THE PERSONAL AND FINANCIAL BURDEN OF ACUTE MYELOID LEUKAEMIA

by

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Berkovic D, Briggs AM, Ayton D, **Parker C** and Akerman I. Arthritis-related work outcomes experienced by younger to middle-aged adults: a systematic review Occupational and Environmental Medicine 2021;78:225-236.

Declaration

This thesis is an original work of my research and contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes five original papers published in peer-reviewed journals and one submitted Publication under review. The core theme of the thesis is personal and financial burden in people with acute myeloid leukaemia. The ideas, concept development, fieldwork and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the School of Public Health and Preventive Medicine under the supervision of Professor Danny Liew, Doctor Darshini Ayton, Associate Professor Andrew Wei and Doctor Ella Zomer. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

My specific contribution to the work for Chapters 2, 4, 5, 6, 7, and 8.

Thesis Chapter	Publication title	Status	Nature and % of student contribution	Co-author names, nature and % of the contribution	Co-author a Monash student
2	Patient perceived financial burden in haematological malignancies: a systematic review	Submitted	Development of search strategy, screening of titles and abstracts, data extraction, quality appraisal, data analysis and interpretation, manuscript preparation and revision. 60%.	Danielle Berkovic - development of search strategy, screening of titles and abstracts, data extraction, input into manuscript. 15% Darshini Ayton - development of search strategy, data interpretation, input into manuscript and manuscript revision. 10% Ella Zomer - data interpretation, input into manuscript. 5% Danny Liew - data interpretation, input into manuscript. 5% Andrew Wei - data interpretation, input into the manuscript. 5%	Yes
4	Characterising experiences with acute myeloid leukaemia using an Instagram content analysis.	Published	Study design, data collection, data analysis, interpretation, manuscript preparation and revision. 70%	Ella Zomer - input into manuscript. 10% Danny Liew - input into manuscript. 10% Darshini Ayton - study design, interpretation, input into manuscript. 10%	No
5	Nursing implications from ongoing symptoms and concerns: a qualitative exploration of health and well-being in remission from acute myeloid leukaemia	Submitted	Study design, data collection, data analysis, interpretation, manuscript preparation and revision. 70%	Andrew Wei - input into manuscript. 5% Danny Liew - input into manuscript. 5% Ella Zomer - input into manuscript. 5% Darshini Ayton - study design, interpretation, input into manuscript. 15%	No
5	It doesn't stop at validation: patient reported outcome measures require ongoing and iterative development.	Published	Study design, data collection, data analysis, interpretation, manuscript preparation and revision. 70%	Andrew Wei - input into manuscript. 5% Danny Liew - input into manuscript. 5% Ella Zomer - input into manuscript. 5% Darshini Ayton - study design, interpretation, input into manuscript. 15%	No
6	'If I don't work, I don't get paid': An Australian qualitative exploration of the financial impacts of acute myeloid leukaemia.	Published	Study design, data collection, data analysis, interpretation, manuscript preparation and revision. 70%	Danielle Berkovic - input into manuscript. 7% Andrew Wei- input into manuscript. 5% Ella Zomer- input into manuscript. 3% Danny Liew - input into manuscript. 5% Darshini Ayton - study design, interpretation, input into manuscript. 10%	Yes
7	Do patients with haematological malignancies suffer financial burden? A cross-sectional study of patients seeking care through a publicly funded healthcare system.	Published	Study design, data collection, data analysis, interpretation, manuscript preparation and revision. 70%	Darshini Ayton - study design, input into manuscript. 10% Ella Zomer - study design, input into manuscript. 5% Danny Liew - input into manuscript. 2.5% Catherine Vassili - data collection, input into manuscript. 5% Chun Fong - input into manuscript. 2.5% Andrew Wei - data collection, input into manuscript. 5%	No
8	Estimating the Productivity Impact of Acute Myeloid Leukemia in Australia Between 2020 and 2029, Using a Novel Work Utility Measure: The Productivity-Adjusted Life Year (PALY).	Published	Model build, data analysis, interpretation, manuscript preparation and revision. 60%	Danny Liew - concept design, input into manuscript. 10% Zanfina Ademi - input into manuscript. 2.5% Alice Owen - input into manuscript. 2.5% Darshini Ayton - input into manuscript. 2.5% Andrew Wei - input into manuscript. 2.5% Ella Zomer - study design, analysis, interpretation, input into manuscript. 20%	No

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I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author, I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor Signature: ……

Main Supervisor Name: Professor Danny Liew

Date:

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Finally, to my Mum, who had an unwavering belief in education. I know you would be so proud.

Abbreviations and acronyms

ALL	acute lympoblastic leukaemia
AML	acute myeloid leukaemia
APML	acute promyelocytic leukaemia
ASR	age-standardised incidence rate
BMT	bone marrow transplant
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CLL	chronic lymphocytic leukaemia
CML	chronic myelocytic leukaemia
COREQ-32	COnsolidated criteria for REporting Qualitative research - 32 item checklist
COST	COmprehensive Score for financial Toxicity
COVID-19	Coronoavirus SARS-CoV-2
CR	complete remission
ELN	European LeukemiaNet
EORTC	European Organisation for Research and Treatment of Cancer
FACT-BMT	Functional Assessment of Cancer Therapy - Bone Marrow Transplant module (instrument)
FACT-Leu	Functional Assessment of Cancer Therapy - Leukaemia module (instrument)
FCR	fear of cancer recurrence
FDA	Food and Drug Administration
GDP	gross domestic product
HL	Hodgkin's lymphoma
HR	hazard ratio
HREC	Human Research Ethics Committee
HSCT	haematopoietic stem cell transplant
JBI	Joanna Briggs Institute (quality appraisal tools)
MBS	Medicare Benefits Scheme
MDS	myelodysplastic syndrome
MM	multiple myeloma
MMAS	Morisky Medication Adherence Scale (instrument)
MN-ET	myeloproliferative neoplasm - essential thrombocythemia
MPD	myelproliferative disease
MRD	minimal residual disease
NHIS	National Health Interview Survey
NHL	non-Hodgkin's lymphoma
NIH	National Institute of Health
NR	not reported
OOP	out-of-pocket
OR	odds ratio
PALY	productivity-adjusted life year

PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	patient-reported outcome measure
QALY	quality-adjusted life year
QLQ-C30	quality of life questionnaire for cancer - 30 items (instrument)
(HR)QoL	(health related) quality of life
SE	standard error
SEER	Surveillance, Epidemiology, and End Results Program
TKI	tyrosine kinase inhibitor
UK	United Kingdom
US(A)	United States of America
WHO	World Health Organization
YLL	years of life lost

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Abstract

Acute myeloid leukaemia (AML) is a haematological malignancy affecting approximately 1,100 Australians of all ages each year. Treatment regimens are intensive and burdensome and administered in tertiary public health services. The public health system bears this cost; therefore, the concept of patient financial burden is easily dismissed. Nevertheless, evidence from overseas and emerging Australian data challenge this assumption. Moreover, financial burden could significantly impact patient outcomes. Therefore, the issue of personal financial burden requires further exploration to better understand its impacts on AML, in order to develop meaningful patient-centred interventions and improve patient outcomes.

The overarching aim of this thesis is to describe the personal and financial burden in adults diagnosed with AML. The specific objectives are to:

1. To explore the lived experience of adults with AML.
2. To explore the financial burden of AML from the patient perspective.
3. To examine the societal financial burden attributable to adults with AML.

The aim and objectives were addressed by employing a sequential exploratory mixed-methods research design. First, a systematic review synthesised the contemporary literature surrounding financial burden in haematological malignancies. This literature examination assisted in identifying the literature gaps and contributed to the questions asked in both the qualitative and quantitative investigations.

Next, a social media study described the AML-related content on Instagram to explore patient health and well-being concepts. A descriptive qualitative study followed, involving AML patients explored the personal and financial burden of AML. The identified themes informed the subsequent quantitative studies: a modelling study to quantify the societal, economic burden from lost productivity attributed to AML; and a survey of patients to measure the extent of financial burden and contributing out-of-pocket costs.

The systematic review identified 20 studies of moderate-evidence quality describing a prevalence of financial burden of between 15 and 59%. Most of the literature (12/20) was drawn from the United States. Financial burden was associated with worsening quality of life and living in metropolitan areas, but there was no evidence for impact on survival. The qualitative studies revealed an opportunity for health professionals to provide messaging to people posting or searching about AML using Instagram. The qualitative interviews revealed important health and well-being aspects affecting patients' lives. Some of these concepts were not appropriately addressed by commonly used patient-reported outcome measures (for example being bothered by changes to vision or taste), suggesting the quality of life impacts from AML may be underestimated. The qualitative data also highlighted that the contributors of financial burden were reduced income and out-of-pocket costs. Patients described employing a range of financial coping mechanisms and worried about future financial circumstances.

The quantitative study revealed that 42% of participants experienced some degree of financial toxicity, with 71% employing a financial coping strategy. Median out-of-pocket expenditure was $100 in the last month ($0-$1,650), with prescription medications and travel costs the most substantial contributors. Approximately 1 in 5 participants indicated debt accumulation of between $350-$40,000. The economic modelling study demonstrated AU$1.43 billion in lost gross domestic product over the ten-year period of 2020 to 2029 inclusive attributable to AML, resulting from underemployment and death.

This thesis raises awareness of the issue of financial burden and broader economic impact of AML. Triangulating this research has identified that many Australian AML patients live with financial burdens, impacting individuals, their families, the health system, and the broader society. A series of recommendations based on the research findings are suggested to stimulate additional investigation to ensure patient-centred evidence-based assistance for these patients.

Chapter 1: Introduction

1.1 Overview

In this thesis I explore the personal and financial burden of acute myeloid leukaemia (AML). The reasoning for this choice of topic is three-fold. First, there was an evidence gap, which meant a contribution to the literature was possible as required to meet the requirements of a PhD thesis. Second, I was interested in the topic and it is a topic important to those with AML, which aligns with my patient-centred research and care values. Third, the topic choice allowed for a research program using a breadth of methodologies, whereby as a researcher, I could learn new research skills during my candidature.

Each Chapter of this thesis builds on the next to provide a holistic body of research examining the personal and financial burden of AML. The research is structured to address the following three objectives:

1. To explore the lived experience of adults with AML;
2. To explore the financial burden of AML from the patient perspective; and
3. To examine the societal financial burden attributable to adults with AML.

An AML survivor, Charlie, who participated in the research study included in Chapter 7 of this thesis, details in her own words the inadequacy of many of our hospital processes and the systemic failures that she has experienced. She eloquently describes the impetus for this thesis and articulates the reasons why we should desire to do better for patients entrusted to our care:

"Although I was handed a lot of printed material when I was first diagnosed and was able to access a spiritual counsellor; ***I felt/feel overwhelmed by the process & not advocated for****. I felt processed by a huge machine, and was not given enough information about what would happen when, which I found* ***traumatic****... I had to* ***stop working****... My Wife found it traumatic, and could not work much so* ***we had to borrow money*** *both from friends/relatives & Credit Card to cover rent and living expenses. Neither of us had any spoons [energy] left to apply for Centrelink Benefits…* ***Social Workers*** *at the hospital, who* ***were overwhelmed*** *by others.... I have* ***received no formal counselling*** *for my diagnosis, and was not offered any….2 years on I found online Facebook groups. However, I needed it earlier, and not to have to ask for it. Due to the Chemo side effects****, I have had to buy expensive (Non PBS) anti-emetic drugs*** *to help. I have also needed to* ***purchase expensive equipment*** *to get about with, like the roller walking frame and a stick. I have had 23 bone marrow biopsies, apparently I have hard bones so it hurts a lot, so I have* ***had to buy strong pain medication on prescription, but still not cheap****. I have come out in rashes, so* ***have needed extra creams*** *to soothe... I reacted to conventional vegetables so I have had to buy organic produce, which increased our food budget easily by* ***$750 per month****; Chemo treatment causes memory loss, so* ***I get frustrated*** *when I forget things****. I have felt isolated*** *from family and friends and* ***completely unsupported by the system****! I would like to see a much better system in place to assist and advocate for suffers of blood cancers and their families, being diagnosed with a terminal illness is stressful enough,* ***we need assistance*** *we do not need to ask for… I would like to be able to keep my home clean to my standards,* ***I do not have the energy…*** *We cannot afford to employ a cleaner, especially for our next rental inspection in 2 weeks- this is way harder than it needs to be! I am* ***so glad to have this opportunity to participate in this study****, I hope that it activates some funding somewhere to assist suffers and their families to access adequate support and advocacy, thank you!"*

Quote: Charlie, 43 years old, an AML survivor (Chapter 7)

This body of research represents a platform for further inquiry and advocacy to better address the needs of people suffering from AML and other high burden, low incidence cancers.

1.2 The epidemiology of AML

1.2.1 Biological aetiology and definition of AML

AML is a malignancy of the blood. Typically, during haematopoiesis in the bone marrow, a multipotential haemopoietic stem cell differentiates into a common myeloid precursor or lymphoid precursor cell. Through a process of cell signalling and stimuli, these precursor cells produce cells of intermediate maturity, finally resulting in mature blood cells, including cells of the immune system (Figure 2). AML occurs within the myeloid branch of haematopoiesis, resulting from acquired chromosomal rearrangements and gene mutations (1).

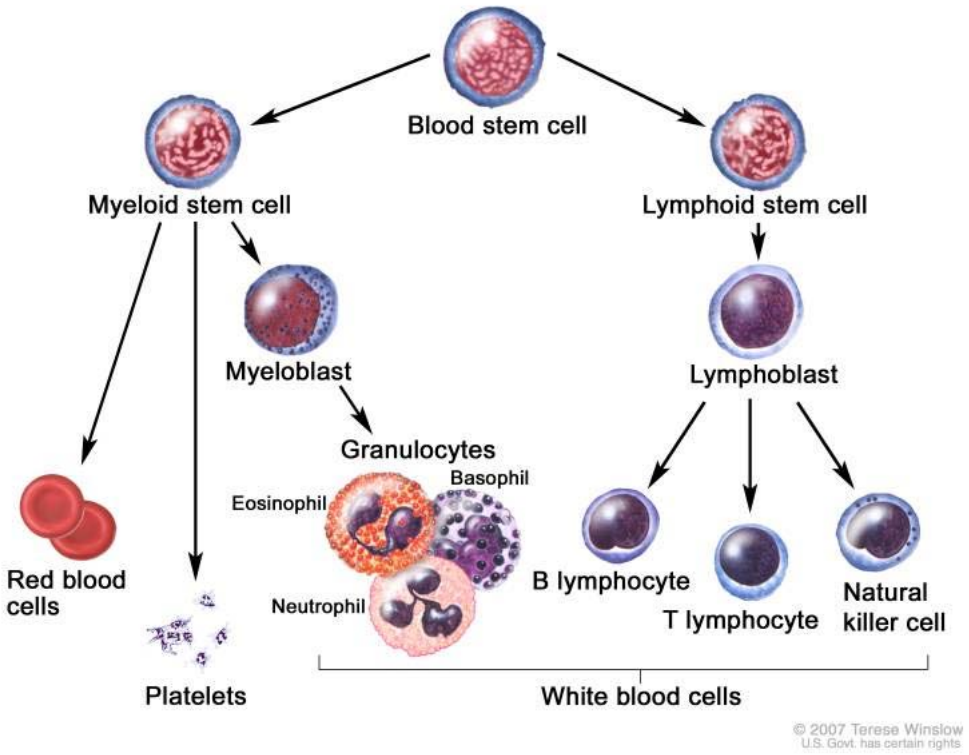

Figure 1. Simplified process of myeloid and lymphoid cell lineage maturation (1)

AML can therefore be described as a heterogeneous clonal disorder characterised by myeloid progenitor cells in the blood and bone marrow with halted maturation (2,3). Cytogenetic and molecular genetic subgroups are defined by the World Health Organization (WHO) for definitive disease classification, definition and subgroups (4). AML arises either *de novo* or secondary to previous therapy or post-antecedent haematologic disease (21).

1.2.2 Incidence and prevalence of AML

AML is a low incidence malignancy, but between the years 1990 and 2017, the global incidence of AML has slowly been rising: the age-standardised incidence rate in 1990 was 1.35 (95% confidence interval [CI] 1.20-1.71), and in 2017, it was 1.54 (95% CI 1.40-1.63) (6). Globally, AML accounted for 18% of total leukaemia cases in 1990, increasing to 23.1% in 2017 (7). Similarly, in Australia, the age-standardised incidence rates were 3.2 in 1982 and 4.0 in 2017 (8). In 2017, there were 1,026 people diagnosed with AML, and it is projected to increase to 1,181 people in 2021 (9). For comparison, in 2019 in the United States (US), 21,450 new patients were diagnosed with AML, but the incidence is similar to Australia's (10). The described increasing incidence can be likely attributed to the ongoing ageing of the global population (11), as well as chemotherapeutic treatment of primary malignancies resulting in therapy-related AML (12), which accounts for up to 7.7% cases of AML (13).

Prevalence is more challenging to estimate due to the inherent limitations of population registries and linked data sets, and estimates are particularly scarce in younger cohorts (3). Data from the internationally-respected Swedish Cancer Registry and the Nordic Society of Paediatric Haematology and Oncology Registry estimate the overall prevalence of AML to be 13.7 people per 100,000 persons (3,14). The Australian estimate is approximately 8.2 per 100,000 people, equivalent to 1,959 people alive at the end of 2015 diagnosed between 2011-2015 (15). In the published literature, prevalence estimates vary substantially across countries (3,16–18), likely due

to the methods of estimation employed and the inherent limitations of population registries and linked data sets (3).

1.2.3 Gender and ethnicity and incidence

There is a male predominance in the diagnosis of AML: the age-standardised incidence rate per 100,000 persons (ASR) in Australia is 6.3 for males and 4.9 for females (19). The US has a lower ASR (4.7 in males and 3.4 in females). In the United Kingdom (UK), these rates are 4.2 and 3.0 for males and females, respectively (20). The observed variations are likely due to low incidence and data collection methods. One US registry study demonstrated that males have worse overall survival outcomes compared with females (HR 1.05, p =.01), and there is recent evidence to suggest this may specifically be due to male predominance of specific mutations, with adverse risk features in the early stages of disease (21,22). Specific subtypes of AML have a gender predominance. For example, therapy-related AML is most commonly observed in females due to previous chemotherapy targeted at female cancers (14).

Non-Hispanic whites have a higher incidence of AML (4.7 per 100,000 person-years) than blacks (3.9 per 100,000 person-years), Asian and Pacific Islander people (4 per 100,000 person-years) and Hispanic whites (3.9 per 100,000 person-years) (23). However, in terms of survival, Acharya *et al.* found in a multivariable analysis that ethnicity was not associated with overall survival (HR 0.958, p = 0.1354) (24).

1.2.4 Age

AML incidence increases with age: the median age of diagnosis in Australia is 67 years, and approximately one-third of cases are in those aged 75 years and older (25). AML is infrequently seen in childhood or young adulthood (Figure 3) and rarely in those under 45 years of age (19). Myelodysplastic syndromes (MDS) frequently progress to AML, with the two diseases

conceptually thought of as existing on the same spectrum (26). There is an increasing incidence of MDS with age, (9) which may partly explain the increasing incidence of AML with age (11).

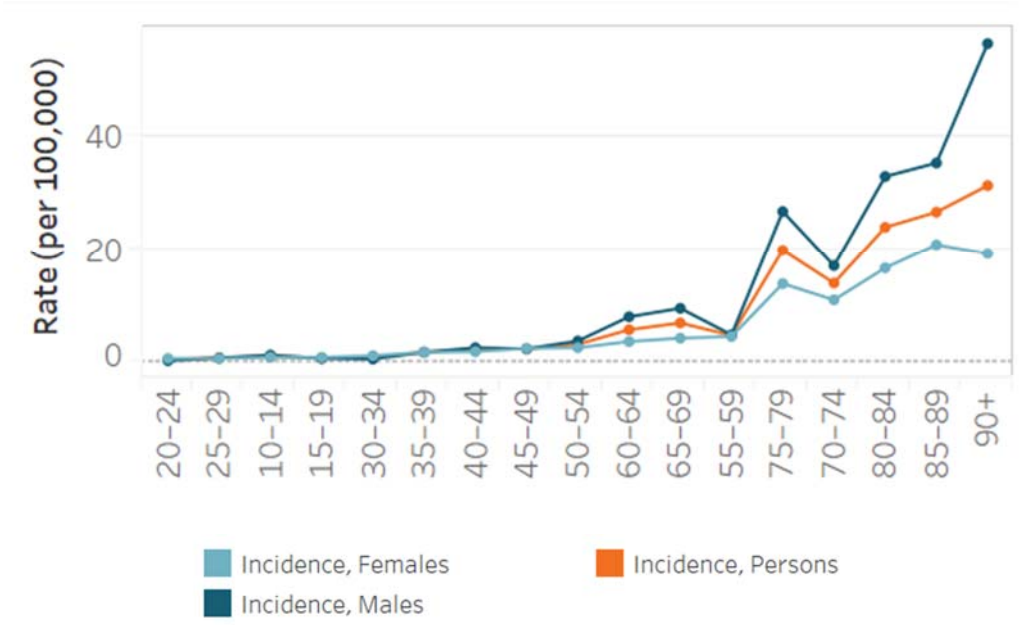

Figure 2. Acute myeloid leukaemia in Australia by sex and age group, 2017 (9)

However, the increasing incidence with age is more likely attributed to an observed exponential increase of complex aberrant karyotypes with age: 0.15 cases per 100,000 at ages 20 to 29 compared with 4.30 cases per 100,000 at ages 60 to 69 years (27). In contrast, genotypes typically found in younger patients representing true *de novo* AML tend to have an approximate flat-rate incidence age profile (11). One US retrospective study observed in their cohort of 968 adults that the incidence of AML with multi-drug resistance (often associated with aberrant karyotypes) was lower in those younger than 56 years compared with those 75 years and older (33% compared with 57%) (28). These age-related compounding effects have a considerable impact on overall survival and the effectiveness of the traditional treatment regimens (11,27,28).

1.2.5 Mortality

Population-based registry studies have observed moderate improvements in AML 5-year survival over the past several decades (Figure 4): in 1975, overall survival was 6.4%, and in 2010, it was

29.8% (29). The progress observed over this period is likely attributable to the increased use of intensive chemotherapy, improved risk stratification for identifying patients suitable for an allogeneic haematopoietic stem cell transplant, and improved supportive care (30,31).

Figure 3. Five-year relative survival for acute myeloid leukaemia in Australia, by sex 1988–1992 to 2013–2017 (9)

Age is considered one of the most significant predictors of AML-related mortality; those diagnosed at a younger age have a much higher 5-year survival, probably related to less exposure to suspected environmental factors and a lower rate of genetic changes (32). For example, 5-year survival for all ages in 2019 was approximately 28% (33). However, adults less than 65 years old have a 5-year survival as high as 60% (depending on genetic changes) compared with approximately 5% of those aged 65 years and older surviving 5-years (33–36). The overall improvement in 5-year survival over time (Figure 4) has been predominantly restricted to younger patients who can tolerate higher intensity chemotherapies and haematopoietic stem cell transplants due to fewer comorbidities, better performance status and minimal age-related frailties (5,37,38).

Some sub-groups have also documented little improvement in mortality. Surveillance, Epidemiology, and End Results (SEER) cancer data from the US sugges the improvements in 5-year survival are not equitable across different ethnic groups, with non-white ethnicities

experiencing only mild improvements. This finding may be explained by disparities in access to care (39). Additionally, a Swedish registry-based study of almost 10,000 patients demonstrated no improvement in survival over 12 years for patients diagnosed with AML with antecedent myelodysplasia (40), which accounts for up to 12% of all AML diagnoses (41).

1.2.6 Risk Factors

Several associations that increase the risk of developing AML have been identified. Inherited genetic disorders or defects are important risk factors, particularly for children (11). Those suffering mutations causing Down syndrome have a 10-20 fold increase in the likelihood of developing AML (42), while other mutations associated with Klinefelter syndrome (43), Li Fraumeni syndrome (44), Fanconi anaemia and neurofibromatosis (43) also increase the risk of AML. The most common risk factor in adults are acquired (somatic) genetic abnormalities found in approximately 50-80% of all AML cases. Genetic abnormalities are powerful prognostic indicators and used as the basis for risk stratification by the European LeukaemiaNet (ELN) (38).

Exposure to ionising radiation has been shown to increase the incidence of AML through observational cohort studies in Japan after the atomic bomb explosions of World War II (45,46) and in patients receiving therapeutic radiation for antecedent solid tumours (47–49).

Benzene is an aromatic hydrocarbon naturally found in crude oil and gasoline and used in many manufacturing industries, including petroleum, rubber, lubricants, plastics, dyes and pesticides. The International Agency for Cancer first assessed benzene in the 1980s as having sufficient evidence to be classified as carcinogenic and, in their 2018 report, concluded that benzene exposure is causative of AML (50). Furthermore, several cohort studies undertaken in various countries have identified a dose-response relationship (51–58). Other chemicals investigated include dioxins (59) and formaldehyde (60). Pesticides and herbicides are inconsistently linked with AML, perhaps due to the studies' inability to separate benzene exposure in the cohort (3).

Some lifestyle factors are also associated with AML, such as a higher body mass index (BMI) (61) and tobacco use (62). There is no association between alcohol consumption and AML based on a meta-analysis of the available literature (63).

1.2.7 Treatment

AML is progressive and rapidly fatal without specific treatment. The current treatment paradigm usually consists of induction, consolidation chemotherapy, and sometimes haematopoietic stem cell transplant to reduce the risk of relapsing disease (64). The therapy consists of combination agents, cytarabine and anthracyclines, introduced in the 1970s (65,66).

