Devi MK, Ang E. Anxiety in women with breast cancer undergoing treatment: a systematic review. Int J Evid Based Healthc. 2011;9(3):215-35.

123. Friese CR, Harrison JM, Janz NK, Jagsi R, Morrow M, Li Y, et al. Treatment-associated toxicities reported by patients with early-stage invasive breast cancer. Cancer. 2017;123(11):1925-34.

124. Skandarajah AR, Lisy K, Ward A, Bishop J, Lacey K, Mann B, et al. Patient-reported outcomes in survivors of breast cancer one, three, and five years post-diagnosis: a cancer registry-based feasibility study. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2021;30(2):385-94.

125. Nardin S, Mora E, Varughese FM, D'Avanzo F, Vachanaram AR, Rossi V, et al. Breast Cancer Survivorship, Quality of Life, and Late Toxicities. Front Oncol. 2020;10:864.

126. Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: How to decide its appropriateness. World J Methodol. 2021;11(4):116-29.

127. Cheung YT, Chan A, Charalambous A, Darling HS, Eng L, Grech L, et al. The use of patient-reported outcomes in routine cancer care: preliminary insights from a multinational scoping survey of oncology practitioners. Support Care Cancer. 2021.

128. Basch E, Barbera L, Kerrigan CL, Velikova G. Implementation of Patient-Reported Outcomes in Routine Medical Care. Am Soc Clin Oncol Educ Book. 2018;38:122-34.

129. Kotronoulas G, Kearney N, Maguire R, Harrow A, Di Domenico D, Croy S, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol. 2014;32(14):1480-501.

130. Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol. 2004;22(4):714-24.

131. Brennan J, Gingell P, Brant H, Hollingworth W. Refinement of the distress management problem list as the basis for a holistic therapeutic conversation among UK patients with cancer. Psychooncology. 2012;21(12):1346-56.

132. Salas AS, Contreras JF, Armijo-Olivo S, Saltaji H, Watanabe S, Chambers T, et al. Non-pharmacological cancer pain interventions in populations with social disparities: a systematic review and meta-analysis. Support Care Cancer. 2016;24(2):985-1000.

133. Alvidrez J, Castille D, Laude-Sharp M, Rosario A, Tabor D. The National Institute on Minority Health and Health Disparities Research Framework. Am J Public Health. 2019;109(S1):S16-S20.

134. Bultz BD, Watson L, Loscalzo M, Kelly B, Zabora J. From foundation to inspiration: implementing screening for distress (6th Vital Sign) for optimal cancer care—international leadership perspectives on program development. Journal of Psychosocial Oncology Research & Practice. 2021;3(2).

135. Smith SK, Loscalzo M, Mayer C, Rosenstein DL. Best Practices in Oncology Distress Management: Beyond the Screen. American Society of Clinical Oncology Educational Book. 2018(38):813-21.

136. Termuhlen PM, Westra RE. Survivorship. Quality Cancer Care2018. p. 103-17.

137. Brownson RC, Colditz GA, Proctor EK. Dissemination and Implementation Research in Health: Translating Science to Practice. New York, NY: Oxford University Press; 2012.

138. Ke Y, Tan YY, Neo PSH, Yang GM, Loh KW, Ho S, et al. Implementing an Inclusive, Multidisciplinary Supportive Care Model to Provide Integrated Care to Breast and Gynaecological Cancer Survivors: A Case Study at an Asian Ambulatory Cancer Centre. Int J Integr Care. 2023;23(1):14.

139. Selove R, Birken SA, Skolarus TA, Hahn EE, Sales A, Proctor EK. Using Implementation Science to Examine the Impact of Cancer Survivorship Care Plans. J Clin Oncol. 2016;34(32):3834-7.

140. Rabin B, Glasgow RE. An implementation science perspective on psychological science and cancer: what is known and opportunities for research, policy, and practice. Am Psychol. 2015;70(2):211-20.

141. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care. 2012;50(3):217-26.

142. Cleary PD, Gross CP, Zaslavsky AM, Taplin SH. Multilevel interventions: study design and analysis issues. Journal of the National Cancer Institute Monographs. 2012;2012(44):49-55.

143. Jacobsen PB, Norton WE. The role of implementation science in improving distress assessment and management in oncology: a commentary on "Screening for psychosocial distress among patients with cancer: implications for clinical practice, healthcare policy, and dissemination to enhance cancer survivorship". Transl Behav Med. 2019;9(2):292-5.

144. Witt CM, Balneaves LG, Cardoso MJ, Cohen L, Greenlee H, Johnstone P, et al. A Comprehensive Definition for Integrative Oncology. Journal of the National Cancer Institute Monographs. 2017;2017(52).

145. Greenlee H, DuPont-Reyes MJ, Balneaves LG, Carlson LE, Cohen MR, Deng G, et al. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. CA Cancer J Clin. 2017;67(3):194-232.