This therapy regimen remains the cornerstone of treatment for AML today. It employs cytarabine and anthracycline with or without a purine analogue, such as seven days of standard-dose cytarabine plus three days of anthracycline (often known as "7 + 3"), fludarabine–Ara-C–granulocyte colony-stimulating- factor–idarubicin, or similar (5,38). While effective, many older patients are intolerant of this regimen and induction therapy-related mortality is between 15-30% (67–70). Although due to improved supportive care interventions and improved health status of older persons more generally, there is evidence to suggest that treatment-related mortality is declining (71). Treatment-related mortality may be expected to improve further as there is now emerging evidence from clinical trials that venetoclax plus either a hypermethylating agent (such as azacitidine) (72,73) or low-dose cytarabine (74,75) may provide an effective alternative treatment paradigm for older patients (≥60 years) unfit for traditional remission-induction therapies (5).

In recent years, it has become standard practice to evaluate the disease response to the initial treatment by measuring the presence of minimal residual disease (MRD), which refers to submicroscopic disease detected by molecular and immunophenotypic techniques (76,77). The presence of MRD is a powerful prognostic indicator for relapse and survival (78–81), and clinical investigations into MRD directed therapy are ongoing (82). For most patients, intensive

chemotherapy induces complete remission (approximately 70% of patients), but 30–80% relapse within the first two years, depending on age and disease characteristics. Relapse, therefore, represents the most typical cause of mortality in AML (38,83).

1.2.8 Physical and psychological impact of AML

AML is associated with various physical and psychological impacts resulting from disease and treatment side effects and changes in work and social roles. Effects (sometimes occurring long after induction treatment) can be irreversible, such as anthracycline cardiotoxicity (84), infertility (85), malnutrition (86,87), reduced physical fitness (88,89), reduced sexual function and satisfaction (90), fatigue (91–95), cognitive decline (96) and emotional distress (94,97–99). These effects can impact the quality of life, which is personal and subjective but overlaps with a persons' health status (100). Quality of life is a subjective measure of an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (101). In this thesis, in which the term 'quality of life' is used, it should be considered within the context of health. This is sometimes termed 'health-related quality of life', but often these two terms are used interchangeably (102). The definition of health-related quality of life expands the definition provides and includes "those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment" (103). Compared with more common cancers, little attention has been afforded to measuring quality of life in AML (95). While the studies addressing this aspect of patient experience have increased over the last decade, they are limited by heterogeneous methods, use of non-disease specific questionnaires, poor representation of sub-groups and high levels of loss to follow-up (104,105,104).

Even so, some patterns have emerged. Quality of life often improves after treatment has finished, but many survivors report ongoing effects, such as emotional distress, reduced sexual functioning, role changes, impaired social functioning, cognitive changes and impaired physical

functioning (105–108). Fatigue is reported irrespective of treatment status for AML and has been repeatedly shown to cause significant quality of life impairment across numerous cancer types (95,105,109–111), and may also be related to physical and social functioning (104). Therefore, people recovering from AML may experience difficulties in returning to the demands of everyday life, including work and household duties (112). However, little research has explored the effects of AML on health and well-being. This research gap is addressed in **Chapters 4** and **5.**

1.3 The cost of AML

Today, an estimated one million people live with or beyond cancer in Australia. This figure is anticipated to rise to almost two million cancer survivors living in Australia by 2040 (113). The increase in survivors has been attributed to improved screening and diagnosis, treatment and an ageing population (114). For perspective, a cancer diagnosis will affect one in two Australians when they reach 85 years (33).

Australians benefit from publicly-funded healthcare, in which the Government utilises to fund a range of services and provisions, including primary, secondary and tertiary health services, population health programs, community health services and research (115).

If hospital care is needed, the government subsidises the direct costs of care in publicly-funded hospitals, and there is little, if any, co-payment [15]. Some Australian patients choose to utilise a parallel private hospital system mainly funded by private health insurance, albeit with some government subsidy [17]. For patients diagnosed with low incidence cancers and requiring complex and specialised care like AML, care is centralised within tertiary public health services [18]. The cost of AML can be broadly categorised as burdening society or the individual.

1.3.1 Societal costs

Societal costs are those paid by the Australian society, regardless of the payer. These costs can be classified as direct (those directly attributable to medical management of disease) or indirect, such as costs incurred through lost productivity of affected individuals.

Direct costs

The expenditure attributable to hospital, primary health care and referred medical services costs in Australia were approximately $11.7 billion, equivalent to 8.8% of the total expenditure on all disease groups in 2018-2019 (116). Of this $11.7 billion, AML, consumed $105 million (116).. The Pharmaceutical Benefits Scheme (PBS) expenditure was $1.3 billion for cancer and $20.2 million for AML in the year 2018-2019(116).

Over time, overall expenditure of cancer drug therapies is expected to rise due to a combination of factors such as an increasing and ageing population and new, more costly targeted therapeutic agents (like immunotherapies) and other interventions (117). This forecast is exemplified by looking at drug expenditure between 1999 and 2012, over which time cancer drug expenditure increased by 19%, compared with 9% for all other drugs combined (118).

As a group, haematological malignancies comprise some of the most expensive cancers to treat: they are estimated to cost 19% of total cancer treatment expenditure (more than $795 million annually) (119) yet account for only 12% of cancer incidence in Australia (15,120). Furthermore,

an improved understanding of the genetic and molecular mechanisms of AML over the past 20 years has resulted in a number of novel molecular targets for pharmacotherapeutic interventions, with many promising candidates currently within the drug development pipeline (5,38). New therapies are good news for patients (5), but they present a significant challenge for socially-funded healthcare systems to provide up to date and effective treatments while balancing the cost of care. Looking forward, the impact of advanced technologies in diagnostics and disease monitoring resulting from improved understanding of AML, is expected to further increase the direct costs across various areas (121,122).

Indirect costs

Reduced work hours or labour output is commonly termed 'lost productivity', representing an indirect cost to society. A 2011 report by the National Institute of Cancer estimated that lost productivity attributable to all cancer accounted for 61% of the overall cost of cancer (123). A New South Wales study found this figure to be 51% of the overall cost of cancer (124), and more recently, the lost productivity due to cancer in Australia was estimated to be $1.7 billion of lost gross domestic product (119). A longitudinal Swedish study of 111 people with an AML diagnosis estimated that approximately half of those diagnosed with AML returned to work five years after diagnosis (125). This estimate of the AML return to work, coupled with the high mortality and morbidity of AML, suggest lost productivity from this disease may represent a significant contribution to current lost productivity estimates. However, the actual contribution of AML to the existing lost productivity estimates remains unknown and represents a research gap addressed in **Chapter 8.**

1.3.2 Individual costs

The burden of out-of-pocket expenses borne by Australians are attributable to direct medical management of disease (for example, the cost of hospital stays, diagnostic tests and treatments)

or are in-direct expenses incurred adjacent to their disease (for example, transportation costs). Indirect costs are also borne by the individual tangentially through reduced or unemployment. Australian patients must bear any cost difference between what is funded by Medicare and the PBS and what is charged by the provider (126). At a population level, Australians' out-of-pocket costs have been rising, and are now estimated to comprise approximately 18 % of the total healthcare expenditure per annum, which exceeds the Organisation for Economic Cooperation and Development (OECD) median of 15.8% (127).

Australians with haematological malignancies incur out-of-pocket expenses of more than $24.6 million ($1,900 per patient in the first 12 months following diagnosis), reflecting 19.3% of total out-of-pocket expenses each year, borne by patients with cancer in Australia (119). Those needing to travel for treatment are disproportionally burdened by out-of-pocket expenditure due to transport and accommodation requirements (128), particularly relevant to malignancies such as AML. Treatment tends to be centralised in specialised tertiary hospitals, requiring lengthy in-patient stays (129). Furthermore, recent therapeutic advances in malignant haematology are more costly than current treatment regimens (130,131). They may not be entirely subsidised by the PBS (132,133), requiring a patient to pay any difference between the medication price and the PBS subsidy.

These expenses borne by patients can be exacerbated by lost income through reduced or unemployment. Being unable to undertake paid work is a demonstrated side-effect of a cancer diagnosis. For example, more than 40% of all cancer diagnoses occur in patients of working age (134), yet half (49%) of Australians aged 45-64 years diagnosed with cancer are not in the workforce (135). Compared to healthy age-matched controls, those with a history of cancer are three times more likely to be unemployed (119). In the literature, there are only limited data regarding labour-force participation for those with AML, particularly beyond the first 12 months after diagnosis (125,136–138). Samadi et al. study estimated that 12 months after diagnosis, 46% of people with AML returned to work in some capacity(125). A Swedish cohort study of

haematopoetic stem cell transplant patients suffering various haematological conditions (including AML) found that 52% of people returned to work ten years and beyond after diagnosis (137). Although the median age of diagnosis for AML is similar to retirement age, the impact of lost income on individuals contributing to their financial distress may be easily dismissed. However, the literature suggests that lost income can compound increased out-of-pocket expenses and financial burden (139–141).

The direct and indirect out-of-pocket expenses borne by Australian AML patients remain unknown, representing a research gap addressed in **Chapters 6 and 7.**

1.3.3 The patient impact of financial burden

Many terms relevant to financial burden are used interchangeably in the literature, including financial toxicity, financial stress, financial hardship, financial distress, economic burden, economic stress, economic hardship and economic distress (139). This thesis is no exception. Whatever the term used, the intent is to describe the stress and hardship arising from the financial burden of cancer treatment (142).

Much like the traditional treatment-related toxicities, recent research has demonstrated that financial toxicity (a synonym for financial burden) is linked with poorer quality of life and other patient-relevant outcomes such as higher symptom burden, depression, anxiety or stress, lower compliance to medications, forgoing or delaying medical care and even reduced overall survival (130,131). Regardless of the financial burden and its impacts, quality of life considerations are essential for patients with AML. The disease and treatment are burdensome and contribute to many physical and psychological impairments (98). A long-held view that quality of life resumes to pre-illness levels upon completion of chemotherapy is recently being challenged. The contemporary literature demonstrates that the most commonly-utilised quality of life instruments in AML may not be suitable for use in this population, as they were not developed with people

who suffered AML (105). Therefore the instruments are not capturing the most salient items that patients experience. The suggestion is that the actual quality of life impairment may not be reflected in the literature. Research in AML is often hampered by the disease's low incidence and high mortality, making it challenging to incorporate into instrument development. To explore this research gap, two qualitative studies explore the health and well-being of AML patients in **Chapters 4 and 5.**

Workforce impacts and out-of-pocket expenses can also be interrelated with physical and psychological impacts for many patients. Estimates of the prevalence of financial toxicity in cancer survivors vary between 7% and 80%, depending on the exact population, definition and measurement instrument utilised (143–149). It may seem reasonable to assume that the prevalence of financial toxicity would be lower in countries with publicly-funded health care and systems designed to reduce out-of-pocket costs to patients, such as welfare assistance for those travelling distances for care (150). However, up to 48% of cancer patients in countries with publicly-funded healthcare experience financial toxicity (151), although less research has been conducted in these health care systems. There remains a dearth of literature undertaken in the Australian context regarding financial burden. Two recently published systematic reviews focused on the financial burden in publicly funded health care system systems identified only small numbers of Australian studies across a range of cancer types (151,152). Longo et al identified six Australian studies from an included 30 (151) in their systematic review and Pauge et al identified 11 Australian studies from a total of 46 included publications (152).
Furthermore, there may be nuances within particular cancer groups due to various factors, such as the disease burden, the disease or treatment trajectory, primary therapies and the treatment modalities used. These variables and their associated costs will differ among oncology sub-specialties, and consequently, so will the financial burden. Presently, it is challenging to assess the literature related to financial burden in haematological malignancies. This research gap is

addressed in **Chapter 2** utilising a systematic review to identify, appraise and synthesise the literature**.**

In the literature, those most commonly suffering from financial toxicity are female (140), younger (140,153), from minority population groups (153), have a lower income when diagnosed (140), suffer cancer recurrence(153), are treated with adjuvant therapies or radiation therapy (140,153), have a higher disease burden and have a more recent diagnosis (140,153). However, caution must be employed when applying these findings to the Australian context and specifically to AML patients, as most of the literature concerning financial toxicity in cancer is heterogeneous and based on data from the US (140), which adopts a user-pays model and does not have publicly funded health care for the majority of citizens (154,155). Predominantly, the literature only includes patients with solid cancers or mixed cancer types (139–141,151,152,156–158), with the most common cancers reported being breast, colorectal, lung and prostate (159). Additionally, interpretation of findings remains difficult if studies report out-of-pocket expenses only with no measure of objective (direct and indirect cancer-related costs) or subjective (perceived experience of the objective measure) burden. Arguably, reporting out-of-pocket expenses only provides an indicative dollar amount without the concept of 'burden' being measured. Finally, many published sources do not define the threshold for burden, define the terminology used, and use various methods to measure financial burden (159).

This methodological heterogeneity presents substantial problems in comparing findings across studies and highlights the lack of conceptual clarity of the financial burden experienced by patients (160). Altice and colleagues proposed a typology representing three broad domains that constitute financial hardship: a) material conditions that arise from increased out-of-pocket expenses and reduced income; b) the psychological response such as distress and concern at managing unexpected health-care-related financial expenditure or reduction in income; and c) coping behaviours which the patients adopt to manage their care while experiencing increased expenditure and reduced income(139). Others have also proposed conceptual frameworks of

financial toxicity: Carrera et al. (161), Pisu et al (162) and Witte et al. (159). While these frameworks are helpful, a shared comprehensive conceptual framework is yet to be elucidated, contributing to the heterogeneous methodology employed by researchers and the paucity of interventions to assist patients (163).

One Australian study found that approximately one-third of cancer patients experienced moderate or heavy financial hardship due to the costs of medicines prescribed for their illness (135), and a large US qualitative study found that 39% of patients with AML cited economic hardship as an impact from their disease (93). The financial burden experienced by AML patients in Australia is unknown and represents a research gap qualitatively addressed in **Chapter 6** and quantitatively measured in **Chapter 7.**

1.4 Rationale and problem statement

The present Chapter has highlighted that AML is an aggressive malignancy with high mortality. It is only treated within specialist hospital units, resulting in some patients travelling to seek treatment and care.

An overview of the epidemiology of AML, the usual treatment regimen, and the physical and psychological burdens have been presented. The financial impact of cancer has been highlighted as particularly poignant, yet to date, the existing literature has failed to include the patient impact of AML from a financial perspective.

With recent advances in the characterisation of the genetic landscape of AML, there are many new targeted therapies in the development pipeline that may become available to patients over the coming years (164,165). The high cost of niche drug development is increasingly being passed on to patients as new drugs become available. Governments tasked with fiscal responsibilities may benefit from novel measures incorporating personal and societal costs in addition to the current quality and disability-adjusted life year paradigm. Additionally, it is essential to identify high-risk groups most likely to suffer financial burden since there is considerable evidence that

this side-effect of cancer impairs patient outcomes. Compounded with the potential high-cost drugs in the current pharmaceutical development pipeline, the treatment options in the future may pose further financial burdens. This low incidence malignancy can have profound effects when considered personally and socially.

1.4.1 Aims and objectives of this thesis

The overarching aim of this thesis is to describe the personal and financial burden in Australian adults (≥18 years) diagnosed with AML. The specific objectives are to:

1. To explore the lived experience of adults with AML.
2. To explore the financial burden of AML from the patient perspective.
3. To examine the societal financial burden attributable to adults with AML.

Chapter 2: Systematic review of the patient-perceived financial burden for those with malignant haematological conditions

In this Chapter I present the systematic review undertaken as part of the thesis. The manuscript is currently under review and is therefore presented in the submitted Microsoft Word format. This systematic review aimed to identify, appraise and synthesise the literature about patient-reported data of their financial burden when suffering from a malignant haematological condition. Specifically how financial burden is assessed, the contributing out-of-pocket costs, the impacts of financial burden and the patient experience of financial burden. The systematic review aligned with objective 2 that sought to explore the financial burden of AML from the patient perspective. It also contributed to the analysis (the deductive coding) of the qualitative study presented in Chapter 6, the development of the survey instrument used in Chapter 7 and contributed to framing the overall thesis findings in the context of the wider liteature in Chapter 9. Supplementary material for the manuscript is provided in Appendices A (Medline search strategy), B (quality appraisal scores) and C (additional supporting quotations).

Patient perceived financial burden in haematological malignancies: a systematic review

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A systematic review of financial burden in haematological malignancies

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Declarations

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Authors' contribution

Catriona Parker: Conceptualisation, Methodology, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualisation and Project administration.

Danielle Berkovic: Methodology, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Project administration

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Ethics approvals

Not applicable.

Consent to participate

Not applicable.

Abstract

Background: Advances in scientific understanding have led to novel therapies and improved supportive care for many patients with haematological malignancies. However, these new drugs are often costly, only available at centralised health care facilities, require regular specialist reviews and lengthy treatment regimens. The leads to a significant financial burden. Understanding the impact of financial burden on haematological patients is important to appreciate the urgency of alleviating this systemic issue.

Objective: To systematically search, synthesise and appraise the literature about haematological patient-reported data of their financial burden. Specifically how financial burden is assessed, the contributing out-of-pocket costs, the impacts of financial burden and the patient experience of financial burden.

Method: Eligible studies were identified by systematically searching Medline, PsycINFO, CINAHL and Embase. Self-reported data reported in both quantitative and qualitative studies that described financial burden for patients with haematological malignancies were included. Quality appraisal of the included studies was undertaken using the Joanna Briggs Institute tools. A narrative synthesis was employed. For quantitative studies, outcomes were extracted, tabulated and categorised to allow comparison. For qualitative studies, quotations, codes and themes were extracted and then clustered. An inductive approach derived qualitative themes.

Results: Twenty studies were identified for inclusion. Of the quantitative studies most (83%) employed un-validated researcher-generated measures to assess financial burden. Between 15-59% of patients experienced financial burden. Out-of-pocket expenditure was frequent for clinical appointments, prescription and non-prescription medication, and travel. Financial burden was associated with worsening quality of life and living in metropolitan areas, but there was no evidence for impact on survival. Patient-centered experiences from the qualitative inquiry complemented the quantitative findings and five themes were determined; familial or household

impact, relying on others, barriers to care due to cost, barriers to accessing financial assistance and sources of out-of-pocket expenses.

Conclusion: The impacts of financial burden are yet to be fully appreciated in haematological malignancies, exacerbated by the heterogeneous methods employed by researchers. Future work should focus on identifying the long-term ramifications of financial burden for patients and trialling interventions to reduce its prevalence and patient impacts.

Introduction

Haematological malignancies are a group of biologically and clinically diverse diseases affecting people of all ages, accounting for approximately 9% of all malignancies in Europe and the United States[1]. Treatment varies from watchful waiting to intensive chemotherapy with or without haematopoetic stem cell transplant[2].

Advances in scientific understanding have led to novel therapies and improved supportive care, which has increased life expectancy and quality of life for many of these patients[2]. However, the increasing use of high-cost novel agents, prolonged treatment durations, regular and ongoing specialist reviews and the centralised nature of care (requiring travel over long distances for some patients) can leave patients with haematological malignancies particularly vulnerable to healthcare-related costs. Some of these costs comprise direct medical expenses, such as paying for treatments and diagnostic procedures; others are more indirect, such as lost income due to an inability to work. Of note is that there is a myriad of terms used interchangeably with financial burden, including financial toxicity, financial stress, financial hardship, financial distress, economic burden, economic stress, economic hardship, or economic distress[3]. Whatever the term used, the intent is to describe the stress and hardship arising from the financial burden of cancer treatment[4].

The literature indicates that the patients experiencing financial burden are more likely to be female, of younger age, from a lower socioeconomic background and with a more recent diagnosis[5,3,6]. Furthermore, financial burden has been associated with a reduced quality of life[7–9], lower patient satisfaction[10], reduced medication adherence[11–14] and reduced overall survival[15]. These findings demonstrate the potential complexity and interrelated factors associated with financial burden.

Even though this is known, there remain gaps in the financial burden literature. To date, systematic reviews on the topic have prioritised quantitative studies, focused on a single country, or have included all cancer types without focusing on the nuances between cancer types.

Additionally, many reviews have included insurance database data which, while insightful, potentially exclude uninsured patients and do not reflect the patient perception of their financial burden. There have also been calls to understand the effects of financial burden by cancer type, given the variabilities between cancer treatments, mode of treatment, cancer trajectory and associated out of pocket costs [16,17]. In our era of patient-centred care, we were interested to understand the financial burden from the patient perspective. Therefore, the present review aimed to systematically search, appraise, and synthesise the literature of haematological patient-reported data of their financial burden. Four research questions that guided the review:

1. How is financial burden assessed?
2. What out-of-pocket costs contribute to financial burden (objective financial burden)?
3. What are the impacts of financial burden (subjective financial burden)?
4. What is the patient experience of financial burden?

2. Methods

2.1 Design

A systematic literature review was undertaken and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[18] (Figure 1).

2.2 Search strategy

Four electronic databases — Medline, PsycINFO, CINAHL and Embase databases — were searched for English language articles published between 2000 and 2021. The comprehensive search strategy was developed with a specialist librarian and included customised search terms and Boolean operators tailored for each database (see supplementary data files). The search strategy was initially developed for Medline and then adapted accordingly for other databases. Grey literature, intervention studies or systematic reviews were not included. The reference lists of previously identified key papers, literature, and systematic reviews were manually searched to identify missing additional primary studies in the original search strategy.

2.3 Study selection

Inclusion criteria of the review included: a) primary studies of qualitative, quantitative and mixed-method designs; b) studies that investigated or described the impact of financial burden with data of financial burden coming from the patient directly in one or more haematological malignancies; and c) patients were aged 18 years and older to ensure that their views or experiences were captured.

We excluded studies if: a) patients aged under 18 years were included, and data could not be separated from the rest of the cohort; b) malignant and non-malignant haematology data were pooled or included all cancer types, and the malignant haematology data could not be separated; c) the population included carers perspectives which could not be separated from those of patients; d) financial burden was not directly reported by patients or was an incidental finding, rather than the focus of the study and e) studies were interventional, randomised controlled trials, systematic reviews or published as a conference abstract, thesis or book.

Titles and abstracts were screened by two reviewers (CP and DB) independently using Covidence software (Veritas Health Innovation Ltd, Melbourne, Australia) to determine which studies met the inclusion criteria. The full texts of studies meeting the inclusion criteria were reviewed independently (CP and DB), and reference lists were checked for potentially relevant studies. Any discordance regarding eligibility was discussed and resolved through consensus between the reviewers.

2.4 Data extraction

Data were extracted from the full-text studies by two independent researchers (DB and CP). A custom template was developed for data extraction, which included the following variables: country of origin, study design, sex, age of participants, haematological malignancy, time of data collection relative to disease, financial burden definition used, financial burden measures and relevant financial impact outcomes (qualitative and quantitative specific).

2.5 Quality and risk of bias assessment

The risk of bias was assessed for all included studies by two authors (DB and CP) using the appropriate standardised critical appraisal tools relevant to the study design from the Joanna Briggs Institute (JBI)[19]. The critical appraisal tools ranged from 8 to 10 items, with different questions used to assess the risk of bias depending on the study design. The items were summed, and scores were converted to percentages to compare the quality of evidence scores across different study designs (supplementary files). Studies were of low quality if they had a score <50% (and were excluded); moderate-quality if they had a score between 51%–70%, and good-quality studies have a score of 71%–100%[20]. None of the included studies were excluded due to a low score. Where there was disagreement between the two reviewers of ±10% on a score, then a consensus was reached through discussion.

2.6 Data synthesis

Due to the heterogeneity of the studies, a meta-analysis was not undertaken; instead, a narrative synthesis was employed, using elements of the framework described by Popay et al. [21]. For the studies reporting quantitative results, characteristics and demographic data such as sample size, gender and age of participants were reported. Then outcomes were extracted, tabulated and categorised to find similarities and differences between the studies. For studies that included other cancer types in addition to haematological malignancies, only the data on haematological malignancies was extracted.

Only those where quotations could be identified for malignant haematological conditions were extracted for qualitative studies that reported cancer-types other than haematological malignancies. The qualitative study narrative synthesis included studies that primarily reported quantitative results and narratives from a free-text field. Quotations, codes used to categorise the data (if available), themes, and other contents related to the systematic review were extracted. These data were then organised into categories and clustered to identify similarities in the data.

An inductive approach derived themes, which further allowed for relationships between the themes to be explored.

3. Results

3.1 Study selection and inclusion

After removing duplicates, the database searches yielded 13,524 studies that were screened, and 241 full-text papers were assessed. Finally, 20 studies met the inclusion criteria and were assessed for quality and risk of bias (see Figure 1 for the PRISMA flowchart). No study was excluded after using the JBI quality of evidence assessment tools (see supplementary data).

3.2 Study characteristics

The included studies described many impacts from financial burden arising from haematological malignancies. The studies were undertaken in various countries but predominantly in the USA: USA (12) [22–33], Australia (5) [34–38], Canada (1) [39], China (1) [40] and Malaysia (1) [41]. Eleven of the twelve quantitative studies adopted a cross-sectional design[22–29,32,33,38] (Table 1.), with the remainder being a cohort study[30]. Four of the Australian studies analysed the same participant interviews with different research questions. Of the nine qualitative studies, six collected data using interviews[31,34–37,41], one used focus groups[40] and another used both interview and focus group data-collection techniques[39] (Table 2). One quantitative paper was included in the qualitative synthesis as it collected patients narratives but used an open-ended question on a survey[27]. The included papers (both quantitative and qualitative) were published from 2013 - 2021.

Patients who had received a haematopoietic stem cell transplant (HSCT) between 5 and 36 months prior were the focus of four studies[22,23,28,30]. Four studies recruited multiple myeloma (MM) patients only[27,29,33,39], while two studies focused on patients with chronic myelocytic

leukaemia (CML)[25,41]. Eleven studies[22,23,26,28,30,31,34–38] had a mixed malignant haematology cohort. The financial impact of acute myeloid leukaemia (AML) was reported in one study[24]; another included patients with leukaemia[40] (type unspecified) or lymphoma[32] (also type unspecified). Included studies had an age range of 18 to 98 years, and the mean percentage of the participants being female was 51%.

Table 1. Included quantitative studies

Author, year, country	Study design	Sample size	Sample mean, median or range (years)	Percentage female (%)	Included haematological conditions	Timing of assessment	Main findings describing financial impact
Abel *et al*[1], 2016, USA	Cross-sectional	325	Median, 61	40	MM, NHL, AML, MDS, HL, ALL, other	150 days post-HSCT	**Unsatisfied with present financial situation** = 49% of sample **Difficulty meeting monthly payments** = 42% of sample **Not enough money at months-end** = 19% of sample **Difficulty paying for HSCT-related costs** = 51% of sample **Difficultly paying for transportation** = 41% of sample **Difficulty meeting costs of changed home environment** = 19% of sample. **Income decline** = 46% of sample **Multivariate analysis of financial hardship measures with patient-reported outcome measures** QOL below median Income decline: OR 1.62 (95% CI: 0.98-2.7, p=.06) Hardship_1: OR 2.9 (95% CI:1.7-4.9, p<.001) Hardship_2: OR 2.16 (95% CI:.99-4.7, p=.05) Self-reported health below the median Income decline: OR 1.33 (95% CI: .81-2.2, p=.26) Hardship_1: OR 2.18 (95% CI: 1.3 - 3.6, p=0.003) Hardship_2: OR 1.88 (95% CI: .89-3.9, p=.10) Perceived stress above median Income decline OR: 2.07 (95% CI: 1.3 -3.4, p=.004) Hardship_1: OR 2.08 (95% CI: 1.3-3.5, p=.005) Hardship_2: OR 3.14 (95% CI: 1.4-6.8, p=.004)
Albelda *et al*[2]*, 2019, USA	Cross-sectional	171	Mean, 57	NR	Any needing BMT, but NR	6-months post HSCT	**Multivariate analysis of financial burden with:** "Dissatisfied with financial situation" (OLS coefficients, 95% CI) Health: −0.331, (−0.501, −0.161), p<0.01 Quality of life: −0.295, (−0.473, −0.118), p<0.01 Perceived stress: -1.093, (-1.496,-0.689), p<0.01 "Difficulty paying bills" (OLS coefficients, 95% CI) Health: -0.270 (0.433,-0.108), p<0.01 Quality of life: -0.177 (-0.348, 0.006), p<0.05 Perceived stress: -0.720 (-1.118,-0.321), p<0.01 "Not enough money at the end of the month" (OLS coefficients, 95% CI) Health: 0.404 (-0.680,-0.128), p<0.01 Quality of life: -0.321 (-0.601, -0.024), p<0.05 Perceived stress: -0.943 (-1.625, -0.261), p<0.01
Bala-Hampton *et al*[3], 2017, USA	Cross-sectional	26	Mean, 58.5 (SD 14.1)	46.2	AML	6 months after diagnosis	**Not enough money to cover the cost of treatments** = 69.2% of the sample **Out-of-pocket expenses greater than expected** = 65.4% of the sample **Increased financial worry** = 77% of the sample **No choice in the cost of the care** = 85% of the sample

Author, year, country	Study design	Sample size	Sample mean, median or range (years)	Percentage female (%)	Included haematological conditions	Timing of assessment	Main findings describing financial impact
							Unable to financially contribute to the household = 62% of the sample **Dissatisfaction with finances** = 73% of the sample **Felt financially stressed** = 69.2% of the sample **Felt not in control of their finances** = 85% of the sample
Buzaglo *et al*[4], 2017, USA	Cross-sectional	318	Mean, 56 Range, 18-85	68	CML	Mean of 5.2 years from diagnosis	**Out of pocket costs (%of the sample)** Spent at least US$100 per month = 49% Spent ≥US$250 per month = 27% Spent ≥US$500 per month = 16% Spent ≥US$1,000 per month = 6% **To reduce the cost associated with CML** (% of sample): Postponed seeking psychological counselling (sometimes, often, or always) = 23% Missing a dose or oral CML drugs at least monthly = 19% Delayed follow-up on recommendations on complementary treatment = 17% Postponed doctor's appointments = 16% Postponed filling prescriptions = 14% Skipped doses or CML oral drugs at least sometimes = 10% **Because of costs associated with CML** (% of sample which varied from 283-287 respondents): Reduced grocery expenditure = 35% Depleted savings = 33% Borrowed against or used money from retirement = 20% of sample Sold personal property = 18% Liquidated assets = 13% Refinanced house = 8% Filed for bankruptcy = 6% Home foreclosed = 4% **Multivariate analysis with financial burden** Suboptimal treatment adherence p <.001
Fenn *et al*[5], 2014, USA	Cross-sectional	NR for haematology	NR for haematology	NR for haematology	leukaemia/lymphoma	NR	**Multivariate analysis with financial burden and QoL of at least 'good'** Adjusted OR = 0.91, 95% CI 0.42-1.95, p=.799
Goodwin, *et al*[6], 2013, USA	Cross-sectional	762	Mean, 61 (SD 9.26)	39	MM	Received intensive treatment at the site	**Out-of-pockets costs as a percentage of income by time since treatment began** <u>% income spent during first year of treatment</u> Treatment began <4years ago = 40% Treatment began ≥4 years ago = 33%

Author, year, country	Study design	Sample size	Sample mean, median or range (years)	Percentage female (%)	Included haematological conditions	Timing of assessment	Main findings describing financial impact
							t=-2.281, p=.023, 95%CI -13.658--1.019 <u>% income spent in past 12 months</u> Treatment began <4years ago = 35% Treatment began ≥4 years ago = 23% t=-5.465, p.0005, 95%CI -16.921- -7.968 **Out-of-pockets costs as a percentage of income by time since treatment ended** <u>% income spent during first year of treatment</u> Treatment ended <4years ago = 37% Treatment began ≥4 years ago = 37% t=-0.14, p=.998, 95%CI -11.015 - 10.854 <u>% income spent in past 12 months</u> Treatment ended <4years ago = 29% Treatment began ≥4 years ago = 22% t= -2.143, p=.033, 95%CI -13.21 - -0.564 **Other findings** **Percentage of income used for out-of-pocket costs** Mean percentage of income used on treatment-related expenses = 36% during the first 12 months Mean percentage of income used on treatment-related expenses = 28% in the past 12 months Treatment costs are somewhat to very much a burden to themselves or family = 42% of the sample. <u>Income use by treatment modality</u> Percentage of income used for those on chemotherapy vs not t = 2.03, p = .025, 95% CI .823-12.443 <u>Single item from the FACT-BMT regarding burden of treatment costs</u> Financial burden for patients on chemotherapy treatments vs not t= −3.51, p = .000, 95% CI: − 0.57 to − 0.16
Gupta *et al*[7], 2018, USA	Cross-sectional	162	Mean, 55.9 (SD 13.5)	49.4	MM	First line treatment: medicated for ≥8 weeks	**Out-of-pocket costs (US$)** Cost of clinical appointments = $318.90 (±637.20) Prescription medications = $388 (±1,063.40) Over the counter medications = $191.40 (±363.80)

Author, year, country	Study design	Sample size	Sample mean, median or range (years)	Percentage female (%)	Included haematological conditions	Timing of assessment	Main findings describing financial impact
						Second line treatment: ≥6 weeks	Transportation = $67.30 (±114.80) Total out-of-pocket = $709 (±1,307.30) **Financial burden related to out-pocket-costs (n, %)** None = 48 (29.6) Some = 46 (28.4) Moderate = 50 (30.9) High = 28 (17.3) Extremely high = 7 (4.3) ****MMAS, out-of-pocket costs and financial burden generalized linear modelling (adjusted mean ± SE, 95% CI)** <u>Cost of clinical appointments</u> Score ≤3 = 147.7 ± 45.7, 80.6-270.6, p>.05 Score 4 = 210.3 ± 49.9, 132.1-334.7 <u>Prescription medications</u> Score ≤3 = 387.9 ± 168.4, 165.7-908.1, p>.05 Score 4 = 220.2 ± 68.4, 119.8-404.8 <u>Over the counter medications</u> Score ≤3 = 130.6 ± 34.0, 78.3-217.6, p=.006 Score 4 = 46.8 ± 9.1, 32.0-68.4 <u>Transportation</u> Score ≤3 = 83.0 ± 18.6, 53.5-128.8, p=.03 Score 4 = 43.3 ± 7.6, 30.6-61.2 <u>Total out-of-pocket</u> Score ≤3 = 828.3 ± 248.7, 459.9-1491.8, p>.05 Score 4 = 395.7 ± 87.2, 256.8-609.5 **Financial burden related to out-pocket-costs by MMAS (adjusted mean ± SE, 95% CI)** Score ≤3 = 0.7 ± 0.1, 0.6-0.9, p>.05 Score 4 = 0.6 ± 0.1, 0.5-0.8
Hamilton *et al*[8], 2013, USA	Cross-sectional	181	NR	55.2	Eligibility: any haematological malignancy requiring HSCT Sample: NR (participants were required to be at least moderately	9-36 months post HSCT	**Perceptions of economic survivorship stressors:** Sources of financial stress occurred most frequently as 'moderately' or 'a great deal' in the past month, including (% of the sample): Reducing or cancelling vacations or leisure activities = 34% Reducing spending on household expenses such as food or clothing = 33% Deciding not to buy something they had planned to purchase = 28% Difficult, very difficult, or extremely difficult to live on their income = 23%

Author, year, country	Study design	Sample size	Sample mean, median or range (years)	Percentage female (%)	Included haematological conditions	Timing of assessment	Main findings describing financial impact
					distressed according to standardised measure delivered pre-study)		Anticipated reducing their standard of living to afford the bare necessities in life 'at least somewhat' = 22% **Hierarchical regression of financial stress and HRQoL (reported F change, significance)** Physical well-being -4.05 p<.001 Social well-being -1.03, p>.05 Emotional well-being -3.36, p<.001 Functional well-being -2.83, p<.01
Huntington *et al*[9], 2015, USA	Cross-sectional	100	Mean = 64.1 (SD 9.8) Median=64.7 (Range: 38.4-90.2)	53	Multiple myeloma	3 months after treatment commenced	55/100 patients reported reduced spending on basic goods 6/98 patients reported reduced spending on leisure 43/94 patients used savings to pay for treatment 21/98 patients borrowed money 17/100 reported delays in treatment of their multiple myeloma because of cost 36/100 patients applied for financial co-payment assistance 59/100 reported out-of-pocket treatment costs for MM were higher than expected Decreased spending on basic goods (food & clothing): p<0.0001 Decreased spending on leisure activities: p<0.0001 Use savings to pay for cancer care: p<0.0001 Borrow money for cancer care: p<0.0001 Delay the start of a myeloma treatment: p=0.0030 Fill only part of myeloma therapy prescription because of cost: p=0.0077 Stop myeloma therapy prescription because of cost: p=0.0011 Refuse recommended test because of cost: p=0.016 Skip clinic visit to save on costs: p=0.027 Apply for financial assistance: p=0.14
Jella *et al*[10], 2021 USA	Cross-sectional (collected annually between 1997-2018)	1619	NR	47	Lymphoma	NR	**Medical care delayed due to cost, past 12 months?** Yes = 161 (10%) No = 1458 (90%) **Needed but couldn't afford medical care, past 12 months?** Yes = 105 (7%) No = 1513 (93%) **Multivariate analysis of financial stressors (adjusted odds ratio, 95%CI, p value)** **Medical care delayed due to cost, past 12 months?**

Author, year, country	Study design	Sample size	Sample mean, median or range (years)	Percentage female (%)	Included haematological conditions	Timing of assessment	Main findings describing financial impact
							Age (years) 18-24 = 0.87 (0.15-5.09), p=.881 25-44 = 4.63 (2.28-9.41), p<.001 45-64 = 5.85 (3.20-10.70), p<.001 ≥65 = Reference Race/ethnicity White = Reference Black = 0.89 (0.44-1.84), p=.760 Hispanic = 1.63 (0.73-3.65), p=.237 Other = 1.08 (0.49-2.36), p=.845 Sex Male = Reference Female= 1.62 (1.06-2.48), p=.027 Born in the United States Yes = Reference No = 0.27 (0.09-0.83), p=.024 Marital Status Married = Reference Single = 1.88 (1.18-3.00), p=.009 Self-reported Health status Good to excellent = Reference Poor to fair = 2.47 (1.59-3.83), p<.001 **Needed but couldn't afford medical care, past 12 months?** Age (years) 18-24 = 0.23 (0.17-1.07), p=.172 25-44 = 3.50 (1.13-8.24),p=.004 45-64 = 4.87 (2.33-10.17), p=<.001 ≥65 = Reference Race/ethnicity White = Reference Black = 0.81 (0.35-1.88), p=.620 Hispanic = 0.42 (0.17-1.07), p=.070 Other = 1.71 (0.69-4.23), p=.247 Sex Male = Reference Female = 2.20 (1.28-3.76), p=0.004 Born in the United States Yes = Reference No = 0.14 (0.02-0.88), p=.037 Marital Status

Author, year, country	Study design	Sample size	Sample mean, median or range (years)	Percentage female (%)	Included haematological conditions	Timing of assessment	Main findings describing financial impact
							Married = Reference Single = 1.63 (0.93-2.85), p= .087 <u>Self-reported Health status</u> Good to excellent = Reference Poor to fair = 2.08 (1.23-3.49), p=.006
Khera *et al*[***11], 2018, USA	Cohort	325	NR	40	MM, NHL, AML, MDS, HL, ALL, other	1 and 2 years survival, post HSCT	**Univariate analysis (Hazard Ratio (95% CI))** <u>Hardship</u> No N=141 1-year survival HR 0.96 (0.92–0.98) 2-year survival HR 0.91 (0.85–0.95) Yes N=182 1-year survival HR 0.94 (0.89–0.97) 2-year survival HR 0.87 (0.81–0.91) <u>Extreme Hardship</u> No N =273 1-year survival 0.94 (0.91–0.96) 2-year survival 0.89 (0.84–0.92) Yes N= 50 1-year survival HR 1.00 (-) 2-year survival HR 0.92 (0.79–0.97)
Paul, *et al*[12], 2013, Australia	Cross-sectional	268	Mean = 59.5 (SD 13.4)	41	NHL, lymphoma, leukaemia, MM	Diagnosed in the previous 3 years	**Difficulty paying bills of other payments (% of the sample by participants residing in metropolitan or non-metropolitan areas)** Metropolitan= 24% Non-metropolitan = 16% X^2 =2.56, p=.11 **Used up savings (% of the sample by participants residing in metropolitan or non-metropolitan areas)** Metropolitan =25% Non-metropolitan=16% X^2=2.98, p=.084 **Had trouble with day-to-day expenses (% of the sample by participants residing in metropolitan or non-metropolitan areas)** Metropolitan = 15% Non-metropolitan = 8% X^2=3.55, p=.06 **Other findings (%of the total sample)** Cancer-related expenses influenced decision about treatment = 2% Cancer related out-of-pocket expense = 45% of the sample Percentage of respondents with out of pocket expenses relating to: - parking for medical appointments = 33%

Author, year, country	Study design	Sample size	Sample mean, median or range (years)	Percentage female (%)	Included haematological conditions	Timing of assessment	Main findings describing financial impact
							- travel costs to appointments = 30% - treatment drugs = 24% - assistance with gardening or housework = 8% - other medical supplies = 4.6% - accommodation while at appointments = 2.3% Difference between metropolitan and non-metropolitan out-of-pocket expenses = F(1,260)= 0.40, p=.528 Financial burden from living in a metropolitan city vs non-metropolitan = $\chi 2$ =6.06, p=.014

ALL=acute lymphoblastic lymphoma, AML=acute myeloid leukaemia, CI=confidence interval, CML=chronic lymphocytic leukaemia, FACT-BMT = Functional Assessment of Cancer Therapy - Bone Marrow Transplantation, HL=Hodgkin's lymphoma, (HR) QoL = (health related) quality of life, HSCT=haematopoietic stem cell transplant, MDS =myelodysplastic syndrome, MM=multiple myeloma, MMAS= Morisky Medication Adherence Scale, MPD = myeloproliferative disorder, NHIS= National Health Interview Survey, NHL=non-Hodgkin's lymphoma, NR=not reported, OR = odds ratio, SD = standard deviation, USA = United States of America,

*This study is a sub-set analysis of the original data collection by Abel et al.

**MMAS 0-4 scale where higher scores represent greater adherence

***This study used the original cohort from Abel et al.

Table 2. Included qualitative studies

Author, year, country	Age range of participants (years)	%female	Included haematological malignancies	Measurement time-point	Study design	Data collection technique	Data analysis technique
Goodwin *et al*, 2013, USA[1]	29-77	39	MM	Patients had received intensive therapy (between 0-42 years prior)	Cross-sectional	Open ended survey question	NR
Head *et al*, 2018, USA [2]	30-67	77	Any	1-5 years after diagnosis. Participants were experiencing financial hardship as defined by three questions from the COST-PROM	NR	Interviews	Thematic (constructivist grounded-theory approach)
McGrath, 2015, Australia*[3]	18-≥70	56	HL, NHL, AML, ALL, APML, CML, CLL, MM, MDS, MN-ET	NR	Descriptive	Interviews	Thematic
McGrath, 2016, Australia* [4]	18-≥70	56	HL, NHL, AML, ALL, APML, CML, CLL, MM, MDS, MN-ET	NR	Descriptive	Interviews	Thematic
McGrath, 2016, Australia*[5]	18-≥70	56	HL, NHL, AML, ALL, APML, CML, CLL, MM, MDS, MN-ET	NR	Descriptive	Interviews	Thematic
*McGrath, 2016, Australia[6]	18-≥70	56	HL, NHL, AML, ALL, APML, CML, CLL, MM, MDS, MN-ET	NR	Descriptive	Interviews	Thematic
Parsons *et al*, 2019, Canada [7]	51-83	31	MM	Relapse or refractory disease	Descriptive	Interviews, followed by focus groups	Thematic
Tan *et al*, 2017, Malaysia [8]	26-67	50	CML	Taking tyrosine kinase inhibitor	NR	Interviews	Thematic
Wang *et al*, 2016, China [9]	42-78	74	Leukaemia	Cancer survivors	NR	Focus groups	Thematic

*These studies analysed the same participants, ALL=acute lymphoblastic lymphoma, AML=acute myeloid leukaemia, APML = acute pro-myelocytic leukaemia, COST-PROM= Comprehensive score for financial toxicity - patient reported outcome measure, CML=chronic myelocytic leukaemia, CLL = chronic lympocytic leukaemia, HL=Hodgkin's lymphoma, MDS =myelodysplastic syndrome, MM=multiple myeloma, MN-ET = myeloproliferative neoplasm - essential thrombocythemia, NHL=non-Hodgkin's lymphoma, NR=not reported, USA=United States of America

3.3 RQ 1: How was financial burden assessed?

Ten of the quantitative studies utilised author derived or questionnaires assessing financial burden for which we could not identify validation data [22,23,25–28,30,32,33,38]. Three of these studies utilised the same 43-item instrument that included financial hardship, household income and employment status[22,23,30]. This instrument came from the literature[42], yet to the best of our knowledge remains un-validated in this population. Another study used a single question from the National Health Interview Survey (NHIS) to measure financial burden on a four-point scale [26]. Hamilton *et al.* utilised a 9-item researcher-derived questionnaire focusing on financial hardship in which a summative standardised (and linearly transformed) higher score indicated more financial stress. Another study also used a 32-item researcher-derived questionnaire which was summarised using two composite scores[25]. The first composite included two items about depleted savings or borrowing money, which was defined as financial burden. The second composite score was deemed an indicator of the short-term financial burden and was composed of two questions where respondents indicated they had reduced grocery expenses and utilised co-payment assistance programs. Gupta *et al* asked two questions to quantify an estimate of out-of-pocket costs (one question for expenses relating to doctors and another question related to expenses for pharmacy, transport etc.)[33]. This study additionally used a Likert scale to understand how overwhelmed patients were by out-of-pocket costs related to their disease. Another study developed a questionnaire comprising of five domains; employment, disability, insurance, retirement and out-of-pocket expenses relating to treatment[27]. Paul *et al* used a series of yes/no questions about whether cost influenced treatment decisions, if there was any difficulty paying day-to-day expenses, bills or other payments and if respondents had drawn financial savings[38]. Another study utilised two research derived questions about whether medical care had been delayed due to cost in the previous 12 months and if respondents needed, but couldn't afford medical care in the previous 12 months[32].

Two other quantitative studies utilised the validated Comprehensive score for financial toxicity - patient-reported outcome measure (COST-PROM)[24,29]. This brief instrument consists of 11 questions, concerned with; satisfaction with finances and income, expenses and the ability to meet them and; level of control concerning finances and cancer care. The instrument provides a summative score between 0-44, where a lower score indicates more financial burden.

3.4 RQ2: What out-of-pocket costs contribute to financial burden?

Two cross-sectional studies reported monetary estimates of out-of-pocket expenses, for multiple myeloma[33] and chronic myelocytic leukaemia[25]. Both of these studies were undertaken in the United States. Patients with multiple myeloma in the previous three months spent US$318.90 (±637.20) on clinical appointments, US$388 (±1,063.40) for prescription medications, US$191.40 (±363.80) on over-the-counter medications and US$67.30 (±114.80) on transport related to their disease. In total respondents were US$709 (±1,307.30) out-of-pocket for expenses related to their multiple myeloma in the prior three months[33]. More than one-third of the sample (34.6%) reported their financial burden as high to extremely high, due to out-of-pocket costs.

Buzaglo *et al* categorised out-of-pocket expenses as at least US$100 per month (49% of respondents), ≥US$250 per month (27% of respondents), ≥US$500 per month≥ (16% of respondents) and 6% of respondents were US$1,000 per month out-of-pocket[25].

A final study took a different approach by reporting out-of-pocket expenses as a percentage of income[27]. They estimated a mean percentage of income used on treatment-related expenses to be 36% in the first 12 months after diagnosis and 28% in the preceding 12 months. Additionally, patients receiving chemotherapy had a higher percentage of income used for out-of-pocket costs ($p=.025$) and experienced more financial burden ($p=.000$)[27].

3.5 RQ3: What are the reported impacts of financial burden?

The prevalence of financial burden in haematological malignancies ranged from 15% to 59% across all studies, but importantly the study designs were primarily cross-sectional, producing low levels of evidence for the impacts of financial burden, with most studies utilising different measures and outcomes.

After adjusting for sociodemographic factors and significant findings in the bivariate analyses,, there was agreement that quality of life was generally worse for patients experiencing financial burden in four studies[22,23,26,28]. There was a reduced overall quality of life demonstrated in three studies[22,23,26]. However, it should be noted that Albelda *et al.* [23] used a subset of the data reported in Abel *et al.* [22] to report on employed patients at the point of HSCT. All studies adjusted for age, gender, ethnicity, income and education level. One study additionally adjusted for employment status[28], another for insurance status[26], while the Abel and Abelda studies additionally adjusted for marital status, time since diagnosis, out-of-pocket expenses and the distance travelled to access treatment[22,23]. Worsening perceived stress in those with worsening financial burden was reported in patients 150 days post-HSCT[22], and in the subset analysis of Albelda *et al.* [23], perceived stress was lower in those with access to paid leave. One paper found that financial burden was associated with reduced functioning in all quality of life domains; physical well-being, social well-being, emotional well-being and functional well-being[28].

There were many ways in which patients coped with financial burdens. Reducing spending on basic goods[29], groceries[25,28] and leisure activities[28,29] was described across three studies,[25,28,29] with up to 55% of patients implementing one or more of these coping mechanisms. Other ways to financially cope were reported to be depleting savings (range 16%-46% of patients)[25,29,38], borrowing money (approximately 20% of patients in both studies)[25,29] and filing for bankruptcy (6% of patients)[25]. The coping mechanisms of depleting savings and borrowing money reached

significance (p<.0001)[29]. One study which analysed a mixed malignant haematology cohort found that living in a metropolitan area had a higher level of financial burden compared with patients living in non-metropolitan areas (p=.014)[38].

Delaying medical appointments (23% of patients), missing medications (19% of patients) or postponing filling prescriptions (14%) were methods employed by patients with CML to reduce their expenditure[25]. Similarly, Huntington *et al.* reported that 17% of patients delayed their treatment of multiple myeloma due to cost[29]. Cost factored into decisions about filling only part of a prescription for multiple myeloma treatment (p=.0077), stopping multiple myeloma treatment (p=.0011), refusing a test (p=.016) and skipping a clinic visit (p=.027)[29]. No confidence intervals were reported. Jella *et al* reported lymphoma patients who delayed medical care due to cost were more than twice as likely to self-report their health status as poor to fair compared with good to excellent (OR: 2.47, 1.59-3.83, p<.001), as were patients who needed medical care but couldn't afford it in the past 12 months (OR: 2.08, 1.23-3.49, p=.006)[32].

Using a medication adherence score Gupta *et al* found a lower adherence to medication with higher financial burden for over-the-counter medications (p=.006) and transportation (p=.03). This association did not reach a significance of p<.05 for cost of clinical appointments, prescription medications or total out-of-pocket expenses (no p-values provided)[33].

A single prospective cohort study of 325 patients investigated the impact of financial burden on survival 1-2 years after HSCT[30]. There was no significant difference in survival between those suffering financial burden and those that did not[30].

3.6 RQ4: What is the patient experience of financial burden?

Five main themes arose from nine qualitative studies[27,31,34–37,39–41] reflecting the patient experience of the impact of financial burden (see supplementary data for additional supporting quotations):

the familial or household impact; relying on others for financial support; barriers to care due to cost; barriers to gaining financial assistance and; sources of out-of-pocket expenses.