146. Lyman GH, Greenlee H, Bohlke K, Bao T, DeMichele AM, Deng GE, et al. Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline. J Clin Oncol. 2018;36(25):2647-55.

147. 孙霓平, 刘胜. 乳腺癌术后患者中医辨证分型的统计分析研究. 中国医药学报. 2003;18:211–4.

148. 王蕾, 邬晓敏, 吕庆, 谢智惠. 乳腺癌术后辅助化疗患者癌因性疲劳的中医证候特点分析. 北京中医药. 2016;35:649–52.

149. 薛娜, 杨国旺, 王笑民. 乳腺癌中医证候研究现状及思考. 中医杂志. 2014;55:168-71.

150. Chien TJ, Song YL, Lin CP, Hsu CH. The correlation of traditional chinese medicine deficiency syndromes, cancer related fatigue, and quality of life in breast cancer patients. J Tradit Complement Med. 2012;2(3):204-10.

151. Yap NY, David SP, Zheng HF, Tan QM, Quek LYP, Tan TK, et al. Evaluation of in vitro cytochrome P450 Inhibition and hepatotoxicity potential of a herbal formula (Xiang Bei Yang Rong Tang) for treatment of cancer-related fatigue. Pharmacogn Mag. 2021;17:603-5.

152. Yap NY, Loo WS, Zheng HF, Tan QM, Tan TK, Quek LYP, et al. A study protocol for HEalth-Related quality of life-intervention in survivors of Breast and other cancers experiencing cancer-related fatigue using TraditionAL Chinese Medicine: the HERBAL trial. Trials. 2020;21(1):909.

153. Dai L, Cheng CW, Tian R, Zhong LL, Li YP, Lyu AP, et al. Standard Protocol Items for Clinical Trials with Traditional Chinese Medicine 2018: Recommendations, Explanation and Elaboration (SPIRIT-TCM Extension 2018). Chin J Integr Med. 2019;25(1):71-9.

154. Toh YL, Tan CJ, Yeo AHL, Shwe M, Ho HK, Gan YX, et al. Association of plasma leptin, pro-inflammatory adipokines and cancer-related fatigue in early-stage breast cancer patients: A prospective cohort study. J Cell Mol Med. 2019;23(6):4281-9.

155. Stovall E, Greenfield S, Hewitt M. From cancer patient to cancer survivor: lost in transition: National Academies Press; 2005.

156. Faupel-Badger JM, Vogel AL, Austin CP, Rutter JL. Advancing translational science education. Clin Transl Sci. 2022;15(11):2555-66.

157. Jones S-L, Hall T, Procter R, Connolly C, Fazlagić J. Conceptualising translational research in schools: A systematic literature review. International Journal of Educational Research. 2022;114:101998.

158. Zarei F, Dehghani A, Ratansiri A, Ghaffari M, Raina SK, Halimi A, et al. ChecKAP: A Checklist for Reporting a Knowledge, Attitude, and Practice (KAP) Study. Asian Pac J Cancer Prev. 2024;25(7):2573-7.

159. Faller H, Schuler M, Richard M, Heckl U, Weis J, Kuffner R. Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis. J Clin Oncol. 2013;31(6):782-93.

160. Cheung YT, Shwe M, Tan YP, Fan G, Ng R, Chan A. Cognitive changes in multiethnic Asian breast cancer patients: a focus group study. Ann Oncol. 2012;23(10):2547-52.

161. Agapito I, Ng DQ, Milam J, Ziogas A, Anton-Culver H, Chan A. Neuropsychiatric complications and associated management in adolescent and young adult cancer survivors: An All of Us study. Cancer medicine. 2023.

162. Molassiotis A, Yates P, Li Q, So WKW, Pongthavornkamol K, Pittayapan P, et al. Mapping unmet supportive care needs, quality-of-life perceptions and current symptoms in cancer survivors across the Asia-Pacific region: results from the International STEP Study. Ann Oncol. 2019;30(3):493.

163. Bergerot C, Jacobsen PB, Rosa WE, Lam WWT, Dunn J, Fernandez-Gonzalez L, et al. Global unmet psychosocial needs in cancer care: health policy. EClinicalMedicine. 2024;78:102942.

164. Taplin SH, Anhang Price R, Edwards HM, Foster MK, Breslau ES, Chollette V, et al. Introduction: Understanding and influencing multilevel factors across the cancer care continuum. Journal of the National Cancer Institute Monographs. 2012;2012(44):2-10.

165. Rodriguez GM, Parikh DA, Kapphahn K, Gupta DM, Fan AC, Shah S, et al. Coaches Activating, Reaching, and Engaging Patients to Engage in Advance Care Planning: A Randomized Clinical Trial. JAMA Oncol. 2024;10(7):949-53.