The **familial or household impacts** of financial burden described individual perceptions or feelings, financial coping mechanisms, making everyday choices and the long term ramifications of financial decisions. Emotionally, the burden of financial worries manifested in patients in different ways "*...the financial impact... is really stressful*"[39]while others felt a "*…feeling of inadequacy and not being to provide for the family and the heaviness that I felt all the time*".[31]

Patients discussed the reality of how the burden of financial impact changed how they lived their everyday lives; "*…we started living like we did back when our kids were little, and we did not have any money"*[61]. Being more budget-conscious was a common financial coping mechanism such as "*...watching my* spending *a lot more"*[61] *and being* "*…mindful of where every penny was going"*[61]. One patient explained, *"[the cost of] medicine was high - sometimes you have to choose between medicine and food*"[27]. There was evidence that financial burden can have future impacts on a person's financial health; "*credit card payments - still paying them after eight years, credit suffered, sold [our] home, borrowed money from relatives*"[27]. Another patient said, "*we lost everything, including our home*"[27].

At times, **patients relied on others** for financial assistance, accepting financial help through friends, family, and religious community. One patient explained the necessity of this income stream to stave off financial ruin "*I have had to rely on gifts from family and friends to keep from filing bankruptcy"* [27]. Another described how utilising the Internet for crowdfunding to raise funds helped them financially; *"…the Go Fund Me is basically what got us through"*[61].

However, for some, their financial burden was significant enough to impact the decisions surrounding their medical care, where **cost represented a barrier to care**; "*I quit doing it (photopheresis) because it was expensive and we are trying to find something more cost-effective*"[31]. Patients also described **barriers to gaining financial assistance** through services designed to financially aid patients. One patient explained how she had to go to great lengths to obtain approval for

financial reimbursement; "*I had to make myself look like a madwoman, messing up my hair, thumping my prescription for morphine injections and my medical certificate showing I had advanced-stage cancer down on the official's desk; only then would he sign the approval*"[40]. Another described how one government body requires "…*you use up all your money and have no money in the bank*.."[34] before granting financial assistance "*which is ridiculous as you don't have money to fall back on. Because that is the money you have saved up for your registration and your rates (bills)'*"[34]. One patient concluded that "*These officials were just inconsiderate and unsympathetic*"[40].

An additional descriptive qualitative study[35] included quotations (see supplementary data) from participants detailing their **sources of out-of-pocket expenditure**; costs associated with travel and accommodation (e.g. flights, parking, food, tolls and fines), costs associated with the care of family and friends (e.g. childminding expenses, phone bills, paying rent when not at home) and costs associated with diagnosis and treatment (e.g. treatments, pharmacy bills and gap payments).

Discussion

This systematic review aimed to provide evidence of the impact of financial toxicity on patients with haematological malignancies.

We identified that most of the quantitative measures utilised to assess financial burden in the literature for patients with haematological malignancies are researcher-designed questionnaires[22,23,25–28,30,32,33,38] (5). In contrast, only two studies utilised a validated PROM (COST-PROM)[24,29], and one final study used a single question from the NHIS[26]. This methodological heterogeneity presents substantial problems in comparing findings across studies and highlights the lack of conceptual clarity of the financial burden experienced by patients[43]. Altice and colleagues proposed a typology representing three broad domains that constitute financial hardship, a) material conditions that arise from increased out-of-pocket expenses and reduced income; b) the psychological response such as distress and concern at managing unexpected

health-care-related financial expenditure or reduction in income and c) coping behaviours which the patients adopt to manage their care while experiencing increased expenditure and reduced income[3]. Carrera et al. [44] proposed a conceptual framework of financial toxicity, as did Witte et al. [45] the following year. While these frameworks are helpful, a shared comprehensive conceptual framework is yet to be elucidated, which may be contributing to the heterogeneous methodology employed by researchers. Furthermore, work needs to be undertaken to explore how the emphasis on different components of the frameworks may vary depending on cancer diagnosis (due to differing disease patient demographics, disease trajectories, treatments) and by country (for example, the difference in out-of-pocket costs borne by the patient in user-pays healthcare models compared with countries with publicly funded healthcare). In the interests of collaborative scholarship and to allow for comparisons within and between cancer types, researchers should be encouraged to utilise existing (validated) financial hardship instruments rather than generating their own question sets.

Our review identified three main categories of impact and patient experience from financial burden: 1) reduced quality of life and well-being (for example, emotional well-being), 2) introduction of financial coping mechanisms and; 3) compromised care due to cost.

The reviewed literature suggests that patients with haematological malignancies experiencing financial burden have a reduced quality of life[22,23,26,28] and other well-being impacts[23,28]. However, all studies reporting these outcomes were in patients that had undergone HSCT. Therefore the quality of life outcomes for patients not prescribed this treatment pathway remain unknown. Each study utilised a different quality of life measure (two utilised two questions from the EORT-QLQC30[22,23]with modified wording, one used the NHIS[26] and another utilised FACT-BMT[28]) and included varying haematological malignancies. While varying measurement instruments were employed across these four studies, the finding of financial burden impacting the quality of life and well-being is congruent with other cancer types[5,8,46]. Future work should

focus on longitudinal studies to explore how the quality of life outcomes vary throughout financial burden and provide evidence of the most appropriate financial burden measurement time points[47].

The financial coping measures employed by patients to reduce usual expenditure in the reviewed studies highlight how patients trade aspects of their comfort and lifestyle to afford expenses related to their healthcare and depleted income[24,25,28,29,38]. The qualitative studies demonstrated how this impacted the wider family and household[31]. Quantitative studies highlighted the prevalence of patients implementing financial coping actions (between 20% and 55%). These findings were complemented by the patient narrative of how these experiences affect the patients' emotional state while relying on other sources of financial support. Patients described bureaucratic and unsympathetic processes to access insurance payments or government financial support, which may present a barrier to patients accessing their financial entitlements, but this needs to be further investigated. While it may seem insurmountable to change big business and government processes, there may be other avenues to assist patients in need. For example, in the United Kingdom, a welfare rights advice program designed to address the financial burden from cancer successfully demonstrated positive effects on social and psychological patient outcomes[48]. Similarly, participation in a debt management program (albeit not specific for those with cancer) in the United States showed similar benefit[49].

The qualitative and quantitative literature were aligned concerning the cost of care impacting patients' healthcare decisions about their medical care. These decisions included delaying or missing clinical appointments or prescription medication, particularly in patients diagnosed with CML. Patients with CML have clinically benefited in recent years from the new era of tyrosine kinase inhibitors (TKIs)-- with medication adherence, these patients can have a life expectancy similar to the general population[50]. However, even with generic pricing, which bought about a

reduction in the cost of TKIs, the medication may remain unaffordable[51] for many patients, potentially affecting progression-free and overall survival through poor medication adherence. Nevertheless, understanding these coping mechanisms employed by patients will be imperative to designing, testing, and implementing meaningful interventions to alleviate financial burden and minimise patient actions that involve sacrificing their health care due to their financial position.

Our review contributes the first systematic appraisal of the literature concerning the impact of financial burden in patients with haematological malignancies. Much of the identified evidence has been drawn from the United States, which adopts a user-pays model of health care in contrast with the hybrid and socialised models employed elsewhere in the world. Therefore, the contributing factors to financial burden and the measurable impacts on patients may vary by healthcare model. However, this is poorly understood. The strengths of this review include searching multiple databases with a thorough search strategy to capture the relevant literature in the past twenty years. Nevertheless, it remains possible that relevant research was missed due to the different indexing used by different databases and the inconsistent terminology used to describe financial burden. To minimise this limitation, a manual search of the reference lists was undertaken of identified reviews during screening, studies known to the authors, and the included literature in the present study.

We limited the review to exclude studies without a financial burden focus to ensure the review was manageable, excluding papers with incidental financial burden findings. Furthermore, due to research questions guiding this review, we excluded papers that only provided a prevalence of financial burden, and as such, the estimate provided in this manuscript should be viewed with that context. Additionally we didn't include changes in employment status and therefore house income changes which conceivably may impact on the patient perception of financial security.

Conclusion

The impacts of financial burden are yet to be fully appreciated in haematological malignancies, exacerbated by the heterogeneous methods employed by researchers. Of concern is financial burden and its association with poor medication adherence to TKIs. Additionally there was evidence of financial burden for patients undergoing HSCT, which may due to the protracted illness, treatment and recovery trajectory. Future work should focus on identifying the long-term ramifications of financial burden for patients and trialling methods to reduce its prevalence and patient impacts.

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Chapter 3: Methods

3.1 Chapter introduction

The PhD aims to describe the personal and financial burden in Australian adults (≥18 years) diagnosed with AML. The specific objectives are to:

1. To explore the lived experience of adults with AML.
2. To explore the financial burden of AML from the patient perspective.
3. To examine the societal financial burden attributable to adults with AML.

This Chapter summarises the methodological approach utilised for this body of research and how each study is interrelated and builds on the next. First, a description of the various mixed-methods research approaches is provided for reader context, followed by a more detailed examination and justification for the adopted mixed-methods research design. Last, an overview of each study included in the PhD research will be presented. Of note is that detailed study-specific methods, including data collection, participant recruitment and data analysis, are found within each of the research manuscripts presented in C**hapters 2, 4, 5,6,7 and 8** of this thesis.

3.2 Overview of mixed-methods research

The research employed in this PhD is a mixed-methods design, which allows for the qualitative and quantitative data collection within the same study design (166). Using a mixed-methods approach maximises the strengths and minimises the individual study designs' weaknesses when used in isolation (167). To be considered a mixed-methods research design, the qualitative and quantitative components must be treated as complementary, integrating both study types at either the design, analysis or interpretation stage (168,169). Mixed-methods research designs lend themselves well to research questions concerned with patient outcomes, such as those posed in this research, because this research paradigm inherently allows for multiple perspectives to be

captured, in addition to exploring and measuring context, meaning, magnitude or frequencies (168,170).

Creswell et al. describe three main mixed-methods research design sub-types summarised in Table 1.

Table 1. Mixed-methods research sub-type design, adapted from Creswell et al. (164)

Sub-type	**Study design**	**Weighting**	**Point of study integration**
Sequential explanatory	Quantitative and then qualitative	Usually quantitative but can be qualitative or equal	Interpretation
Sequential exploratory	Qualitative and then quantitative	Usually qualitative but can be quantitative or equal	Interpretation
Convergent design	Concurrent collection of qualitative and quantitative data	Equal	Interpretation or analysis

The present study employed a *sequential exploratory mixed-methods design,* where qualitative exploration was undertaken first to inform and guide the quantitative measurements, integrating the findings during the interpretation stage of the study. The qualitative and quantitative studies had equal weighting in addressing the overall research aim and objectives.

Regnault et al. support the use of mixed-methods research by arguing that the complementary perspectives of qualitative and quantitative approaches contextualise the patient experience within a measurement framework that is clinically meaningful (171). This contextualisation is highly relevant to the objectives of this PhD and the patient group being studied. For example, in **Chapter 6**, the qualitative study provides a patient perspective of their experiences of financial burden. **Chapter 6** then informed and was complemented by quantitative work undertaken in **Chapter 7**, which measures the magnitude of the issue identified and additional context and

characterisation that is more generalisable beyond just the experiences of the few individuals sampled in the qualitative study.

Furthermore, mixed-methods research is valuable when neither a qualitative or quantitative study alone can answer the research question (172–174). Therefore, the sequential exploratory mixed-methods approach allows for a more holistic investigation into the issue of financial burden attributable to AML. The integration and merging of the individual studies may provide more clarity in identifying approaches, interventions or strategies to ultimately improve patient outcomes.

3.3 Thesis study design

As previously stated, this thesis employed a sequential exploratory mixed methods design, which was operationalised in three broad phases of work, as shown in Figure 5.

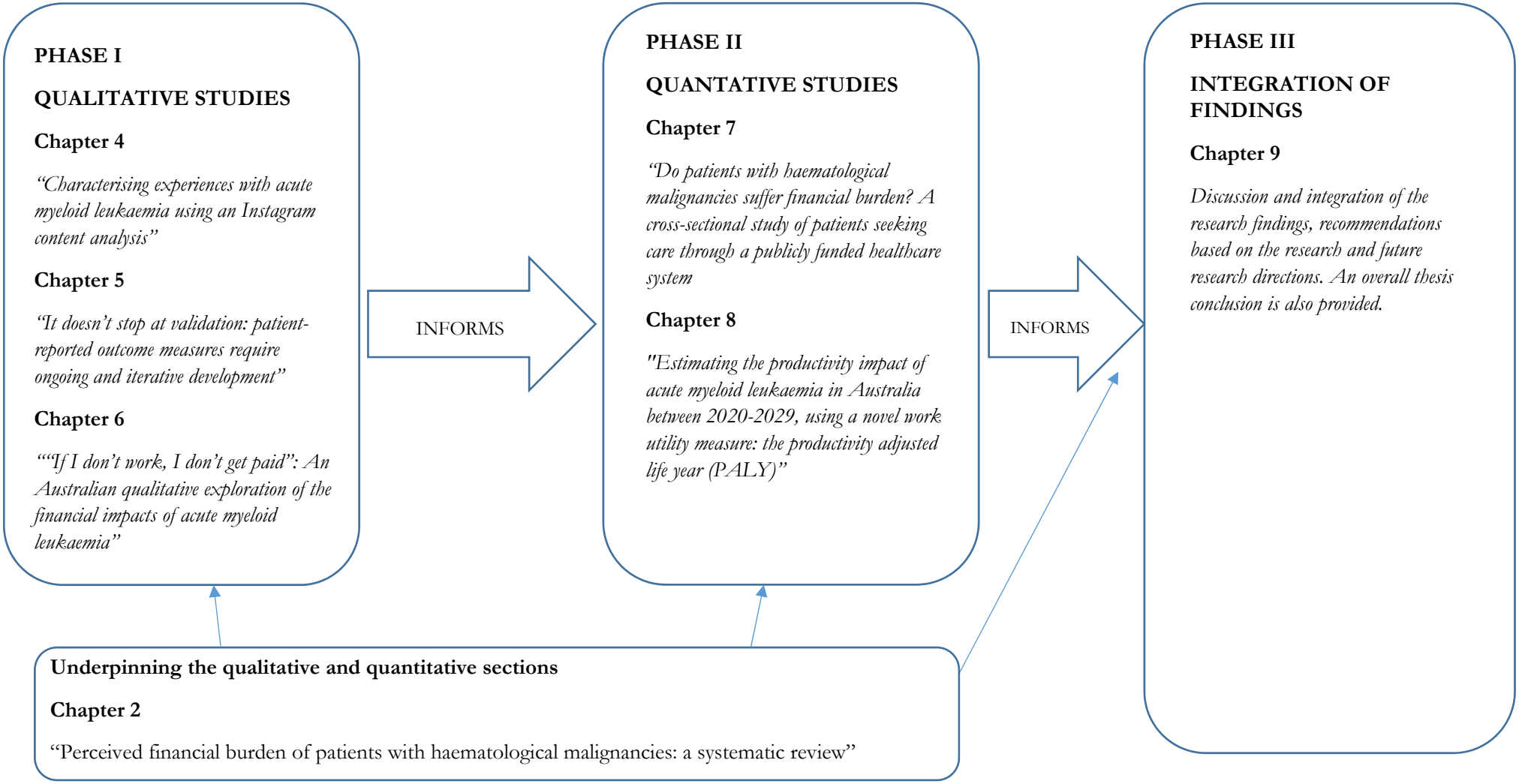

Figure 4. Individual study placement in the adopted sequential exploratory mixed-methods research design.

Beginning with a qualitative study allowed for a broad exploration of the lived experience of AML and ensured the program of research prioritised issues or concerns most salient to patients. This aspect was considered essential to mirror best practice of patient-centred care and mitigate potential future participant recruitment challenges from an already small recruitment pool by ensuring the research focused on subjects of importance to patients. Additionally, in this first phase, given the small sample pool of people with AML at any given time, a novel method of data collection was trialled using Instagram. These qualitative studies informed the quantitative stage of the research, which further investigated the qualitative finding of financial burden based on only a few individuals in the initial first phase. The first and second phases were underpinned by a systematic review designed to identify, appraise, and synthesise the evidence relating to the drivers and consequences of financial toxicity in people with haematological malignancies to ensure the identified concepts were captured in the research design. Finally, the third phase brings together the findings of the first two phases and integrates the contemporary literature of the underpinning systematic review into a discussion of policy recommendations and future research priorities.

The chosen mixed-method subtype provides a flexible research program that allows each research study to build on the next to create a holistic body of work, prioritising the patient experience.

Table 2 demonstrates how each of the individual studies maps to the thesis objectives and the Chapters arising from each of the studies. The systematic review is an underpinning piece of work that informed the research program at various points described in the study descriptions in Section 3.3.1.

Table 2. Each objective mapped to the relevant section in this chapter and the thesis

Objective mapping	Discussed below in section:	Chapter, Chapter title and manuscript title
Objective 1 Exploring the lived experience of AML	**3.3.2** A qualitative social media (Instagram) study	**Chapter 4: Qualitative results - Exploring the utility of Instagram for insights into the lived experience of people with acute myeloid leukaemia** Manuscript: Characterising experiences with acute myeloid leukaemia using an Instagram content analysis
	3.3.3 A descriptive qualitative study with people who have an AML diagnosis	**Chapter 5: Qualitative results - Exploring the health and well-being of people with acute myeloid leukaemia** Manuscript: It doesn't stop at validation: patient-reported outcome measures require ongoing and iterative development
Objective 2 Exploring the financial burden of AML from the patient perspective	**3.3.1** A systematic review of financial burden in patients with haematological malignancies	**Chapter 2: Systematic review of the patient-perceived financial burden for those with malignant haematological conditions** Manuscript: Describing the impact of patient-perceived financial burden in haematological malignancies: a systematic review
	3.3.3 A descriptive qualitative study with people who have an AML diagnosis	**Chapter 6: Qualitative results - Exploring the financial experiences of people with acute myeloid leukaemia** Manuscript: "If I don't work, I don't get paid": An Australian qualitative exploration of the financial impacts of acute myeloid leukaemia
	3.3.4 Quantitative measurement of financial burden in people with haematological malignancies	**Chapter 7: Quantitative results - Cross-sectional study describing the financial burden of people with malignant haematological conditions** Manuscript: Do patients with haematological malignancies suffer financial burden? A cross-sectional study of patients seeking care through a publicly funded healthcare system
Objective 3 Examining the societal financial burden attributable to adults with AML	**3.3.5** Quantifying productivity loss attributable to AML	**Chapter 8: Quantitative results - Estimating the productivity loss attributable to acute myeloid leukaemia** Manuscript: Estimating the productivity impact of acute myeloid leukaemia in Australia between 2020-2029, using a novel work utility measure: the productivity adjusted life year (PALY)

3.3.1 A systematic review of financial burden in patients with haematological malignancies

Previous systematic reviews have been published about the financial burden of cancer (139–141,151,152,156,157,159,175–178). However, the varying inclusion and exclusion criteria, such as including a mixed cancer cohort, varying restrictions on the country of the study origin, restrictions on study design (e.g. the exclusion of qualitative studies), and varying definitions employed for financial burden, has made it difficult to generalise the findings to an Australian haematological population. The inclusion of qualitative research can complement the quantitative findings that have been the focus of previous systematic reviews (179). Mixed-method systematic reviews that integrate and analyse quantitative and qualitative studies can be beneficial to ensure a complete appraisal of the literature that includes the patient experiences of the phenomenon being investigated (180,181).

The systematic review in this thesis aimed to identify, appraise and synthesise haematological patient-reported data of their financial burden. Specifically how the financial burden is assessed, the contributing out-of-pocket costs, the impacts of the financial burden and the patient experience of financial burden.

Eligible studies included observational studies of quantitative or qualitative design that contained self-reported data from the patient. A search strategy developed in consultation with an academic librarian identified studies through Medline, PsycINFO, Embase and CINAHL. Two reviewers undertook screening and data extraction. Study quality assessment used validated quality appraisal tools sourced from the Joanna Briggs Institute (182). Twenty studies were included in the final review, which found that of the quantitative studies, most (83%) employed un-validated researcher-generated measures to assess financial burden. Between 15 and 59% of patients experienced financial burden. Out-of-pocket expenditure was frequent for clinical appointments, prescription and non-prescription medication, and travel. Financial burden was associated with worsening quality of life and living in metropolitan areas, but there was no evidence for impact

on survival. Patient-centred experiences from the qualitative inquiry complemented the quantitative findings. Five themes were determined; familial or household impact, relying on others, barriers to care due to cost, barriers to accessing financial assistance and sources of out-of-pocket expenses.

The systematic review findings were used to frame the analysis of the qualitative work (Section 3.3.2 and 3.3.3, particularly the manuscript in **Chapter 6**), inform the survey instrument used for the quantitative investigation of financial burden (Section 3.3.4 and **Chapter 7**), and inform the discussion in **Chapter 9.** The manuscript for the systematic review is presented in **Chapter 2**.

3.3.2 A qualitative social media (Instagram) study

Social media platforms offer a variety of avenues to pursue a plethora of research questions relating to cancer prevention and screening (183,184), cancer treatment (184,185), cancer communication (including clinical trial recruitment) (186–188), peer support (189–191) and cancer survivorship (192,193). While social media research is still in its infancy, it represents a novel avenue to access research data through a patient-centred lens, particularly in traditionally hard to reach (or engage) populations, across international borders and in low incidence cancers (194). Researchers are beginning to recognise the emerging use and benefits of social media in healthcare (195), and yet for haematological malignancies, little research exists using social media as an avenue to collect or create research data.

The exploratory study in this thesis was undertaken in the context of a relatively rare haematological malignancy, with high disease burden during treatment, high relapse and high mortality, and, therefore, only a small available cohort is available, from which to recruit through traditional means (196). More than half of all users with Instagram are aged less than 35 years of age, and there are more than 1 billion monthly users (197,198). As the incidence of AML

increases with age (196), fewer younger patients were interviewed in **Chapters 5 and 6**. Therefore, Instagram represented a potential avenue to view the patient experience. This novel study aimed to characterise AML-related content on Instagram, what is being posted, and by whom to understand the patient experience and whether there may be opportunities to utilise the platform for other means, such as information dissemination, promotion, or promotion as a research platform. Due to publicly available data and technology restrictions, a novel data collection method was presented in the manuscript (**Chapter 4**). The method utilised 'hashtags' that indicated the post was about AML (e.g. #acutemyeloidleukemia). Hashtags are a way Instagram users denote a topic of their post and group like content. As limited demographic data are available through Instagram, all posts involving AML-related content were included unless they concerned children with cancer (which was ascertained by accompanying other hashtags such as #childhoodcancer). Therefore, the cohort included a mixed demographic of various nationalities, age groups, organisations, and genders. The analysis was framed using an adapted mixed-method social network from Williams et al., which outlines sourcing data (Instagram), constructing data (organising data for analysis) and analysing the data (using an appropriate analysis technique) (199). An inductive approach was employed to identify frequently occurring content categories and themes (200), reported using frequencies (percentages).

The research provided a 'proof of concept' for the method presented and demonstrated some initial findings that could be leveraged and explored further in future studies. The study was approved by the Monash University Human Research Ethics Committee (Project ID 18540)) and the manuscript is presented in **Chapter 4**.

3.3.3 A descriptive qualitative study of people with a diagnosis of AML

Quantitative research uses predetermined variables that quantify a phenomenon being investigated and, through statistical inferences, measure the relationships among variables and

outcomes using numbers (201). In contrast, qualitative research seeks to explore the individual, social and cultural experience of a phenomenon through the lens of an individual, which provides context and meaning. The participant narrative is examined for prominent themes arising through interviews or focus groups (201–203). Data collection in qualitative research can offer the advantage of interactivity, allowing the researcher to clarify concepts and gain an in-depth understanding of the population of interest and its experiences (201,202). Utilising this paradigm naturally adopts a patient-centred approach in line with the reorientation of modern-day healthcare (204). The analysis of qualitative research takes place using 'coding', in which similar patient narratives are grouped to identify themes arising from the collated data. This grouping allows conceptual patterns to be presented in a coherent and meaningful manner that can illuminate our understanding of the patient experience and ultimately improve patient care (201–203). For example, through 35 semi-structured interviews, Nissim et al. found that AML patients transitioning to ambulatory care have common concerns around personal expectations and care responsibilities as well as unmet information needs (205). These findings can potentially influence how clinicians and health services approach the transition from inpatient to ambulatory care. Similarly, the qualitative research undertaken in this thesis can improve patient outcomes, the patient experience and the approach to care through the appreciation of patient experience.

The specific aims of the study presented in this thesis were to identify the symptoms and concerns of people with AML that impact their health and well-being and explore their experiences and perceptions of the financial impact of their disease. While extensive work has been undertaken to characterise and measure quality of life in diverse cancer populations, compared with more common cancers, little attention has been paid to those with AML and even fewer focus on AML patients in remission (95) using a qualitative study design. Additionally, the personal financial impact of the disease is only beginning to be appreciated,

particularly in countries with socially funded healthcare (151). As this study was exploratory, the interview guide was developed using existing literature relating to AML patient experience (93,206,207), clinical input and a consumer (a previous AML patient). The study participants were recruited from a single tertiary hospital and were 18 years and older at the time of their diagnosis of AML (including acute pro-myelocytic leukaemia, a subtype of AML), in remission at the time of the interview and able to provide consent. Analysis was undertaken using a thematic approach through deductive and inductive coding techniques; the study identified a breadth of issues and concerns impacting the health and well-being of people in remission from AML, including the financial impact.

Two manuscripts were derived from this study as they were guided by separate analysis questions and are presented in **Chapter 5** (focusing on the issues of health and well-being) and **Chapter 6** (focused on the patient financial impact of AML). Ethics approval was granted from the Alfred Hospital Human Research Ethics Committee (Project #638/17).

3.3.4 Quantitative measurement of financial burden in people with haematological malignancies

While there is an increasing appreciation of the financial burden of cancer on patients within publicly funded health care systems (151), only a small amount of Australian literature currently exists. These studies have focused on breast cancer (57), prostate cancer (209), colorectal cancer (210), mixed cohorts (135,211) or those living in remote areas (128,212,213). Additionally, in the international literature, haematological malignancies remain underrepresented in research seeking to measure financial burden (139–141,151) and may not be generalisable to the Australian population due to inherent differences in the health systems where the studies were undertaken (151).

Observational studies help examine the relationship between variables and outcomes of interest before committing effort and resources to a more intensive and costly interventional study design (214). Given the dearth of literature concerning financial burden for people with haematological malignancies, it was considered appropriate to utilise a cross-sectional study design as an initial investigation, as this is relatively quick and efficient to undertake (which is additionally helpful for the constraints of a PhD program) (215).

The COmprehensive Score for financial Toxicity (COST), validated for Australian cancer patients (216), provides a quantitative measure of the patient perception of financial distress. The method involved using the COST questionnaire, and therefore this study represented the first empirical investigation into the financial burden of people diagnosed with haematological malignancies in Australia using a validated instrument. The study also sought to characterise common sources of out-of-pocket expenses and the correlates associated with financial burden to understand how Australian haematology patients most at risk might be identified for an early intervention to reduce the incidence of this phenomenon. Ethics approval was obtained from the Alfred Health Human Research Ethics Committee (Project # 58355) with site-specific approval at both the Alfred and Austin hospitals.

The survey sent out to participants contained a combination of validated scales and researcher-generated questions developed from the literature (Section 3.3.1) and the interviews (Section 3.3.3) conducted in the first phase of this thesis. The survey instrument was piloted with a haematology consumer volunteer and tested with peers for comprehension and acceptability.

Demographic data were described using descriptive statistics. Non-parametric testing was employed for univariate analysis, and linear regression was used to explore factors associated

with financial toxicity. Variables with $p<.05$ on univariate analyses were included in the multivariable model that included the length of time since diagnosis. Spearman's correlation was used to assess the association between out-of-pocket expenses and COST score. This exploratory analysis was undertaken in STATA (StataCorp, College Station, USA). The findings confirmed that Australians with haematological malignancies experience financial burden, with some sub-groups being more at risk. The manuscript is presented in **Chapter 7**.

COVID-19 impact

As this study was due to commence, the coronavirus disease 2019 (COVID-19) pandemic began to affect Australia, and Victoria was subject to strict lockdown protocols. In light of this, the study was initially delayed due to advice from local ethics staff as hospital resources were redirected towards the pandemic effort. Originally, the study planned to recruit only AML patients from each of the tertiary hospital services that offer centralised and specialised AML treatment and surveillance. However, owing to the pandemic and rapidly evolving health and medical priorities, recruitment occurred at just two metropolitan tertiary health services and participant recruitment and data collection were undertaken primarily via post. Due to these challenges and being mindful of having a meaningful and publishable sample, the study included adults (aged ≥18 years) with acute leukaemia, chronic leukaemia and multiple myeloma. Additionally, questions were incorporated to ascertain the impact of COVID-19 on this population and the influence the pandemic may have had on their responses relating to finances.

3.3.5 Quantifying productivity loss attributable to AML

The economic cost of disease can be viewed from the patient's perspective or broader society. An indirect cost to society results from lost productivity due to an incapability of workforce

participation (because of side effects or disablement) or premature death. Productivity loss is another metric by which quantification of disease burden can be calculated and allows for cross-country comparisons (217). Disease burden is a valuable measure, particularly for governments, when assessing the potential benefit of new drugs or devices and productivity loss provides an additional helpful concept to include in these drug and device benefit assessments (217). Methodologically, disease burden estimates are usually achieved by utilising known data points (for example, incidence and death rates) to mathematically model and predict future burden (218). Previous estimates of the societal cost of cancer among Australians using modelling techniques are available (219,220), but these collate data from all malignancies, and the contribution of AML remains unclear.

Participants interviewed in the qualitative study (Section 3.3.3 and **Chapter 6**) cited that a contributor to financial worry was being unable to partake in paid work due to their treatment and disease morbidity. At a societal level, this translates to lost productivity among working-age workers and represents a disease burden that could be incorporated into future drug benefit assessments. Therefore, the present study aimed to quantify the work productivity loss attributable to AML over a ten-year period using population-level data. A novel measure was utilised, the productivity-adjusted life year (PALY), which is similar in concept to the quality-adjusted life year (QALY) but adjusts for productivity loss due to disease rather than the impaired quality of life. The PALY has been previously utilised for diabetes (221–223), hypertension (224), migraine (225), smoking (226,227), hypercholesterolaemia (228), coronary heart disease (229), occupational hearing loss (230) and epilepsy (231), but this is the first example of its use in a malignant condition. Dynamic life table models for those with and without AML and working age (15-65 years) were constructed using published data inputs that enabled an estimate of the impact in terms of years of life, PALYs and gross domestic product (GDP) lost.

The study demonstrated that even in a low incidence cancer, the loss of productivity is appreciable and highlighted the value of investing in improved treatments and technologies to improve morbidity and mortality.

3.4 Integrating the individual studies

A hallmark of mixed-method research is integrating or mixing both the qualitative and quantitative strands of the research (232). Creswell and Clark describe four integration methods: connecting, building, merging, and embedding (170). The sequential exploratory mixed methods design integrates the studies using the phase I qualitative component findings to inform the phase II quantitative component. In this way, Phase II 'builds' on Phase I. Both Phases I and Phase II components benefited from the additional integration of the findings from the systematic review to ensure the research met a research gap in the evidence. The discussion and final interpretation of the findings (**Chapter 9)** integrate the findings of the qualitative and quantitative components.

3.5 Researcher positionality

Positionality in research refers to the researcher's stance about their social and political influences surrounding the research (233). Positionality is influenced by individual experiences, the interpretation of the surroundings, and the meaning of events (234). These influences can manipulate how a researcher approaches research questions, research participants, and the questions asked of them.

For context, I had personal experiences with cancer, including a diagnosis as a young adult, although not related to AML. I have previously worked in professional roles with Cancer Council Victoria, a philanthropic organisation concerned with cancer research, patient support,

cancer prevention and advocacy. During this time I was primarily involved with clinical trials in addition to advocacy and policy, both related to improving the outcomes and experiences of cancer patients. These lived experiences have fostered an interest in patient-centred outcomes of those living with and beyond cancer.

The disclosure of positionality has been incorporated into the validated checklist for the explicit and comprehensive reporting of qualitative studies: Consolidated Criteria for Reporting Qualitative Research (COREQ-32)(235). The COREQ-32 aims to improve the rigour and credibility of qualitative studies (235). Furthermore, the Joanna Briggs Institute (JBI), an international research organisation concerned with promoting and supporting evidence-based healthcare (182), also advocates for researchers to critically examine the influence of their positionality on qualitative data collection and analysis (236). Therefore, conveying research positionality and potential influence on the research stance is essential to research validity and transparency (234).

3.6 Summary

This Chapter has summarised the mixed-methods research design employed for this thesis, including a discussion of the researcher's positionality and the impact of the COVID-19 pandemic on the planned research. Additional detail concerning the specific research methods employed for each of the individual studies and their findings are presented in **Chapters 2, 4, 5, 6, 7 and 8**.

Chapter 4: Social media study - Exploring the utility of Instagram for insights into the lived experience of people with acute myeloid leukaemia

In this Chapter I present an innovative study utilising Instagram with a content analysis performed to examine the social media activity concerned with AML. Social media can provide access to hard-to-reach populations, cohorts with few members and across international boundaries. Instagram is particularly utilised by those younger in age and has more than one billion monthly users (198). As AML is predominately a disease of older people, much of the literature concerning quality of life and lived experience, reports older AML cohorts (104,105,205) Therefore, Instagram presented a potential avenue to access existing data regarding the lived experience of younger people touched by AML.

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RESEARCH ARTICLE

Characterising experiences with acute myeloid leukaemia using an Instagram content analysis

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Data Availability Statement: The data underlying the results are available from Instagram (www.instagram.com). The coding framework to generated the results are published in the paper, but the data cannot be shared publicly as they contain personal information. Additional information about our ethics or data requests/availability can be addressed by the corresponding author or directly to the ethics committee at: Monash University Human Research Ethics Committee Executive Officer Human Ethics, Dr Souheir Houssami Email: muhrec@monash.edu Phone: +61 3 990 52052.

Abstract

Instagram has more than one billion monthly users, which presents a unique research opportunity particularly in rare diseases or hard to reach populations. This study focuses on acute myeloid leukaemia, a rare haematological malignancy and aims to characterise who posts acute myeloid leukaemia-related content and the type of content created. The findings can provide information and a method for future studies, particularly those focused on online or social media based interventions. Acute myeloid leukaemia-related Instagram posts were identified by searching specific and relevant hashtags (#). A content analysis systematically classified themes in the data. A convenience sample of 100 posts (138 photos) were manually extracted and coded. Data are described using descriptive statistics and demonstrated by qualitative examples. The most frequent users in our sample were patients (66%), patient support networks (24%) and professional organisations (10%). Patients who were communicating their health update (31%) were the most frequently posted content and 25% of these posts described a symptom experience. Our findings demonstrate that patients and their support networks are frequenting Instagram and therefore may be able to receive and benefit from tailored intervention, however there is an identified gap in health-organisations participating in this virtual online community.

Introduction

Foreseeably, past generations of patients have used their physicians as the key source of health related information, however, there is evidence that people are increasingly turning to the Internet to supplement their information needs [1]. For example, a Swedish study found that just over three-quarters (76.2%) of people diagnosed with cancer accessed the Internet for cancer-related information and more than one quarter used social media relating to their health [2]. Patients commonly report using webpages, blogs, interactive forums and social media to obtain information to help make informed decisions, find practical information or answers to health related questions, stay in touch with others, and share experiences [2, 3].

Social media has become ubiquitous to our lives where we share, connect and communicate our experiences with friends, family, organisations and people otherwise unknown to us.

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Competing interests: The authors have declared that no competing interests exist.

Worldwide, approximately 2.5 billion people use social media and almost two-thirds of American adults use social networking sites: an almost ten-fold increase over the past decade [4]. The portability of these websites via mobile applications has no-doubt accelerated their uptake and allows for the capture of life's most ephemeral events. The differences in user demographics that are seen between platforms (such as age, ethnicity, gender, education or income), lend themselves to being targeted for various health campaigns, health promotions or health research seeking to reach different audiences [5, 6]. Social media data collection foreseeably provides large-scale and easily accessible data for patient reported information, particularly when compared with traditional patient-focused data collection methods [7].

One of the most popular social media platforms, Instagram, has almost one billion active monthly users [8]. Instagram is differentiated from other social media platforms by user-posts' being dominated by a photo. Most users choose to add accompanying text to their photos as well as tags or labels, termed 'hashtags' denoted as #*label*, (e.g. #cancer). The accompanying hashtags provide a method of grouping photos to create virtual social communities of similarly themed content or purpose and allows users to easily connect and share content.

Acute myeloid leukaemia (AML) is a relatively rare and aggressive blood cancer that can occur at any age [9, 10]. The standard treatment is immediate intensive chemotherapy, requiring lengthy hospital stays [11]. Additionally, research shows most patients have a reduced quality of life and persistent side effects or symptoms even after the completion of therapy or in remission [12–14].

AML makes up less than 1% of all cancer diagnoses per year, making research challenging to accrue participants, particularly in young adulthood where incidence is at its lowest [9, 10]. However due to the popularity of Instagram, particularly in early adulthood [15] and the search functionality of hashtags, the Instagram platform presents an opportunity for proposing unique research questions, particularly those focused on rare-diseases (as with AML), or research with participants that are traditionally difficult to access. Despite the popularity of Instagram, and the unique participant group it can reach, little health research has been undertaking using this platform [1].

Given large numbers of people with cancer are accessing online health-related messages and the relative absence of Instagram research, this exploratory study will be the first to characterise AML-related content on Instagram; specifically who is posting AML-related content and what types of content are being posted. Characterising AML-related content on social media could be useful for targeting people most likely to benefit from health messages, interventions, or support. Using Instagram for this type of extant research has the potential to provide unique insights into the lived experience, as well as observing individuals providing or receiving support through virtual communities and the sharing of health-related information. Additionally we detail a method potentially of interest to other researchers.

Materials and methods

The methods outlined in this paper adhered to Instagram's terms of service at the time of the research and all the content analysed in this study was publicly available on Instagram (available at www.instagram.com/instagram). However the data is not owned by the authors and they do not have permission for reproduction of the data used in the analysis. Ethical approval for the study was granted from Monash University, Human and Research Ethics Committee (Project ID 18540) and included a waiver of consent (no individual consent was necessary from Instagram users). The ethics approval prohibits the publication of data that may inadvertently identify any individual.

Data collection

Instagram is primarily a mobile application but has a desktop website with limited functionality. Only the website accessible version of Instagram was used in this study, to ensure complete separation between the researchers and their private accounts. This also ensured that only publicly available posts were being accessed (no Instagram account or login required). One hundred posts were chosen as a convenient number for a time-consuming manual exploratory method. The posts were found by using Instagram's search bar at the top of the webpage using hashtags that had been previously scoped as being used by people with AML: #acutemyeloidleukemia, #acutemyeloidleukaemia and #amlsurvivor. Each hashtag was searched for separately.

Posts were excluded from the study if they were videos (we were unable to extract these using our context extraction method), had non-English accompanying text or the subject matter was focused on children's cancer. Children's cancer was able to be determined by accompanying hashtag, such as #childhoodcancersucks or though examining the post photo and/or the accompanying text.

This study was undertaken after Instagram removed the automatic application program interface (API), which allowed for automation in downloads and much of the accompanying meta-data. Therefore, we detail a manual method of data extraction that may be of use to other researchers. This manual method allowed for retrospective capture for all eligible posts made over seven consecutive days in February 2019; eight consecutive days in April 2019 and twelve consecutive days in May 2019, to obtain a consecutive sample of 100 posts during the collection periods. Posts in chronological order (as opposed to most popular) can be found by scrolling past the initial "top posts" to the "most recent". It is was these most recent posts that were accessed taking note of the date of the post to ensure it complied with our sampling timeframe. This sampling method was used to avoid awareness campaigns or trending content, (which may generate atypical Instagram posts and traffic), cultural and ethnic influences between users' geographical location and for researcher convenience. One hundred posts was deemed to be sufficient given practicality of methods employed and the rarity of AML for an initial exploratory study.

As a user can modify or delete the content or their Instagram account, a screenshot was taken of the post and the user profile, thereby creating a 'post-record', which became the main unit of analysis. The post-record was made using Microsoft Word. We analysed the content of a post to include both the photo and the accompanying text and hashtags but excluded subsequent comments (and hashtags) that were made by either the 'post-owner' or other users.

For each post, basic data points were gathered about the user and the post: age and gender of the user (self-reported in the user profile), and country of origin data by using the location specified as part of the post or contained in the user profile, as well as post-specific information (description of the photo/s, accompanying text and hashtags and the number of likes and comments etc.). We also captured the username, but as duplicates became apparent, we adopted our identification system for each post to be able to distinguish between different posts from the same users.

Whilst the Instagram posts are publically available the data cannot be reproduced to comply with the Instagram terms of service, comply with the ethical approval of this study and to protect the privacy of the individuals posting on Instagram.

Data analysis

We used an adapted mixed-method social network model to frame our analysis [16]. The model describes sourcing data (Instagram), constructing the data (organising and preparing for analysis) and analysing the data (using network analysis or linear modelling). The

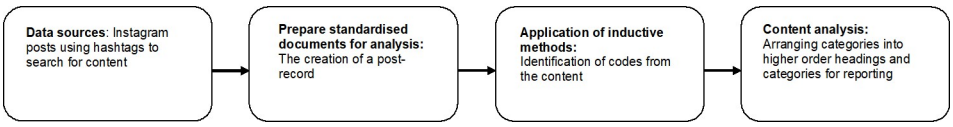

Fig 1. Method process, adapted from a mixed methods social network analysis framework [16].

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framework was appropriate as the study was exploratory and observational and employed a content analysis, however it was modified as we did not employ the network analysis or linear modelling. Fig 1 demonstrates our approach.

The content analysis is ideal for exploratory research, as this method seeks to unobtrusively explore the explicit description of the communication and the trends, patterns and frequency of this communication found within data [17, 18]. No *a priori* coding was developed owing to an absence of literature relating to the content of AML on Instagram. An inductive approach was employed to identify frequently occurring content categories and themes [18].

In brief the process included open coding, creating higher headings and then categories. After reviewing the post records multiple times, open codes were developed in a consultative and iterative process of reviewing the first ten post-records, at which time an open coding scheme was generated, that we thought could be applied to the whole data set [19]. A further ten posts were classified according to our coding scheme and codes were refined as necessary. The first initial ten posts were re-coded as per this scheme. This process was repeated twice, until we had a open coding scheme (after coding 40 posts) that could be applied to the entire data set. Higher order headings were then able to be developed from the open codes using researcher interpretation as to which codes belong in each higher order heading and then into categories (Fig 2) [20]. The process was undertaken by two reviewers and any discordance in coding between reviewers was discussed to reach consensus [18].

After the process was finished and the researchers were reflecting on the findings, we went back and coded for a single theme: 'hope and/or gratitude', as the researchers felt that even though this was outside the content analysis it was an interesting finding relevant to the research. This theme was based on the researchers' interpretation of the image and accompanying text.

Most data were expressed as both means with standard deviations, medians with interquartile ranges (IQRs), as well as frequency and range because the content and distribution varied considerably. Microsoft Excel was used for these descriptive statistics.

Results

During the search period, almost all posts were found using #acutemyeloidleukemia (94%). During the window of analysis, 51 unique users posted content and 16 of these posted more than once resulting in the analysis of 100 posts, consisting of 138 photos—one post can contain up to 10 photos.

Age and gender were mostly unavailable. Only two profiles stated age but we have chosen to conceal this for re-identification protection. Gender was rarely specified in the user profile, and we deemed it unreliable to discern gender either, from self-description (e.g. mom, wife etc.), appearance or socially gender-normative names, so this has not been reported. As shown in Table 1, we were mostly unable to determine the country of the post origin for most users (34/51).

We identified three user categories from the data: patient personal stories, personal support networks and professional organisations (Table 2). The most frequent users were patients themselves (66% of the posts), followed by personal support networks that we interpreted as family and friends (24% of the posts) and lastly professional organisations (10% of the posts).

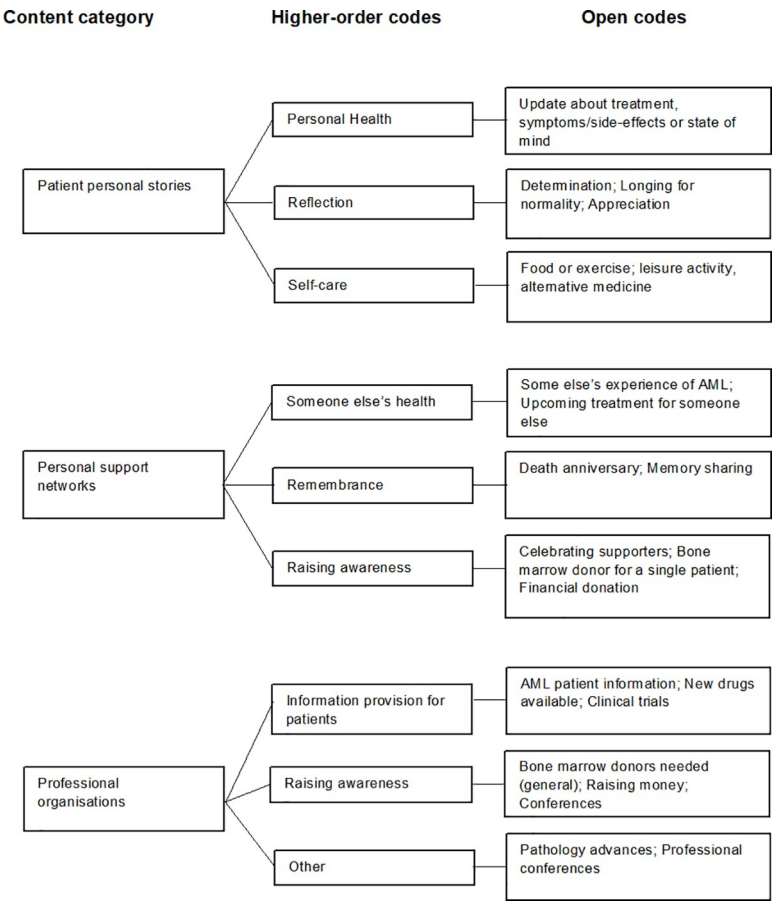

Fig 2. Process of generating categories.

https://doi.org/10.1371/journal.pone.0250641.g002

As shown in Table 3, the most frequent content posted in the analysis was patients communicating their health update (31% of the whole sample). The majority of posts made by personal support networks was a health update on behalf of a patient (50% of the personal support networks user category). Professional organisations only accounted for 10% of the total sample and the majority of the content was either patient information provision (40% of the posts) or raising disease awareness (50% of the posts).

The 10 organisational posts comprised of seven users and thirteen photos. Five of the seven users had an unknown country of origin, while one was based in the United States and the other in the United Kingdom as discerned from their profile or dot-org websites.

Table 1. Country of post origin of the post or user account (n = 51).

Country	Frequency n (%)
United States	11 (22)
Canada	1 (2)
United Kingdom	3 (6)
Hong Kong	1 (2)
Malaysia	1 (2)
Unknown	34 (66)

https://doi.org/10.1371/journal.pone.0250641.t001

Table 2. Frequency of posts and photos in each user category.

User categories	Number of posts (n = 100) n (%)	Number of photos (n = 138) n (%)
Patient personal stories	66 (66)	99 (72)
Personal support networks	24 (24)	26 (19)
Professional organisations	10 (10)	13 (9)

https://doi.org/10.1371/journal.pone.0250641.t002

One-quarter of all posts detailed symptoms that were being experienced by patients and 19/25 posts containing symptoms came from patients with the remaining posts being made by personal support networks. Please note to the protect privacy of individuals (for example via reverse identification), the quotes chosen below have been altered to encompass the overall sentiment of the quote [21].

"#selfie #nofilter long term chemotherapy effects have mostly subsided. Still can't shake that #red eye. . ." (picture of a person smiling into the camera). ***Patient personal story***.

". . .Hubby had platelets to fix his bleeding gums. . ." (picture of a person sitting upright in bed, surrounded by medical equipment) ***Personal support networks***.

Likes and comments were used as a proxy measure for engagement (Table 4). Overall there was between three and 394 likes and between zero and 54 comments. There was little engagement with organisational posts as measured by 'likes' and comments. There were between eleven and 41 likes on the posts and five posts had no comments.

Additionally, throughout the analysis, we noticed a prominent theme of hope often accompanied by gratitude, in the posts, either implicitly but commonly through the use of the accompanying text or hashtags (e.g. #gratitude or #grateful or #thankyou or #hopeful). Almost half (49%) of all the posts demonstrated this theme hope and/or gratitude. Thirty-four of these were made by the user category of patient personal stories, eleven by personal support networks and four by professional organisations.

". . .Each day has something good in it, even on the toughest of days. . ." (Image of a motivational meme) ***Patient personal story***.

Discussion

While much of the social media cancer communication research has focused on Facebook and Twitter, very few studies have focused on Instagram, particularly with a focus on such an

Table 3. The content classification frequency by user category and content classification.

User category	Content classification	Frequency of posts for each user category n (%)	Frequency of content classification for whole sample (n = 100) %
Patient personal stories (n = 66)	Personal health	31 (47)	31
	Reflection	24 (36)	24
	Self-care	11 (17)	11
Personal support networks (n = 24)	Someone else's health	12 (50)	12
	Remembrance	4 (17)	4
	Raising awareness	8 (33)	8
Professional organisations (n = 10)	Information provision for patients	4 (40)	4
	Raising awareness	5 (50)	5
	Other	1 (10)	1

https://doi.org/10.1371/journal.pone.0250641.t003

Table 4. Engagement with posts by user category as measured by likes and comments.

User category	Likes			Comments		
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range
Patient personal stories	67.41 (68.61)	36.5 (51.5)	251	7.47 (10.16)	4 (8.75)	54
Personal support networks	79.71 (41)	91.87 (52.75)	391	5.58 (7.9)	3 (4.75)	31
Professional organisations	28.9 (8.64)	31 (12.75)	30	1 (1)	1 (1)	11
All posts	66.51 (73.59)	35 (50)	391	6.43 (9.35)	3(6)	54

https://doi.org/10.1371/journal.pone.0250641.t004

emotionally and physically burdensome cancer like AML. Instagram differs from Facebook and Twitter by incorporating visual cancer communication and to our knowledge this is the first study to describe the content of Instagram communication concerning AML, thereby addressing this research gap. The novel method we have outlined is most useful for other investigators looking to utilise social media in the their research and our findings should be considered in the context of the limitations of our methods.

Our exploratory descriptive research showed in our sample, that people with AML communicating personal health updates, was the most common content being posted about AML on Instagram. Personal story sharing related to AML was also prominent by the personal support networks user category of people with AML. This finding was congruent with other Instagram disease-related research [3, 22, 23].

Why people tell such personal stories through Instagram may be explained by social media use being linked with patient empowerment through improved self-management and enhanced psychological and subjective well-being [1, 3]. These benefits may be obtained through real or perceived social connectedness of users of Instagram where they feel a sense of intimacy through sharing or social support, through community [24–26]. By posting intimate stories, users may also provide and receive social and emotional support through these virtual online communities [23]. This is further supported by the high prevalence of hope and/or gratitude in our data, where Steffen et al found in a study of advanced lung cancer patients, that hope may be important in providing support to social and role functioning, irrespective of physical symptom severity [27]. In sentiment analysis, Cho and colleagues also found hope was the most commonly expressed emotion in their melanoma study [23]. Whether hope is a common finding on social media contained to people with a malignant disease remains unknown.