166. Buchanan A, Nangia J, Badr H. Multilevel barriers and supportive care preferences of metastatic breast cancer patients and their caregivers: a mixed-methods analysis. Support Care Cancer. 2025;33(3):177.

167. McConnell KM, Shen MJ. The need for multilevel supportive care infrastructure for cancer caregivers. Cancer. 2024;130(11):1913-5.

168. Stal J, Miller KA, Mullett TW, Boughey JC, Francescatti AB, Funk E, et al. Cancer Survivorship Care in the United States at Facilities Accredited by the Commission on Cancer. JAMA Netw Open. 2024;7(7):e2418736.

169. Coschi CH, Bainbridge D, Sussman J. Understanding the Attitudes and Beliefs of Oncologists Regarding the Transitioning and Sharing of Survivorship Care. Curr Oncol. 2021;28(6):5452-65.

170. Kantilal K, Hardeman W, Whiteside H, Karapanagiotou E, Small M, Bhattacharya D. Facilitating healthcare practitioners to deliver self-management support in adult cancer survivors: A realist review. Res Social Adm Pharm. 2022;18(11):3870-83.

171. Arana-Chicas E, Zhang Y, Chavez-Iniguez A, Lin PJ, Mattick LJ, Kamen C, et al. Use of cultural appropriateness strategies and behavioral frameworks in behavioral interventions for black and hispanic cancer survivors: a systematic review. BMC Cancer. 2025;25(1):835.

172. Cao W, Cho H. Culture in Cancer Survivorship Interventions for Asian Americans: A Systematic Review and Critical Analyses. Asian Am J Psychol. 2021;12(1):65-75.

173. Mekonnen BA, Anagaw YK, Kassahun BA, Worku MC. Evaluation of female university students' knowledge, attitudes, and practices toward human papillomavirus infection and vaccination. Multicenter cross-sectional study. BMC Womens Health. 2024;24(1):437.

174. Roji R, Stone P, Ricciardi F, Candy B. Placebo response in trials of drug treatments for cancer-related fatigue: a systematic review, meta-analysis and meta-regression. BMJ Support Palliat Care. 2020;10(4):385-94.

175. Berkhout C, Berbra O, Favre J, Collins C, Calafiore M, Peremans L, et al. Defining and evaluating the Hawthorne effect in primary care, a systematic review and meta-analysis. Front Med (Lausanne). 2022;9:1033486.

176. Mustian K, Lacchetti C, Zick S, Bower JE. Management of Fatigue in Adult Survivors of Cancer: American Society of Clinical Oncology - Society for Integrative Oncology (ASCO-SIO) Guideline Update Clinical Insights. JCO Oncol Pract. 2024;20(12):1575-9.

177. Carlson LE, Ismaila N, Addington EL, Asher GN, Bradt J, Mehta A, et al. Integrative Oncology Care of Symptoms of Anxiety and Depression in Adults With Cancer: SIO-ASCO Guideline Summary and Q&A. JCO Oncol Pract. 2023;19(10):847-51.

178. Chan A, Ashbury F, Fitch MI, Koczwara B, Chan RJ, Group MSS. Cancer survivorship care during COVID-19-perspectives and recommendations from the MASCC survivorship study group. Support Care Cancer. 2020;28(8):3485-8.

179. Tabataba Vakili S, Haywood D, Kirk D, Abdou AM, Gopalakrishnan R, Sadeghi S, et al. Application of Artificial Intelligence in Symptom Monitoring in Adult Cancer Survivorship: A Systematic Review. JCO Clin Cancer Inform. 2024;8:e2400119.

180. Pan LC, Wu XR, Lu Y, Zhang HQ, Zhou YL, Liu X, et al. Artificial intelligence empowered digital health technologies in cancer survivorship care: A scoping review. Asia Pac J Oncol Nurs. 2022;9(12):100127.

181. Fernandez-Escabias M, Jurado J, Carrilho-Candeias S, Orellana-Jaen A, Corres P, Marmol-Perez A, et al. Impact of exercise-based prehabilitation on cardiometabolic health in surgical patients with cancer: a systematic review and meta-analysis. Support Care Cancer. 2025;33(10):879.

182. Ben-Arye E, Sehouli J, Seifert G, Samuels N, Blakeslee S, Gressel O, et al. Integrative gynaecological oncology in prehabilitation: scoping review of patient-centred care models. BMJ Support Palliat Care. 2025.

183. Li C, Meng H, Wei Y, Liang Y, Xu Y, Huang X, et al. Postoperative outcomes of preoperative exercise training in patients with operable non-small cell lung cancer: a systematic review and meta-analysis. Front Oncol. 2025;15:1563478.

184. Molina Beltran EE, Nedellec ND, Hilmi M, Delaye M, Raynard B, Hiret S, et al. Implementation and challenges of prehabilitation in gastrointestinal oncology: a national cross-sectional survey in France. Clin Nutr ESPEN. 2025.