In contrast to a Facebook content analysis including breast, prostate and other reproductive cancers, Instagram users concerned with AML do not appear to be information seeking, which may be due to the inherent functionalities of the platform [28]. This means that health professionals, researchers and professional organisations should endeavour to tailor their communication respectively to the most appropriate platform. However, if users are predominately seeking or providing support through personal storytelling, Instagram presents an opportunity for health providers and other organisations tasked with awareness-raising or support and wellbeing. Furthermore, it is likely patients and their friends and family are highly motivated to sustain the engagement with cancer communication initiated by reputable professional organisations [28, 29]. It is worth noting, we were unable to identify any health providers (individually or part of a health facility) posting during our data extraction period. The content of what patients communicate via social media outside the immediate doctor-patient consult provides an unique viewpoint unhindered by bustling waiting rooms or the interpretation of clinicians, to contextualise patient experience and decision making [7]. In our study, only about 10% of posts were organisational suggesting that Instagram may represent an untapped resource for cancer support communities and awareness campaigns. This suggestion possibly

holds relevance for all cancer types. Furthermore, public awareness is particularly relevant for malignant haematological diseases where up to 70% of patients need to seek bone marrow transplant donors outside of their family and only 7% of the American population are registered bone marrow donors [30]. Increasing public awareness through emotional appeal and capitalising on hope as a concept, may increase the number of registered donors to ensure sufficient diversity in the donor pool to meet the patient demand for bone marrow transplant [31, 32].

Social media research can complement other research methods: Crawford et al used YouTube to complement a literature review about the patient experience of haematological malignancies and found that YouTube provided supplementary information that highlighted the multifactorial experiences of patients that may not have been otherwise apparent through traditional research methods [7].

Certainly some individual healthcare professionals can and are using social media. A recent Italian study of neurologists showed that 56% of the sample used social media to have direct contact with patients and most of these health professionals were in favour of this communication method [33]. Instagram may provide an opportunity for clinican-led content that is trustworthy and appeals to patients, yet clinician-led social media posts are lacking, yet [34]. Moorhead et al. [35] suggests that both health professionals and their patients may need training to maximise the use of social media in their healthcare interaction. However, as yet it remains unknown how effective social media can be in its' perceived role in healthcare [35] and how this applies to inherently passive platforms such as Instagram where interactivity between user and viewer is limited.

Given the popularity of Instagram and the potential reach of posts, further research is warranted to understand the implications of online visual communication and how this information can be harnessed to improve health communication, patient experience and the experience of healthcare and balancing this with minimising the perpetuation of misinformation to vulnerable individuals.

Our study is not without limitations: critics rightfully observe that Instagram is often curated and may not reflect real life—experiences are complex and Instagram is a snapshot in time. Additionally, our sample may not reflect the breadth of posts due to our sample size, which was limited by the practicality of employing a manual method and resourcing. The manual method we employed and limitations in the search function also meant the study was unable to capture videos and Instagram stories (which are only available for 24 hours from posting). The sample used in this study had many users posting multiple times, potentially meaning our results may be less diverse and biased towards fewer individual experiences of AML. The retrospective nature of this study only allowed for the capture of data about age, gender and location that the user chose to share and it is therefore unknown whether there are dominating age groups, gender or country of origin in our analysis.

The strengths of this study are that we have demonstrated a unique and innovative way to potentially reach and/or observe hard to reach populations or people suffering rare conditions. Additionally, photos are a unique and expressive medium not conventionally used in cancer support services so other researchers with appropriate research question could also choose to employ an interactive image-based study design.

Conclusion

This exploratory study, presents a novel method whereby we have characterised AML-related Instagram content that contributes to the understanding of how social media fits into the lives of people affected by AML. Our results suggest that social media may have a role to play

particularly for social connectedness and support and that there is a potential role to play for health professionals and health organisations.

Further research should focus on exploring the feasibility and effectiveness of targeted awareness campaigns, as well as deploying support networks or health interventions to aid people by providing or seeking support.

Author Contributions

Conceptualization: Catriona Parker, Danny Liew, Darshini Ayton.

Data curation: Catriona Parker, Darshini Ayton.

Formal analysis: Catriona Parker, Darshini Ayton.

Funding acquisition: Danny Liew.

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Methodology: Catriona Parker, Darshini Ayton.

Project administration: Catriona Parker.

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Visualization: Catriona Parker, Ella Zomer, Danny Liew, Darshini Ayton.

Writing – original draft: Catriona Parker.

Writing – review & editing: Catriona Parker, Ella Zomer, Danny Liew, Darshini Ayton.

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Chapter 5: Descriptive qualitative study - Exploring the health and well-being of people with acute myeloid leukaemia

In this Chapter I detail the patient-described lived experience of the impact of the disease on their health and well-being. Two papers are presented in this Chapter that both address Objective 1; to explore the lived experience of adults with AML. The first is a submitted manuscript containing a qualitative descriptive study that explores the lived experience of AML as it pertains to their perception of health and well-being.

A second (published) manuscript in the form of a Commentary reports on a mapping exercise of the patient-reported issues to the most commonly utilised quality of life instruments in the AML literature. The purpose of this exercise was to understand whether the most salient issues for AML patients are being addressed by these instruments.

Parker, C., Wei, A., Liew, D. Zomer, E., and Ayton, D. It doesn't stop at validation: patient reported outcome measures require ongoing and iterative development. Support Care Cancer (2021). https://doi.org/10.1007/s00520-021-06553-7

Nursing implications from ongoing symptoms and concerns: a qualitative exploration of health and well-being in remission from acute myeloid leukaemia

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Declarations

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The authors have no financial or non-financial interests to disclose relevant to this research.

Availability of data and material:

Due to the potential identifying nature of the data, data is not publically available but any reasonable request can be made to the owning Ethics Committee for consideration.

Ethics approval

Alfred Hospital Human Research Ethics Committee: Project No, 638/17, approved on 19 December 2017 and the project was registered with the Monash University Human Research Ethics Committee (Project No. 12058).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Consent to publish was obtained from participants but does not extend to potentially identifying or identifying information.

Authors' contribution

Catriona Parker: Conceptualisation, Methodology, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualisation and Project administration.

Andrew Wei: Investigation, Writing - Review & Editing, Supervision, Funding acquisition

Danny Liew: Writing - Review & Editing, Supervision, Funding acquisition

Ella Zomer: Writing - Review & Editing, Supervision

Darshini Ayton: Conceptualisation, Methodology, Data curation, Writing - Review & Editing, Visualisation, Supervision

All authors read and approved the final manuscript.

Keywords:

Interviews, qualitative methods, quality of life, leukemia, symptoms, remission

Key message:

This paper demonstrates that patients previously thought to have symptoms and concerns that resolve after intensive treatment for acute myeloid leukaemia, actually continue to experience symptoms and concerns that potentially impact on their quality of life and the way in which these patients should be clinically managed and supported.

Abstract

Background: Acute myeloid leukaemia (AML) is an aggressive disease treated with intensive chemotherapy. The literature suggests a resolution of quality of life to near pre-illness levels, at the completion of intensive chemotherapy treatment. However, these data conflict with clinical observation in our service.

Objective: To explore and describe symptoms or concerns that affect the health and well-being for people in remission from AML to better equip nursing staff in clinically managing these patients.

Methods: A descriptive qualitative study design was undertaken using semi-structured interviews with people in remission from AML. Data were transcribed and NVivo managed the analysis. Themes were identified through inductive and deductive analysis using open, axial and thematic coding.

Results: Eleven adults in remission from AML were interviewed. Four broad themes were identified; physical outcomes, psychological outcomes, life disruptions and coping strategies, along with a number of sub-themes. There were a range of issues and concerns affecting the health and well-being of these patients.

Conclusions: People in remission from AML experience ongoing symptoms and concerns that are potentially unappreciated that affect their health and well-being.

Implications for practice: Practically, this has implications for patient care as persistent symptoms and concerns affecting peoples' health and well-being should be identified for improved clinical management and assisting people to access resources to improve patient outcomes and experiences.

1. Background

In the United States, acute myeloid leukaemia (AML) accounts for about 1% of all cancers, (approximately 19,500 people) making it a rare malignancy [1]. The incidence of AML increases with age - the median age at diagnosis is approximately 68 years old - but AML affects people of all ages, including children [1].

AML is an aggressive disease, displaying an abrupt onset of symptoms of severe pancytopenia including fatigue, recurrent or ongoing infection or unexplained bruising [2]. The impact of the illness and treatment on patients' lives can be profound. They are faced with uncertainty due to a relatively poor prognosis and high relapse rates: 5-year survival is approximately 27.5% [1]. Treatment options are limited and involve lengthy hospital stays for intensive chemotherapy to prevent premature death. Treatment is often associated with severe toxicity, which contributes to physical symptoms, significant emotional distress and impaired quality of life and other patient report outcomes.

Literature reviews reveal that studies commonly conclude that quality of life steadily improve to almost pre-illness levels once patients finish intensive chemotherapy treatment [3–5]. However in a recent systematic review, Buckley et al reported that the most commonly utilised quality of life instruments in AML were either not developed or validated with AML populations [3]. This is in contrast to best-practice, that dictates that instruments are developed with the population of intended use, which allows for measurement of salient outcomes from the patient perspective [6]. An absence of an AML-specific instrument introduces uncertainty surrounding the extent of improvement and/or resolution of symptoms and other domains of quality of life, particularly those in remission [3].

Through our clinical observations, we anticipated that those in remission from AML, due to the length and toxicity of their treatments, may have specific symptoms and concerns affecting their

health and well-being that are currently underappreciated in this sub-set of survivors. This has potential important implications for how these patients are clinically managed in remission.

The overarching goal of this study was to explore symptoms or concerns that affect health and well-being for people who are in remission from AML after initial intensive chemotherapy. This knowledge is anticipated to better inform and equip nurses caring for patients in remission from AML.

2. Methods

A qualitative design using semi-structured interviews conducted between January 2018 and July 2018.

Inclusion/exclusion criteria: AML patients aged ≥18 years. Patients were to be in remission from AML after being treated with IC, no longer in hospital and fluent in English. They were required to have no other active malignancy and could provide consent for participation.

Recruitment: Potential participants were identified by clinical staff involved in the care of AML patients at a major metropolitan hospital in, Australia. A member of the clinical team approached suitable candidates to scope interest in participating. With patient agreement, the primary author (CP) contacted the patient to confirm eligibility, explain the study and answer any questions. If the patient agreed, the participant information and consent form was posted or emailed and an interview scheduled with the interviewer (CP). Informed consent was obtained from all individual participants included in the study, including consent for the interview to be audio-recorded.

Data collection: Immediately prior to the interview (conducted at the research facility), participants completed a brief survey regarding demographics and current health status.

The interview guide was based on the minimum concepts required to capture quality of life; physical (including symptoms), psychological (including emotional and cognitive), and social

functioning [7] . Three broad open-ended questions with probing sub-questions were developed to capture these elements and piloted with two peers (see supplemental information for the interview guide).

The interviews were iterative and the interview guide evolved over subsequent interviews. Probing questions were either asked or modified based on the participants responses and questions related to themes arising in previous interviews were included. Field notes and observations were made immediately after the interview.

One female author (CP) not known to the participants conducted all the interviews either in person or via the phone. Author DA, (an experienced qualitative researcher, also not known to the participants and female) attended three of the interviews as an observer.

Ethics: The study was approved by <redacted for peer review> (Project No, 638/17, approved on 19 December 2017) and was registered with <redacted for peer review> Human Research Ethics Committee (Project No. 12058).

Analysis: Each interview was audio-taped, transcribed verbatim by a professional and imported into NVivo for analysis. Because the research was exploratory thematic analysis was an appropriate approach [8].

Thematic analysis provides a flexible approach that is able to identify, analyse, organise, describe and report themes and yet maintain the complexity found within the data-set [9]. It can be useful summarising key features of data using a structured approach of examining the perspectives of different participants, highlighting similarities and differences between participants, and contextualising unanticipated insights [9,10].

Open codes were generated from initial concepts identified in interview transcripts using the well-accepted concepts of quality of life (physical, psychological and social). Axial codes were developed to link the concepts, which enabled the themes to be connected. This inductive

coding occurred by analysing the experiences of individual patients as a collective to identify themes.

Participant recruitment and data collection ceased when data saturation was reached [9,11]. This was defined as when the interviews were not generating new themes and occurred at the ninth interview. However, an additional two interviews were undertaken to ensure a broad range of individuals and experiences were captured and to confirm data saturation.

Reporting of the study was undertaken according to the COREQ-32 Checklist with the exception of returning the transcripts to participants for comment or correction. This was deemed impractical due to the high relapse rates of AML and that this process could be burdensome for these patients.

3. Results

Fourteen patients were approached, eleven participated in the study (table 1). One patient declined for personal reasons and two others were uncontactable to schedule an interview.

Table 1. Participant Demographics

Characteristics	**Participants** ***n=11***
Age (years), mean (range)	59 (40-69)
Male	8 (73%)
Months since diagnosis at time of interview, mean (range)	7 (5-14)
Place of residence	
Metropolitan/capital city	8 (73%)
Regional or rural	3 27%)
Living arrangements	
With spouse or partner	11(100%)
Primary carer	
Spouse or partner	10 (91%)
Other family	1(9%)
English as first language	8(73%)
Highest level of education	
High school or less	2(18%)
College or university	9 (82%)

Interviews ranged in length from 30 - 95 minutes. During the interviews, participants recalled the entire journey of their AML experience to provide context and comparisons within their responses. In this analysis, we present four themes and various sub-themes in the data that were found to be important to patients' health and well-being: *physical outcomes, psychological outcomes, life disruption*, and *coping strategies* (Table 2).

Table 2. Identified Themes And Sub-Themes Of Important Symptoms Or Concerns That Impact People In Remission From AML

Theme	**Sub-Theme**
Physical outcomes	Physical outcomes described included; Fatigue (including impaired memory and/or concentration and sleep problems) Weakness related to muscle deconditioning Pain Changes in taste Vision problems Heart problems Changes in physical appearance
Psychological outcomes	Living with uncertainty Awareness of mortality Worry and anxiety for family
Life disruption	Diagnosis shock Changes in life plans (doing things sooner or delaying plans)
Coping strategies	Finding reasons why they got AML (why me?) Importance of positive mindset Comparing self to others Beliefs and faith Seeking to restore normality

3.1 Physical outcomes

Participants identified numerous transient and persistent symptoms from the disease and/or treatment that were not present prior to their disease (see table 3). They used the term 'weakness' to illustrate levels of fitness or (in)ability to undertake physical activity which was attributed to a lengthy hospital stay and reduced activity. They emphasised how this physical manifestation impacts their role functioning and perception of self.

Table 3. Supporting Quotations From Participants For The Theme 'Physical Outcomes'.

Sub-Theme	Quote
Fatigue	"*It's just tiredness, heavy eyelids every afternoon. I have to take afternoon naps, yeah.*" (Participant K1) "*I wake up tired. So it's like a fatigue sort of feeling… It's like a hangover. You wake up not fresh.*" (Participant B1) "*you struggle to concentrate or just a bit tired.*" (Participant B1) *"Before I used to say, "Oh I'll do it" and I do it in one day but now you get tired, you put it off and you put it off and you say I'll wait until the weather is a little bit better.*" (Participant K1) "*I get tired…I didn't used to get tired when we went up and visited and looked after our granddaughter..."*(Participant D1)
Weakness related to muscle deconditioning	*"[before] I would have had no trouble at all opening … a jar of say pickled onions. My brother and his wife were over this weekend, I couldn't open a jar of pickled onions."* (Participant D1) "*My muscles have shrunk. …they've gone weak.,. And it gets depressing because I've never asked nobody to open a jar for me or anything. I've been asked always."* (Participant V1)
Changes in physical appearance	"*I was changed, yes… I don't have hair... I was looking like a horror film character.*" (Participant P1) "E*very time I used to look in the mirror, I say, "That's not me. That's no me". Bald, you know*" (Participant V1)

Self-perception through changes to appearance were described and their reactions varied as people grappled with their sense of self-identity and self-recognition.

Almost all participants identified fatigue as a present and persistent experience affecting both them psychologically and physically. Participants described how this pervasive symptom affected multiple facets of their lives and demonstrated the mental or cognitive, physical and social dimensions of fatigue.

When prompted, participants admitted to poor sleep quality or needing more sleep than usual as a contributor to fatigue.

3.2 Psychological outcomes

When interviewed, participants spoke of living with a disease that they know to be life threatening and the resulting **uncertainty** they now live with. One person described how the **uncertainty** resulted in living a life-in-limbo (Participant P1, table 4).

Table 4. Supporting Quotations From Participants For The Theme 'Psychological Outcomes'.

Sub-Theme	Quote
Living with uncertainty	"*I used to think a lot ahead, what I'm going to do in the next three to five years and sorts of thing but now I can't. You plan only one year ahead or maybe a few months ahead because you never know, especially now every three months you've got to come back…*" (Participant P1) *"If it comes back, it comes back. I'll cross that bridge when I get to it if I get to it."* (Participant C1)
Awareness of mortality	*"When I was diagnosed…I shit myself. I thought I was going to die."* (Participant V1)
Worry and anxiety for family	"*The worst thing about the whole thing was actually the fact you could die… I could've probably dealt with it a lot easier if I didn't have kids. Having kids makes it a lot worse…They don't understand it; they shouldn't be without a parent.*" (Participant B1) *"And it's not that I'm scared about dying or anything like that, it's more leaving kids behind that need family and people that need me."* (Participant L1)

The **uncertainty** was intertwined with an acknowledgement that this experience is a life-altering event with a fear of cancer recurrence:

"It's not the matter of the actual dying. It's a matter of how am I going to be afterwards. You know, even though I don't pass away, but how am I going to be with it? Am I going to be always weary, afraid or scared that it's going to come back, or is it just going to stop and not come back at all? You don't know. There's no real answer to it." **Participant V1**

Ones' **mortality** was acutely felt at diagnosis particularly through **worry and anxiety for family** they would be leaving behind. **Mortality** and dying was a particularly poignant concern for parents of children.

Mortality was sometimes discussed contemplatively: "…*mortality is an honest thing about people…that is something that I've thought about, and that's the bit that probably… at 2 o'clock in the morning, has kept me awake...*" **Participant P2**

3.3 Life disruption

Even though the interviews concentrated on life in remission, many participants narrated their journey to the present time, often starting their story at their diagnosis. They talked about **diagnosis shock**, describing that the diagnosis, 'came as a bit of a blow', 'shocking' or feeling 'shell-shocked'.

Participants described how **life plans have changed** such as retirement and planning to travel: *"I've been working so many years…, I was planning to retire a little bit earlier than normal retirement age and go on holidays…but now I'm scared because of the long-distance flight as well as the insurance… Previously I wanted to go to places like Europe, America, Canada and others. But now I don't think I dare to do it because of my illness.."* **Participant K1**

3.4 Coping strategies

Strategies that were used by individuals to come to terms with their diagnosis and subsequent experience, were sub-themed into finding reasons why they got AML (why me?), the importance of having a positive mindset, comparing self to others and personal beliefs and faith (see table 5). Some focused on **finding the reason why they got AML**: "*there are no answers*", "*God is the only one who knows*", "*bad luck*" or past exposure to chemicals through a vocation was an explanation. Others researched their condition more systematically and utilised this information to frame their recovery.

Table 5. Supporting Quotations From Participants For The Theme 'Coping Strategies'.

Sub-Theme	Quote
Finding reasons why they got AML (why me?)	*"And then I'm the kind of person if something new is happening in my life, I want to know every single bit of it…And then because I know if I know more about my condition, I can beat it better… So the more I know, the better I feel."* (Participant H1)
Importance of positive mindset	*"Look, there are a lot of positives and there are a lot of negatives. But if you make the negatives overdo the positives, you'll go before your time... Because your mind does play a big part in it."* (Participant V1)
Comparing self to others	*"And you just say to yourself there's always one worse than you. If you think your case is bad, sometimes turn around and look around. There's always one worse than you."* (Participant V1)

Having **a positive outlook or mindset,** a positive frame of mind or just trying not to worry about being or having been sick, was considered to be important in recovery. Some participants talked about enhancing their positivity through **comparison with other patients.** Perceived attitudes of other patients was also used to explain others worsening situation and affirmation of the usefulness of their own positive mindset

"I could see that he had given up even before it started. He had simply given up... That's not the way to face it. " **Participant P1**

Faith and belief was also used as a coping strategy for some patients, providing for them an explanation as to why their treatment was successful.

"But you think well, I'm over the worst part. Oh well, have God or whatever people … You know, he doesn't want me." **Participant M1**

Seeking to restore normality or restoring things to how there were before an AML diagnosis was a common theme throughout the interviews. **Restoring normality** was related to reinstalling familiar routine and in those of working age it was linked with returning to work. Participants equated being able to return to their work as signifying a complete recovery - the experience of AML was now behind them.

"…this has been a hiccup in the road type thing…It's not so much the drive of oh, I want to go back and do [my job] thing. It's the – I can do what I used to do and…[pause] It's the fact that I am in a way over this condition" **Participant P2**

Interpretation and discussion

This study set out to explore symptoms or concerns that affect the health and well-being for people who are in remission from AML. The reported themes reveal the complexity of the issues patients are grappling with when in remission from AML. . Many of the symptoms affecting health and well-being identified are congruent with the literature about people with AML [3–5,12,13]. In particular, fatigue was common in our interviews and this included co-existing symptoms such as impaired memory and/or concentration, sleep problems and weakness related to muscle deconditioning. These issues have previously been reported as a symptom cluster and often occurs with pain and/or depression and/or reduced QoL when systematically measured [14–16]. Symptom clusters are complex and interconnected, however an improved understanding of clustering of related symptoms could lead to the development of preventative measures and corrective interventions to reduce the negative impact on patients [17].

The other themes developed from the interviews are also known to affect quality of life. However, the sub-themes; living with uncertainty, the awareness of mortality and worry and anxiety for family are all findings supported by the Lee-Jones et al model of fear of cancer recurrence (FCR) [18]. FCR is a common concern and may represent a unique and specific psychological disorder [19]. Data from cross-sectional studies demonstrate that FCR is associated with depression, impaired quality of life and daily functioning and has been found to be a predictor of other unmet needs in survivorship [20–22].

This study exemplifies the need to be mindful when interpreting contemporary literature that suggest quality of life resolves for this patient group at the conclusion of intensive

chemotherapy. More specifically these findings demonstrate that patients in remission struggle with ongoing concerns that affect their health and well-being not necessarily identified through the non-disease specific quality of life instruments commonly used. The current work by Buckley et al developing an AML-specific instrument to measure quality of life is promising, yet nuanced differences between patients at various disease and treatment stages need to be considered either for use in research or using clinically [23].

Arguably, the themes of coping mechanisms and the sub-themes of diagnosis shock and changes in life plans were incidental findings. However, they reveal insight into the new reality cancer brings; an attempt to gain control, bring hope and give meaning to the profound life changing experience of a life-threatening diagnosis: they may represent avenues of additional psycho-social support needed for patients at various stages of the diagnostic, treatment and survivorship phases.

This research also highlights challenges facing physicians to identify and respond to the wide breadth of symptoms and issues affecting health and well-being for individual AML patients in remission and ongoing survivorship. A lack of confidence in psychosocial competency has been linked with a reluctance by physicians to initiate discussions with patients about their wellbeing[24]. Additionally some patients may prefer their physician to initiate these types of discussions, while physicians generally expect patients to tell them any concerns resulting in a mis-match of expectation[25]. These challenges highlight the complexity of identifying and addressing health and wellbeing issues for patients.

Limitations: Some interviews were undertaken in person, and others via telephone. There was no discernible difference in the data between the two, but the possibility of an effect cannot be discounted. Participants were interviewed at varying lengths of time since entering clinical remission, which likely enriched the findings. However, interviewing people at consistent time-

points after they entered clinical remission would result in a more homogenous sample and may have added insights into how patient experiences vary over time. We also acknowledge some selection bias as participants were identified by the clinical team and those agreeing to be interviewed may have had different experiences to non-participants. Our small sample size is reflective of researching a disease with low incidence and high remission rate. The symptoms or concerns identified as affecting health and well-being in this study are reflective of the individuals interviewed and not necessarily generalisable to all people in remission from AML.

4. Conclusion

People in remission from AML have ongoing symptoms or concerns that affect their health and well-being that are potentially underappreciated. A fear of cancer recurrence should be noted as important to the ongoing support and management of survivors of AML. Additionally patients have numerous ongoing symptoms requiring medical and supportive management. Being mindful of this, will allow for an improved assessment of symptoms and concerns salient to patients, and therefore improving nursing care provided to these patients.

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COMMENTARY

It doesn't stop at validation: patient reported outcome measures require ongoing and iterative development

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Abstract

Patient reported outcomes (PROs) are a pillar of modern-day patient-centered care and clinical trials. PROs complement clinical information with the patient's own report about their experiences of health, without influence or interpretation by other people. However, choosing an appropriate PRO measure from the many available remains challenging for clinicians and researchers. One of the common pitfalls in instrument selection is that the instrument is often developed with a different patient population than the group being cared for or researched. This difference can result in salient items of importance to the patients, being under-reported or missed altogether. We highlight, through the reporting of some of our own data, that PRO instrument development does not stop with a validation study and we provide suggestions for future research for further improvement in this space.

Keywords Patient reported outcome measures · Acute myeloid leukaemia · Acute leukaemia · Cancer

Commentary

Patient reported outcome (PRO) measures are used extensively to understand the patients' experience of their health, quality of life, well-being, psychological and functional status without the interpretation of a clinician [1–3]. PROs are underpinned by the principle that patients are the best judge of their own needs and experiences [4].

Incorporating PROs into clinical trials has been aided by consensus committees that have produced useful guidelines about how PROs are to be utilised for FDA approval [5, 6]. However, the incorporation of PROs into routine care at a local level is usually based on clinical judgement about the best instrument to use, which can lead to pitfalls that limit the collection of useful and meaningful data [1]. We highlight one such example in this discussion.

Published literature suggests those with acute myeloid leukaemia (AML) report poor PROs at diagnosis and during initial treatment, but that PROs resume to pre-illness levels during the recovery and survivorship phases [7–9]. However, our experience and clinical observation of adult patients recovering from AML do not fully support this observation. There are numerous explanations for this disconnect. A response shift bias is a concept where the patient has changed their internal rating of 'normal' due to their most recent experience with illness [10]. Additionally longitudinal PRO studies in patients with AML may suffer from responder bias, where significant attrition in responses are observed over time likely due to clinical deterioration and disease mortality [7]. Furthermore the timing of PRO administration with the treatment or illness trajectory is important as side-effects, symptoms and emotional toll vary throughout the cancer journey. Finally the instrument itself, may not be specific enough to detect changes in PROs or even include items of most relevance for the population being studied.

Given AML is a relatively rare disease (accounting for about 1% of all cancers, or approximately 19,500 people in the United States [11]), it is feasible that the instruments

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themselves could be less than optimal. One reason the instrument may not be performing optimally, is that the measurement tool has not been developed with AML patients which is accepted best practice[12].

The most common PRO instruments used for AML populations is the European Organization for Research and Treatment of Cancer QLQ-C30, (developed with lung cancer patients) and the Functional Assessment of Cancer Therapy (FACT), supplemented with a leukaemia specific module (FACT-LEU) with questions more relevant to chronic leukaemia [13, 14]. Neither of these instruments were developed or validated with people diagnosed with AML [7]. To explore how the validation of these instruments in different patient populations may affect the collection of data in people with AML, we undertook a descriptive qualitative study. Qualitative inquiry is one of the first steps to ensuring content validity of any PRO instrument [15]. Patient interviews with eight men and three women, were conducted to capture the health and wellbeing concerns of people in remission from AML [average time since diagnosis was seven months (range 5–14 months) and the average age of participants was 59 years (range 40–69 years)]. The identified themes were then compared with the items from the PRO instruments most commonly used in AML (QLQ-C30 and the FACT-LEU). We were purposive and diverse in our participants to ensure a range of experiences were collected [15]. Content analysis was used to analyse the 11 interviews [16]. Four main themes arose from the data: *physical outcomes, psychological outcomes, life disruption and coping strategies*. Mapping these themes (and sub-themes) back to the QLQ-C30 and the FACT-LEU (Table 1) demonstrated that some items were not discussed by the participants at all. Conversely, some identified sub-themes from the interviews were not included in the instruments. Using the physical outcomes domain as an example, the FACT-Leu asks about chills, night sweats, bruising, bleeding and lumps or swelling, but these symptoms were not mentioned by *any* of our study participants [14]. The QLQ-C30 asks about shortness of breath, vomiting, constipation and diarrhoea, which were also not commonly cited during our interviews (8). Neither instrument captured changes to vision or taste which were bothersome to a number of participants. Where the instrument domain captured only some of the concerns discussed by participants or the instrument domain contained some concerns that were not discussed by the participants, this was mapped as 'partially' (Table 1).

Our identified sub-themes of living with uncertainty, the awareness of mortality and worry and anxiety for family were all findings supported by the Lee-Jones et al. model of fear of cancer recurrence (FCR) [17]. FCR is a common concern among patients [18] across a variety of cancer types and therefore arguably warrant consideration for researchers to include and validate these concepts into current PRO instruments beyond AML specifically. It is possible that the timing of our data collection affected our findings also. For example, chills or night-sweats may be more relevant for a population treated with a particular drug or at a particular time-point in their treatment trajectory. This highlights the importance of considering the timing of PRO administration. Serial PROs may provide a more meaningful picture, particularly in cohorts where little PRO research has been previously undertaken for usual care, where serial measurement may guide timing by specifically discovering (a) the issues affecting patients and (b) when patients are more likely to be affected by particular issues.

Importantly qualitative research does not seek to be generalizable so the findings from our small sample warrant investigation in a larger study, incorporating patients at various disease stages and disease experiences. Such a study would utilise inductive methods and incorporate confirmatory testing through the use of focus groups to ensure the concepts resonate with the population of interest [15].

Table 1 Mapping interview themes to commonly used instruments (QLQ-C30 and FACT-Leu) using the FDA domains for health-related quality-of-life (HRQoL)

	Issues or concerns from participants captured by instrument	Instrument contains items that were not issues or concerns from participants
QLQ-C30[a]		
Physical (incl. symptoms)	Partially	Partially
Psychological (incl. emotional and cognitive	Partially	No
Social	Yes	No
FACT-Leu[b]		
Physical	Partially	Partially
Psychological (incl. emotional and cognitive	Partially	No
Social	Yes	No

[a]European Organization for Research and Treatment of Cancer QLQ-C30 quality-of-life questionnaire [13]

[b]Functional Assessment of Cancer Therapy (FACT), supplemented with a leukaemia specific module [14]

More broadly, this descriptive exploration highlights the need to be mindful of selecting the most appropriate PRO measures for the patient population and understanding the limitations of the chosen instrument. Developing disease-specific instruments may be warranted in some instances, however researchers should preference validating existing instruments in sub-populations or modify previously developed instruments by confirmatory testing using qualitative and quantitative techniques [15].

As it is of paramount importance that PRO instruments are developed or validated with the intended patient population, the issue of PRO selection to incorporate into research or routine care, may be of particular relevance to rarer cancers where less research effort is often directed. The development and validation of a PRO instrument should evolve and constantly iterate. PRO measures can change over time due to patient, treatment and policy factors. For example, in the last decade or so, extensive research into the objective and subjective financial consequences of cancer has shown that these affect clinically relevant patient outcomes, yet financial burden questions have not been routinely incorporated into PRO instruments [19].

We hope that this provides a snapshot of the many complexities of PROs and that qualitative research can elicit improved PRO instruments to measure nuances between patient populations and their outcomes. Ongoing research in this space has many practical implications for the clinical management of patients through identifying the most salient patient concerns and assisting people to access care and resources to ultimately improve their outcomes and experiences.

Author contribution CP and DA made substantial contributions to the conception and design of this work. CP carried out data acquisition, data analysis and interpretation and drafting of the commentary. DA contributed to data acquisition, data analysis and interpretation and revising commentary drafts. AW was involved in the data acquisition and commentary revision, whilst DL and EZ contributed to the commentary revision. All authors read and approved the final commentary submission.

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Data availability The datasets generated and/or analysed during the current study are not publicly available due to their potentially identifiable nature but are available (de-identified and redacted where needed), from the corresponding author on reasonable request and after review of the owning Human Research Ethics Committee.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (The Alfred Hospital 638/17) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Conflict of interest CP declares a departmental PhD candidature scholarship from Monash University. CP declares grants from Cancer Australia, unrelated to this research. AW declares Honoria or participation in advisory boards for Novartis, Astellas, Pfizer, Macrogenics, Abbvie, Genetech, Servier, Celgene, Amgen, AstraZeneca and Janssen, unrelated to this research. AW declares grants or grants pending, unrelated to this research, from Novartis, Abbvie, Servier, Celgene, Amgen and AstraZeneca. AW declares receiving personal fees from Servier for consultancy and royalties from Abbvie, unrelated to this research. DL declares receiving personal fees for the participation in advisory boards unrelated to this research with AbbieVie, Astellas, AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer and Sanofi. DL declares grants or grants pending unrelated to this research with Abbvie, Astellas, AstraZeneca, Bristol-Myers Squibb, CSL-Behring, Novartis, Pfizer, Sanofi and Shire. DL declares travel, accommodation or meeting expenses unrelated to this research, paid for by AstraZeneca and Bayer. EZ declare consultancy or advisory roles with Amgen, AstraZeneca, Pfizer and Shire unrelated to the submitted work. DA has nothing to disclose.

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Chapter 6: Financial qualitative study - Exploring the financial experiences of people with acute myeloid leukaemia

In this Chapter I present a manuscript reporting the financial experiences of those with AML from the qualitative exploratory study. In the paper the patient perception of the financial impacts and the financial concerns of those with AML as result of their diagnosis are discussed. The Chapter addresses the second objective of this thesis, which was to explore the financial burden of AML from the patient perspective. Additionally, the findings from this study informed the development of the domains and the questions of the survey used in the Chapter 7 study. The findings from this study also contributed to the recommendations from research made in the discussion section of Chapter 9.

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Health and Social Care in the community

WILEY

ORIGINAL ARTICLE

'If I don't work, I don't get paid': An Australian qualitative exploration of the financial impacts of acute myeloid leukaemia

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Abstract

A cancer diagnosis can have significant financial impacts for patients, often resulting from unexpected out-of-pocket expenses and a reduced capacity to work. These financial implications have been well characterised quantitatively in common cancers. However, less is known about the lived experience of financial stress, particularly outside the United States and in rarer cancers. This study aimed to explore the perceived financial impact of acute myeloid leukaemia (AML)—a rare haematological malignancy where patients may be particularly vulnerable to financial stress due to the lengthy, specialised and centralised care. The findings provide insight into the patients' lived experience of the personal financial impact of the disease. This Australian qualitative study was undertaken with 11 adults in remission from AML and recruited from their treating hospital. Semi-structured interviews were transcribed, and data were managed using NVivo. Themes were identified through inductive and deductive analysis using open, axial and thematic coding. Four themes were identified: burden of AML-attributable costs (e.g. out-of-pocket parking and medication expenses); accommodating the AML-impact on paid work (e.g. early retirement and modifying job tasks); the consequence of financial strain from AML (e.g. using savings and accessing Government welfare) and concerns about the future and future familial financial burden (e.g. securing finances and worry about depleting financial resources). A reduction in or stopping work was perceived as the most burdensome to their current and future finances. The findings demonstrate people with AML experience financial difficulty even within a publically funded healthcare system. Opportunities exist for health services to alleviate some financial burden through reducing or abolishing parking fees for oncology patients and ensuring adequate access to social workers to facilitate access to Government welfare. Improving patients' financial difficulties contributes to improved quality of life, which is congruent to cancer survivorship.

KEYWORDS

acute myeloid leukaemia, direct costs, employment, expenses, financial impact, indirect costs, qualitative

1 | BACKGROUND

Acute myeloid leukaemia (AML) is a relatively rare haematological malignancy, accounting for approximately 1% of all cancers (National Cancer Institute, 2018). This aggressive disease requires care in highly specialised facilities where patients spend a considerable period of their treatment as in-hospital patients (Leukaemia Foundation, 2019).

A cancer diagnosis is generally an unexpected event in life and affects some patient's financial situations. The cause is primarily due to the unexpected out-of-pocket costs, expenses related to travel for care and a reduced capacity to work (Altice et al., 2017). Financial toxicity (FT) is used to describe the 'toxic' economic consequences cancer can impose on patients (de Souza et al., 2017). Much like treatment-related medical toxicities that are well-described in oncology, FT is linked with reduced Quality of Life (QoL), higher symptom burden, lower compliance to medications and reduced overall survival (de Souza et al., 2017; Zafar et al., 2013). FT is primarily quantitatively measured using Likert scales, either embedded in quality of life measure (e.g. EORT-QLQC30), or a standalone patient-reported outcome measure (PROM) such as the COmprehensive Score for financial Toxicity (COST) instrument (Witte et al., 2019). These measures provide a score or grade of FT but do not explain the lived experience of financial duress.

For people with AML, the impact on their lives can be profound as they are additionally faced with poor prognosis and high relapse rates (Leukaemia Foundation, 2019; National Cancer Institute, 2018). AML is a costly disease to treat, and out-of-pocket costs incurred by individuals are rising particularly in the new era of molecular and immune therapies. People with AML may be particularly vulnerable to FT due to the centralised nature of their treatment, requiring many patients to travel for care (Bradley et al., 2011; Cancer Council Victoria, 2017; Tran & Zafar, 2018; Wang et al., 2014).

The prevalence of FT varies from 22% to 73%, depending on cancer type, perspective (monetary or subjective) and study country of origin (Desai & Gyawali, 2020; Gordon, Merollini, et al., 2017; Pearce et al., 2019). Few estimates of FT exist for AML; initial research shows that up to 54% of patients meet the criteria for FT, defined as scoring four or less (where 10 is the maximum) using two questions from the COST instrument (Knight et al., 2018).

Existing literature on FT focuses on more common cancers and often uses cohorts with multiple cancer types (Altice et al., 2017; Azzani et al., 2015; Chan et al., 2019; Gordon, Merollini, et al., 2017). FT literature is absent for rarer cancers such as AML, which conflicts with our modern emphasis on patient-centred care. Understanding the broad spectrum of impacts on patients comprises a vital component of psychosocial care.

Much of the literature is from the United States (Azzani et al., 2015; Gordon, Merollini, et al., 2017), which adopts a model where the user pays for services (Dixit & Sambasivan, 2018). In contrast, most Western models of healthcare are hybrid (Australian Institute of Health and Welfare 2016, 2016; Mason, 2008), where the Government provides basic-level health insurance (publically provided healthcare). Individuals can supplement this level of insurance by purchasing additional private health insurance (Dixit & Sambasivan, 2018). Nevertheless, Australian patients are burdened with increasing gap payments, particularly for expenses that are tangentially related to treatment (e.g. travel costs, reduced income and cost of prescribed medicines; Australian Government, 2019; Newton et al., 2018; Paul et al., 2016). In similar healthcare systems such as Canada, 200 lung cancer patients were found to experience high levels of FT (Ezeife et al., 2019), and 502 cancer patients with a variety of cancers in Germany endured burdensome out-of-pocket costs (Büttner et al., 2019). Whilst this contemporary literature provides an estimate of the prevalence of FT, little is understood about the patients' perceived impact of the financial consequences of cancer, with a dearth of literature in rarer cancers such as AML (Gordon, Merollini, et al., 2017).

Therefore, this study aimed to explore the perceived financial impact of AML. The objectives were to: (a) identify factors contributing to patients' financial burden; and (b) explore the management strategies that patients' utilise to manage the financial burden of AML in the context of a publically funded health care system.

What is known

- Financial burden is well described in common cancers. Less is known about the patient experience of financial stress, particularly outside of the United States healthcare system and in rarer cancers such as AML.

What this paper adds

- Costs are still burdensome for AML patients treated within publically funded healthcare, mainly costs associated with parking and travel—many patients need to travel for specialist and centralised haematological care. The reduced capacity for paid work due to AML was a contributing factor to the perceived financial burden.
- Patients highlighted the difficulty in accessing Government welfare which presents an opportunity to help alleviate the financial burden by reprioritising expenditure towards improved access to social workers and streamlined Government services for cancer patients.

2 | METHODS

2.1 | Design

An exploratory qualitative study was conducted, given little is known about the financial impact of AML through the patient lens. The analysis question guiding the present study was 'What was the

perceived financial impact of an AML diagnosis and treatment, and how did this affect you?'

The study's methods and results are reported according to 'Consolidated Criteria for Reporting Qualitative Research' (COREQ-32). The study was approved by the [The Alfred Health] Human Research Ethics Committee (Project No, 638/17).

2.2 | Participants

Patients were eligible for the study if they were aged ≥18 years old, in clinical AML remission, not currently inpatients of the hospital, had no other malignancy, were well enough to consent and be interviewed, and spoke fluent English. Patients in remission from AML are clinically reviewed at least monthly for disease recurrence. This routine follow-up allowed eligible patients to be approached by clinical staff while attending a major metropolitan hospital in Melbourne, Australia. With agreement from the patient, the primary author (CP) contacted the patient to confirm eligibility, explain the study and answer any questions. If the patient agreed, the patient information and consent form was posted or emailed and an interview was scheduled with the interviewer (CP).

Patients were purposively sampled to explore the experience of perceived financial impact thoroughly. This sampling approach involves using an iterative sampling process of selecting participants to reflect a breadth of ages, genders, sociodemographics and experiences and increases the validity and efficiency of the study (Palinkas et al., 2015; Robinson, 2014).

2.3 | Data collection

Data were collected via semi-structured interviews, with a brief form used to gather demographic information. CP and DA developed the interview guide based on existing international and Australian patient financial impact literature (de Souza et al., 2017; Gordon et al., 2007, 2009; Gordon, Beesley, et al., 2017; Gordon, Merollini, et al., 2017; Lathan et al., 2016; Newton et al., 2018; Zafar et al., 2013). Given the exploratory nature of this study, questions were intentionally broad and tailored for language and content after piloting with cancer consumers and incorporating their feedback. The guide used open-ended questions and probing questions to elicit more detailed information (Table 1).

Questions were iterative, and responses that related to new themes were incorporated in later interviews. For example, participants described costs related to house maintenance activities that they could no longer undertake (e.g. gardening, cleaning etc). This led to the addition of the probing question "Do you now pay someone to do the things, you used to be able to do?"

One female author (CP) not known to the patients conducted all interviews either in person or via phone. Author DA (experienced qualitative researcher, female and not known to the patients) attended three interviews as an observer. Each interview was audiotaped with participant consent.

2.4 | Data analysis

Each interview was transcribed verbatim and imported into NVivo version 12, a qualitative data analysis software supporting thematic analysis. Because this research was exploratory and included patients with varying demographics and experiences, a thematic approach to data analysis was appropriate (Vaismoradi et al., 2013). Thematic analysis provides a flexible approach that can identify, analyse, organise, describe and report themes and yet maintain the complexity found within the data set (Liamputtong, 2009). Thematic analysis can be useful in summarising key features of the data using a structured approach of examining the perspectives of different participants, highlighting similarities and differences between participants and contextualising unanticipated insights (Nowell et al., 2017).

Participant recruitment and data collection concluded when we could demonstrate data saturation, defined as when the interviews were not generating new themes (Saunders et al., 2018). By the ninth interview, no new codes were being developed, which indicated that data saturation had been reached. However, an additional two interviews were undertaken to ensure that the purposive sampling was complete and to confirm data saturation.

Open codes were generated from initial financial concepts identified in interview transcripts. Axial codes were developed to link the concepts, which enabled the themes to be connected. This inductive coding occurred by analysing the experiences of individual patients as a collective to identify themes. The three broad topics covered by

TABLE 1 Interview guide mapped conceptual elements of financial distress of people with cancer

Topic	Open question	Probing question/s
Direct and indirect costs	How have you found having AML has impacted your finances?	How has AML affected your work? What sort of out-of-pocket costs do you have? Do you now pay someone to do things, you used to be able to do? Are there other costs you now have that you didn't used to have?
Financial strain and distress	What sort of different things have you had to do to manage your finances since having AML?	Have you accessed insurance, Government welfare or subsidies? Have you accessed retirement savings or accumulated debt? What other measures have you put in place or been forced to use?
Outcomes	Are you concerned for your financial security in the future?	Are you worried about the financial burden on those around? Have you made changes in your financial life to secure your future?

the interview guide (see Table 1) served as the deductive codes, and themes within the data were mapped to these topics. For example, initial open codes were 'parking costs' and 'household modification costs' that were linked with the axial code 'indirect, unexpected expenses'. This then made up the theme 'Burden of AML attributable costs'.

Using a deductive approach to triangulate our findings, we undertook a mapping process to match the themes identified in interviews to a commonly used FT patient reported outcome measure (PROM), the COmprehensive Score for financial Toxicity (COST; de Souza et al., 2017). The purpose of this was to: (a) indicate whether the instrument is relevant to and covering salient items for the AML population of interest and (b) triangulate our findings, thereby increasing the robustness and validity of the results. As the mapping was undertaken after theme development was completed, the COST instrument did not influence the interview guide or analysis of the interviews.

3 | FINDINGS

Fourteen patients were approached to participate in the study, 11 consented and were interviewed (Table 2 links the participant code with the patient demographics). One patient declined for personal reasons (male, aged >60 years), and two others (one female aged >60 years and one male aged 18–45 years) were unable to be contacted to schedule an interview. Interviews ranged in length from 30 to 95 min.

Most participants were male (73%), a mean age of 59 years and lived in metropolitan areas (73%). More than three-quarters (82%) were educated beyond high school, and 73% of people spoke English as their first language. On average, seven months had passed since the initial AML diagnosis (range 5–14 months; Table 3).

Four themes were identified: (1) burden of AML-attributable costs, (2) accommodating the AML impact on paid work, (3) consequence of financial strain from AML and (4) concerns about the future and familial financial burden. These themes mapped to the COST instrument are summarised in Table 3.

TABLE 2 Participant numbers, gender and age bracket

Participant code	Gender	Age bracket (years)
B1	Male	18–45
C1	Female	46–60
D1	Male	>60
H1	Male	18–45
K1	Male	46–60
L1	Female	18–45
M1	Male	>60
P1	Male	46–60
P2	Male	46–60
S1	Female	>60
V1	Male	46–60

3.1 | Theme 1: Burden of AML-attributable costs

AML-attributable costs included any direct or indirect expenditure that occurs because of AML. For example, treatment for AML involves lengthy hospital stays and is only available at specialised centres requiring some patients and families to travel for care. Participants frequently mentioned travel costs as being burdensome:

> Probably the only [costly] thing was coming in every day the petrol and parking. Although we had the $10 a day parking, it still adds up over that period of time. (S1)

For some, '*the parking has been the most [biggest] cost*' (C1). This participant went on to estimate she was more than $1100 out-of-pocket just for parking: '*we would be in there maybe six or seven days a week. And even at $10, that's $70 a week. And it was for 16 weeks or something like that*' (C1). Another patient explained that they '*expect to use the car maybe about 12,000 kilometres a year – roughly… we've just done 12,000 kilometres in three months*' (D1). Unexpected vehicle use highlighted the indirect cost of seeking care. Another described the parking costs as *'a fundraiser for the hospital'* (M1).

Participants described numerous examples of additional unexpected expenses related to treatment, managing symptoms and treatment effects. For example, some reported that they had out-of-pocket expenses '*on and off for some medicines*' that '*added up*' (P1) once they left the hospital;

> They give you the stuff while you're in hospital of course, and you've got to take some home, that's when it costs you…[for] scripts for other stuff. (C1)

Juggling medication costs with household expenses were echoed by other patients

> You've got to pay [for] your medicines. When you're in hospital, it's not too bad there. They supply them all for you. But when you're outside, no. And they're ongoing bills. Not only that you've got your bills of the house, you've got those bills. (V1)

Unexpected expenses extended into the home and demonstrate the effect that the treatments and symptoms can have on physical functioning, where when one patient had '*to get [pay-for-service] home help*' (V1). Another patient described having to move his bedroom downstairs because of reduced mobility, and that then

TABLE 3 Participant demographics

Characteristics	Participants $n = 11$
Age (years), mean (range)	59 (40–69)
Male	8 (73%)
Months since diagnosis at time of interview, mean (range)	7 (5–14)
Place of residence	
Metropolitan/capital city	8 (73%)
Regional or rural	3 (27%)
Living arrangements	
With spouse or partner	11 (100%)
Primary carer	
Spouse or partner	10 (91%)
Other family	1 (9%)
English as first language	8 (73%)
Highest level of education	
High school or less	2 (18%)
College or university	9 (82%)
Employment status at time of interview	
Working	2 (18%)
Unemployed	2 (18%)
Sick leave (employer or insurer paid)	4 (36%)
Retired	3 (27%)
Alternate income streams being accessed at time of interview	
Government welfare	4 (36%)
Income protection insurance	2 (18%)
None	5 (45%)

required *'paying to have the curtains changed because they were old and I was concerned about the dust and my low immune system'* (D1).

Patients described unexpected and additional home maintenance expenses, for example needing to *'employ a gardener to come in and renovate it [the garden] which cost a couple of thousand dollars'* (D1) due to reduced physical functioning. He explained that they have a *'big garden, but now that's problematic'*.

Another patient stated that they had to *'get somebody in to do the gardening because [there are] spores in the soil and I can't do it with my lowered immune system. Every month it's a cost we didn't expect to have'* (P2). Patients expressed that these additional unexpected costs made it *'even hard[er] to catch up with all your expenses'* (H1).

The burden of AML-attributable costs aligned with items 2, 4 and 10 of the COST instrument (Table 4) as these items all related to disease attributed expenses and satisfaction with their financial position.

3.2 | Theme 2: Accommodating the AML-impact on paid work

Financial commitments that existed before a diagnosis was mainly of concern given the lengthy hospitalisation and treatment regime for AML leaving individuals unable to work:

> I asked the doctors, "When can I go back to work?" and they said, "We don't know. Maybe after six months, 12 months, after one year, we can't say to you exactly". That worried me. That worried me. That worried me because we have a housing loan to pay, we have two car loans to pay, these are the biggest burdens on us. (P1)

Some participants were frustrated that they had to resign from their position or retire earlier than planned unwillingly; *'I'm retiring in eight weeks. I don't want to but I'm going to'* (M1). They described how this will cause financial difficulties; *'because how am I going to accommodate [early] retirement?'* (M1). One participant who had exhausted their leave allocations and felt pressured to resign; *'I had to tell them 'look, I'll just resign'* (K1). For another, their position coupled with their disease was too burdensome saying, *'It's too much. The job's become overwhelming'* (C1), even though there was often a desire to return to work participants were not able to go due to their symptoms.

> I want to go back. I feel like I've got a lot of life in me still.... but there's days ... I'll stay at home. (V1)

TABLE 4 Mapped coding to questions from the Comprehensive Score for financial toxicity (COST) patient reported outcome (de Souza et al., 2017; secondary analysis)

Theme	COST instrument item	Item number
Burden of AML-attributable costs	My out-of-pocket medical expenses are more than I thought they would be	2
	I feel I have no choice about the amount of money I spend on care	4
	My cancer or treatment has reduced my satisfaction with my present financial situation	10
Accommodating the AML-impact on paid work	I am frustrated that I cannot work or contribute as much as I usually do	5
	I am concerned about keeping my job and income, including work at home	9
Consequences of financial strain from an AML diagnosis	I am able to meet my monthly expenses	7
	I feel financially stressed	8
	I feel in control of my financial situation	11
	My illness has been a financial hardship to my family and me	12
	I am satisfied with my current financial situation	6
Concerns about the future and future familial financial burden	I know that I have enough money in savings, retirement, or assets to cover the costs of my treatment	1
	I worry about the financial problems I will have in the future as a result of my illness or treatment	3

Some patients described how their ongoing symptoms (e.g. fatigue and reduced mental cognition are common with AML) hindered their ability to work; '*I did do quite a bit [of work] so I was no longer able to do that*' (D1), and the resulting financial pressure placed on them because of this; '*financially you want to work, carry on working and get the same salary as before, but you can't do it now because your body can't take it any more*' (K1).

This situation was particularly poignant for younger patients '*I'm too young to retire, way too young. If I was 60 onwards, I'd probably say oh well it's time to retire. But I'm still too young*' (V1). In addition to these concerns, participants stated that they were worried about their employment security; *'I don't know if I'm going to have a job to go back to'* (L1). Being unable to work or contribute as much as usual as well as concerns about keeping employment and income was able to be mapped to the COST instrument item numbers 5 and 9 (Table 4).

Some participants also communicated their modified work activities to accommodate their symptoms and energy levels; *'I've made it less physical and I move at a slower pace'* (M1). Others reduced their hours because of their fatigue and energy levels; *'I used to probably get to work around 6:30 in the morning; I can't get there around 9:00 now'* (B1). Another participant *'went back just once a week for a couple of hours, but not going to the workshop, just sitting at the computer'* (H1).

3.3 | Theme 3: Consequence of financial strain from AML

Patients described compromises in everyday expenditure that were being made to save money; *'[we] don't go out as much, don't try and waste fuel, eat at home. You can't go out and get takeaways [as] much as you used to'* (V1). Recurrent home expenses were also scrutinised; *'I just cancelled a couple of my contracts with [my] cell phone company and, the internet, to just drop the expenses as much as I can'* (H1). When asked about the sacrifices made to control their finances, leisure travel was postponed because of reduced income '*I had these plans of going around Australia … I think that's got to go on hold I reckon*' (B1). Others described missing out on planned leisure travel altogether due to stopping work earlier than planned:

> I was planning to retire a little bit earlier than normal retirement age and go on holidays. Not now. (K1)

In contrast, one patient prioritised leisure travel due to the serious nature of their illness; *'I'm using all my savings to travel … I don't want to regret that if anything should happen within the next two or three months, the things I want to do and I haven't done'* (P2).

More than half of the participants accessed Government welfare or utilised their income protection insurance (commonly offered through retirement plans). Income protection insurance pays a benefit when the insurance holder cannot work due to illness or injury. The payment is often lower than a person's actual income and for a defined period (Australian Government, n.d.). *'I've got income protection … that I've had since I was a teenager, but they only pay 75 per cent of your wages, which is pretty* pathetic' (L1). The effects of AML sometimes exceeded the time the insurance was payable, '*I have my claim against my superannuation, which is paying me my loss of income, but it's finishing*' (K1).

Accessing Government welfare was frequently described as 'difficult' or 'a nightmare' (L1) due to the paperwork and proof of illness or financial hardship patients had to supply.

Financial strain combined with pride was an extra barrier for some patients. These patients felt the need to add self-justification to access Government welfare;

> I applied for a disability pension. I see no reason not to. I did do quite a bit [of paid work] so I was no longer able to do that. So my argument was, well, yep, I could no longer get an income. (D1)

In contrast, another participant couldn't justify accessing Government support even though they were likely eligible 'A *carer's pension or a disability pension, no, I didn't want that at all. No, I don't like using things*' (M1). This perhaps demonstrates the importance of Government support systems to be structured in a way to allow applicants dignity through the process of application and receipt of services.

Participants explained they were forced to utilise other financial resources to accommodate their changed financial position. For example, using savings or early access to retirement funds; *'I mean we [have] both got superannuation (retirement funds) that we've … had to call on'*(D1). Another patient explained that their *'savings [are] all gone. I reckon about $1,000 out-of-pocket every week'* (V1).

The financial consequences of illness and the inability to work represented a financial burden sequelae where some participants described severe financial distress such as accumulating debt. Concerning their day-to-day expenses, one participant said, *'we are surviving off credit card'* and *'our credit card is up to $25,000'* (L1). This patient went on to describe the resulting worry - *'Financially we are completely screwed. I'm getting really concerned about that because we are racking up a fair bit of debt to be perfectly honest'* (L1).

The consequences of financial strain from an AML diagnosis described by the participants were related to items 6, 7, 8, 11 and 12 in the COST instrument (Table 4).

3.4 | Theme 4: Concerns about the future and future familial financial burden

Patients reflected on how their AML experience had affected them financially, *'I'm a different person. Definitely. Financially more cautious*' (B1). A common thread was worry about their family's financial future *'it's only the family, I still worry about…. Because of [a lack of] money'* (C1) and this, in turn, refocused financial priorities. One participant explained, *'I'm not as risky in business. I've set up the family with more money and haven't put it out to risk losing it'* (B1).

Financial planning was used as a mechanism to secure their financial future *'we've been seeing the financial advisor with looking to retire*' (C1), and found this avenue to alleviate financial stress *'[I] consulted a tax agent and then he told [me], "There are a lot of options". So that helped me. That helped me, so my stress level came a little down*' (P1). In contrast, not everyone found consulting a financial expert helpful; *'[I] contacted a financial company, but what they told didn't help me at all*' (P2).

To some, the prospect of running out of money due to illness or the inability to work was inevitable. One participant explained that having a stepped out plan is helpful for them; '[I am] *always think[ing] what should I do next month when I run out of funds… what is my next step, what is my worst scenario where I'm totally broke'?* (K1). Another said, *'I'm worrying about money and the future all the time'* (L1). A different philosophy was that *'money does concern you when you haven't got it, you know, just got to get on with the life the way it comes. You've got to just take it on the chin. Be strong about it, strong-minded'* (V1).

This theme was mapped back to the COST instrument item 3 as participants discussed worry and making financial changes to accommodate their future (Table 4). Item 1 was also relevant for this theme. Of note is that the wording of item 1 may not resonate with Australian patients, as their treatment and hospitalisation costs are covered mainly by publically funded healthcare.

4 | DISCUSSION

This study aimed to qualitatively explore the perceived financial impact of the diagnosis and treatment of AML. This study is one of the first to qualitatively demonstrate a range of financial impacts that have burdensome effects on the lives of people with AML. These include costs attributable to AML, having to accommodate work due to diagnosis and treatment, adapting their lives due to the financial consequences and concerns about the future and familial financial burden.

Transport costs (e.g. parking, fuel and accommodation) are reported as significant non-medical out-of-pocket expenses for cancer patients in Canada (Longo et al., 2021), Japan (Isshiki, 2014) and Australia (Newton et al., 2018). In this study, paying for hospital parking featured prominently in participants' narratives and has previously been investigated in Ireland and the United States and through Government policy in Australia (Balfe et al., 2017; Cancer Council Victoria, 2015; Lee et al., 2020; Newton et al., 2018; Premier of Victoria, 2020). Transport costs are a demonstrated barrier for patients receiving timely and optimal cancer care (Newton et al., 2018; Resio et al., 2018). In the complexity of cancer care, alleviating the patient burden of parking costs should be straightforward with support from health services and guided by Government policy (Balfe et al., 2017; Cancer Council Victoria, 2015; Premier of Victoria, 2020). As financial distress is linked with poorer quality of life, a higher symptom burden and lower compliance to medications, there should be a driving impetus to reduce this burden for patients (Lathan et al., 2016; Neugut et al., 2011; Ramsey et al., 2016; Zafar et al., 2013).

As a consequence of their new financial strain, participants took steps to manage their expenditure, such as reducing household expenditure, drawing on savings or using credit cards for purchases. Some strategies inevitably have far-reaching consequences for an

individual's financial security. The methods employed by our participants were similar to those described by Timmons et al. in Ireland and increasing in severity, presumably as the economic impact worsened (Timmons et al., 2013). International research shows that bankruptcy is an increased risk factor for mortality (Ramsey et al., 2013), and while none of our participants reported bankruptcy, some admitted to significant debt accumulation. This level of financial impact may still negatively impact overall survival rates (Ramsey et al., 2016), further supported by preliminary research undertaken in acute leukaemia, which found an association between decreased survival and worsening financial distress (Knight et al., 2018).

Most of our participants were working-age and many people in this age-group who develop cancer will suffer some loss of income (Zajacova et al., 2015). Therefore, unsurprisingly our participants described the current and future effects of underemployment or forced early retirement (Ramsey et al., 2013). This finding is consistent with cross-sectional data in other cancers and the association of financial toxicity and employment status, demonstrating the importance of employment for practical financial reasons (Kodama et al., 2012; Pearce et al., 2019; Shankaran et al., 2012). Additionally, forced early retirement and underemployment may have concurrent effects on cancer patients' psychosocial functioning and quality of life (Hamerschlak et al., 2014).

Some patients reported the process of accessing Government financial welfare as exceedingly bureaucratic, whilst others justified their application for welfare or described pride acting as a barrier to access. Moffat et al. found in Ireland that presumptive welfare advice in conjunction with collaboration with health and social professionals can help alleviate financial stress for patients (Moffatt et al., 2010). Long wait lists, large workloads and limited capacity of social workers in the health system may be contributing to access barriers for the patients in our study (Victorian Allied Health Workforce Research Program, 2018). Prioritising access to social workers in our health systems in conjunction with streamlined Government processes may help alleviate this barrier.

Mapping our qualitatively derived themes to the COST instrument was novel for an Australian cancer cohort. The development of the COST instrument involved reviewing the literature, interviewing cancer patients and expert medical input. It is possible that in developing our interview guide, the literature we reviewed may have informed the development of the COST instrument, which may explain the alignment of the themes to the COST instrument.

However, the instrument was developed in the United States with a user-pays model of health care (Tikkanen et al., n.d.) compared with Australia, which adopts a socially funded health care system (Dixit & Sambasivan, 2018). Intrinsically, the financial concerns of Americans may differ from that of Australians, and the circumstances of Australian patients may not be fully captured by the questions asked in the COST instrument. Even though we successfully mapped all themes to the COST items, the changes described by patients to activities of daily living (e.g. having to pay for a gardening service) were not well captured by the COST instrument. This may reflect the rationalisation of questions in PROM development, which balances instrument length and issue importance (de Souza et al., 2014). However, these findings may also signify the importance of exploring patient concerns by subgroups of populations before embarking on large scale studies using PROMs. The COST instrument likely contains relevant items to the Australian AML population, and the triangulation of our findings adds robustness and face validity to the identified themes.

5 | STRENGTHS AND LIMITATIONS

This study contains many strengths. It is one of the first to explore the financial impact of people affected by AML. The study design was purposely exploratory, and the inclusion criteria allowed for the recruitment of a hospital-based sample of participants, which provided a breadth of patient experiences for analysis. In a disease with a high remission rate and mortality rate, we could still reach data saturation in the present study. This qualitative narrative colours the commonly reported quantitative findings with everyday patient experiences and the lived effect on their lives, with the capacity to translate these findings into practical discussions between a clinician and a patient.

It is also important to acknowledge the research limitations. Participants were interviewed at various stages of their remission, which likely enriched the findings. However, interviewing people at consistent time points may have added insights into how patient's financial experiences vary over time. We also acknowledge some selection bias as participants were identified by their clinical team. Those agreeing to be interviewed may have had different experiences compared with non-participants. The perceived financial impact of AML found in this study is reflective of the individuals interviewed and not necessarily generalisable to all people in remission from AML.

Some of the core findings, such as out-of-pocket costs related to parking and the unwillingness of patients to seek Government financial assistance due to their sense of pride, require confirmatory research and further exploration. Only then can we begin to understand the contribution of these factors of financial burden and identify those most at risk and design systems to alleviate financial strain.

6 | CONCLUSION

Our study demonstrates that people with AML perceive a financial impact mainly through out-of-pocket expenses attributable to their AML and under-or-unemployment, even when cared for in a publically funded health care system. Patients employ a range of strategies to deal with their new financial situation. Still, opportunities exist for health services to alleviate the financial burden through reducing or abolishing parking fees for oncology patients and their families. Doing this will reduce the need for patients to request this financial support which may be impeded by a sense of pride. Further opportunities may exist in ensuring that patients have adequate

access to social workers to facilitate access to Government welfare programs where eligible.

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CONFLICT OF INTEREST

CP declares that she has no conflict of interest. DB declares that she no conflict of interest. AW declares that he has no conflict of interest. EZ declares that she has no conflict of interest. DL declares that he has no conflict of interest. DA declares that she has no conflict of interest.

AUTHORS' CONTRIBUTIONS

Catriona Parker: conceptualisation, methodology, investigation, data curation, writing—original draft, writing—review and editing, visualisation and project administration. Danielle Berkovic: data curation, visualisation and writing—review and editing. Andrew Wei: conceptualisation, investigation and writing—review and editing. Ella Zomer: writing—review and editing, visualisation and supervision. Danny Liew: writing—review and editing, supervision and funding acquisition. Darshini Ayton: conceptualisation, methodology, investigation, data curation, writing—review and editing, visualisation and supervision. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Chapter 7: Quantitative results - Cross-sectional study describing the financial burden of people with malignant haematological conditions

In this Chapter I present the findings from a cross-sectional study which measured the financial burden of those with haematological malignancies. The paper included in this Chapter quantifies the financial burden suffered by those with these diseases, as well as describes the key out-of-expense categories, employment changes and financial coping mechanisms utilised by individuals. The results suggest which patients with haematological malignancies may be most at risk of financial burden and addresses the second objective of this research which was to explore the financial burden of AML from the patient perspective.

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Do patients with haematological malignancies suffer financial burden? A cross-sectional study of patients seeking care through a publicly funded healthcare system

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ABSTRACT

Background: It is increasingly appreciated that some patients with cancer will experience financial burden due to their disease but little is known specifically about patients with haematological malignancies. Therefore, this study aimed to measure financial toxicity experienced by patients with haematological malignancies in the context of a publicly funded health care system.

Method: All current patients diagnosed with leukaemia, lymphoma or multiple myeloma, from two major metropolitan health services in Melbourne, Australia were invited to complete a survey capturing; patient demographics, employment status, income sources, financial coping and insurances, OOP expenses and self-reported financial toxicity using a validated measure.

Results: Of the 240 people approached, 113 (47 %) participated and most had leukaemia (62 %). Forty-seven participants (42 %) experienced some degree of financial toxicity using the Comprehensive Score for financial toxicity (COST) instrument. On multivariate linear regression, older age (>65 years, $p = 0.007$), higher monthly income (>$8000, $p = 0.008$), not having and being forced into unemployment or early retirement ($p < 0.001$) remained significantly associated with less financial toxicity.

Conclusion: Financial toxicity is present in Australian haematology patients and those at higher risk may be patients of working age, those without private health insurance and patients that have been forced to retire early or have become unemployed due to their diagnosis.

1. Background

Many cancer patients suffer financial implications resulting from their condition [1–5]. Cancer patients tend to experience financial stress from direct healthcare-related expenses (for example, the cost of medicines) and indirect healthcare expenses (for example, travel costs to seek care, loss of income, *etc.*) [6]. According to the National Cancer Institute there are a myriad of terms used interchangeably to describe money problems related to care [7]. The term' financial toxicity' is commonly seen in the oncology literature, and encompasses the direct and indirect financial stress associated with cancer [8–10]. Measurement of financial toxicity is usually self-reported from the patient through the use of Likert scales to capture subjective financial distress or *via* reporting of the actual expenses incurred. In the literature, single items from quality of life tools asking the patient to rate their level of financial distress have been used, and increasingly validated questionnaires such as the Comprehensive Score for financial toxicity (COST) are frequently utilised [11,12]. Other studies collect direct out-of-pocket costs, with or without income data which can be helpful for inter-patient and inter-study comparison [11,13,14].

Much of the literature describing financial toxicity has arisen from the United States, which adopts a user-pays healthcare system [6]. Hence these findings may not apply to health systems adopting a publicly funded approach, primarily due to the inherent differences in the

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costs passed onto the patient for their care and differences in social welfare systems providing income safety nets for citizens.

Australians benefit from publicly-funded healthcare, where the Government subsidises the direct costs of cancer, and there is said to be little, if any, co-payment required of patients [15] - this is similar to many other Western countries such as; Canada, Japan, the United Kingdom, and numerous countries throughout Europe [16]. Some Australian patients choose to utilise a parallel private hospital system mainly funded by private health insurance, albeit with some government subsidy [17]. Some cancer types, particularly those of lower incidence and requiring complex and specialised care like haematological malignancies, have centralised medical care within tertiary public health services (Government subsided) [18]. Regardless, patients still meet out-of-pocket (OOP) expenses. Indeed, an estimate based on linked data found that co-payments for haematological malignancies in Australia were higher than any other cancer type [19]. Possibly factors contributing to this include the frequent need for blood and platelet transfusion support, the high prevalence of fatigue and life-threatening infectious complications limiting capacity to work and long periods of hospitalization to recover from intensive chemotherapy, as well as stem cell transplantation, resulting in prolonged periods of absenteeism and physical incapacity.

Patient-reported data suggest that Australian cancer patients incur travel-related costs, supportive care expenses and lost income even when treated in the public system [20–22]. These findings are supported by a recent systematic review of financial toxicity in publicly funded healthcare systems [14]. However, patients suffering haematological malignancies remain under-represented in financial toxicity research in user-pays and publicly funded healthcare systems [6,14,23,24]. The contemporary literature concerning financial toxicity has tended to focus on mixed cancer cohorts with solid tumours, which provides an overview of the patient impact of financial toxicity [6,14,23,24]. Yet there may be nuances within particular tumour groups due to various factors, such as the disease burden, the disease or treatment trajectory, primary therapies and treatment modalities used. These variables and their associated costs will differ among oncology sub-specialties, and consequently, so will the financial burden.

Such diagnosis-specific financial burden information will benefit clinicians usually working within sub-specialities to understand whether their patients are more likely to experience financial toxicity, which patients are most at risk and the possible source of hardship within their patient cohort. Such knowledge will help clinicians take steps to minimise the adverse effects of financial hardship experienced by patients.

In the present study, we aimed to measure the financial toxicity experienced by patients with haematological malignancies and characterise the most common OOP expenses.

2. Materials and methods

2.1. Eligibility and data collection

Patients were recruited from two metropolitan tertiary health services based in Melbourne, Australia, that are publicly funded. Patients were eligible if they were ≥18 years of age, lived in Australia, and were diagnosed with leukaemia, lymphoma, or multiple myeloma. They were required to read and write in English.

Invitation letters, patient information, an opt-out form, the survey (an option of paper based or online) and a reply-paid envelope were posted to eligible participants. Participants could complete the survey (implied consent) or opt-out indicating they wished not to participate. Participants were phoned to clarify participation intent if there was no response within eight weeks of the initial mail-out. Where data was returned by post it was manually entered into Qualtrics XM (Provo, Utah, USA), which also provided a platform for patients choosing to respond to the survey online. Data was collected between April 2020 and February 2021.

Human Research Ethics Committee approval was granted under project number 58355.

2.2. Survey development

The data collection instrument was informed by the current literature and qualitative research conducted at one of the sites.

We collected data on diagnosis, prior haematopoietic stem cell transplant, patient demographics, postal code, and time since diagnosis. Data about current employment, monthly income and other income streams besides employment were collected. For OOP costs, participants were asked to recall the last month and provide approximate expenditure in predetermined categories.

Financial coping or behaviour was also captured; participants were asked about their strategies to access or save money, including delaying or missing medication or appointments. In addition to the prescribed categories in this section participants could comment using free text. Data about the accumulation of debt since diagnosis due to OOP costs or lost income was also collected. Finally, we included a patient-reported outcome Comprehensive Score for financial toxicity (COST) [1], validated for use in Australian cancer populations [5].

The survey was piloted with peers and a former patient for comprehension and flow. The feedback was incorporated into the final survey design.

2.3. Financial toxicity outcome measure

The COST tool is a 12-item patient-reported outcome measure that includes questions on satisfaction with finances and income, expenses and the ability to meet them, and level of control concerning finances and cancer care [1]. Eleven of the 12 items are included in the scoring, with the twelfth item included as a single summary measure of financial burden. Additionally, the scoring algorithm allows for missing items to be addressed in the scoring. Scores range between 0−44, with a lower COST score indicating more financial burden [1].

2.4. COVID-19 impact

The impact of COVID-19 in Australia caused shutdowns of industries and workplaces and the reorientation of health services to deliver face-to-face appointments *via* telehealth where possible. While the planned study went ahead, questions were included to determine whether participants responses were affected by the evolving COVID-19 restrictions. Additionally, the COVID-19 pandemic resulted in the reorientation of health services towards the pandemic effort, and we were forced to be pragmatic about our approach and limit the number of health services (and therefore patients) involved. We decided to approach all eligible people and obtain as many responses as possible in the study's time frame.

2.5. Analyses

Participant demographic data were analysed using descriptive statistics. Non-parametric testing was employed for univariable analysis, and linear regression was used to explore factors associated with the COST score. Variables with a significance of $p < .05$ on univariable analysis were included in the multivariable model. We also included variables that were determined *a priori* based on the literature. Due to their low frequency, other insurances (life insurance, income protection insurance, trauma or critical illness insurance, and total and permanent disability insurance) were excluded from the multivariable analysis. Spearman's correlation assessed the association between OOP expenses and the COST score, and the analyses were undertaken using the statistical software, STATA (StataCorp, College Station, USA). Monetary values are expressed in Australian Dollars.

3. Results

Of the 240 people approached, 113 (47 %) participated. Participant demographics and their level of financial burden are shown in Table 1. The most frequent age group, were participants aged between 40 and 65 years (48 %), 53 % were male, and 35 % travelled to the metropolitan centre for specialist care. Leukaemia made up 62 % of the cohort, 27 % had a multiple myeloma diagnosis, and 11 % were people with lymphoma.

3.1. Financial burden

In this cohort, the mean COST score was 27 (±SD11.83) and a median score of 28 (range 0−44).

Table 1 shows the factors that were significantly associated with financial toxicity based on univariate analyses. When multivariate linear regression was applied, older age (>65 years, $p = 0.007$), higher income (>$8000, $p = 0.008$) and being forced into unemployment or early retirement ($p < 0.001$) remained significant (Table 2). Additionally, not holding private health insurance was independently associated with worse COST scores (higher financial burden) even though patients could not have been required to access this insurance as care was provided through public health services. When applying the grading criteria [25, 26], 47 (42 %) participants experienced some degree of financial toxicity (Table 3).

3.2. Employment and household income sources

Of our sample, 42 people (37 %) were employed in some capacity, and an additional 29 (26 %) indicated they were unemployed or forced to retire due to their diagnosis. Twenty-two of those (76 %) who were forced into unemployment or early retirement suffered frank unemployment due to their illness −COVID contributed to unemployment for another three people. The pandemic reduced work hours (from full-time to part-time or casual employment) for five people (12 % of the working sample). The free text responses indicated COVID-related employment changes mainly were due to being immunocompromised and the type of work undertaken (*e.g.* general public-facing duties). Twenty-five participants (22 %) indicated they suffered personal income loss in the past month.

Mindful that participants were able to select multiple household income sources, employment was the most frequent income source (51 %), followed by pensions, entitlements or Government support (34 %), retirement funds (30 %) and investments in property or shares (28 %). Approximately 9% of households were accessing an income stream from either income protection insurance, trauma or critical illness insurance or total and permanent and disability insurance cover. However, one-third of the cohort (37 people) admitted to having one of these insurances, yet 12 participants (33 % of the people holding one of these insurances) had not made a claim.

Eighteen people (16 %) answered 'often' or 'almost' to the question regarding how often they were concerned that their income sources might be affected by COVID-19.

3.3. Financial coping

Most respondents (71 %) indicated that they had used other means to cope financially. Of the cohort, 53 (47 %) reported using some or all of their savings; 18 (16 %) borrowed money from friends or family, and 14 (12 %) participants had utilised credit cards to cover expenses. Additionally, two people had obtained a personal loan from a banking institution to cover their financial shortfall. Since their diagnosis, 21 participants (19 %) had accumulated debt ranging from $350 to $40,000 (median $5000, IQR $11,875).

More than half of the participants (56 %) responded that they could not access any Government fiscal payments made available due to the

Table 1
Patient demographics and COST scores.

Variable	N (%) = 113	COST score mean (±SD)	COST median	Min-Max	Univariate p-value[a]
Gender					
Female	53 (47)	27.19 (±11.93)	28	0−44	.865
Male	60 (53)	26.95 (±11.85)	27.5	0−44	
Age (years)					≤65 years *vs* >65 years
18−39	15 (13)	20.40 (±10.84)	20	0−41	<.001*
40−65	54 (48)	23.80 (±12.51)	24	0−44	
>65	44 (39)	33.34 (±8.03)	36.4	10−44	
Diagnosis category					
Leukaemia	70 (62)	28.07 (±11.48)	30	0−44	.124
Lymphoma	13 (11)	20.15 (±13.41)	20	0−38	
Multiple Myeloma	30 (27)	27.70 (±11.36)	29	4−44	
Length of time since diagnosis					
≤1 year	26 (23)	30.62 (±11.59)	32	6−44	.058
>1 year	87 (77)	26.00 (±11.77)	27	0−44	
Previous HSCT					
Yes	26 (23)	28.15 (±10.20)	27	8−44	.069
No	84 (77)	26.74 (±12.32)	30	0−44	
Private Health Insurance					
Yes	55 (49)	31.60 (±10.97)	35	0−44	<.001
No	58 (51)	22.76 (±11.08)	23	0−42	
Financial dependents					None *vs* 1 or more dependents
0	71	29.04 (±10.66)	30	0−44	.030*
1−2	30	23.83 (±13.40)	21	4−44	
3−4	10	23.10 (±13.84)	23.5	0−43	
>4	2	25.00 (±7.07)	25	20−30	
Employment status					Unemployed or retired due to diagnosis *vs* did not retire or become unemployed
Full time	32 (28)	27.19 (±10.87)	28	4−44	.015*
Part time	10 (9)	29.10 (±11.25)	29	10−44	
Casual work	6 (5)	22.33 (±8.71)	23	9−36	
Unemployed and was before diagnosis	3 (3)	17.00 (±20.66)	11	0−40	
Unemployed because of diagnosis	22 (20)	15.05 (±9.21)	16	0−37	
Retired and was before diagnosis	31 (27)	35.94 (±5.93)	38	25−44	

(*continued on next page*)

Table 1 (*continued*)

Variable	N (%) = 113	COST score mean (±SD)	COST median	Min-Max	Univariate p-value[a]
Retired and retired because of my diagnosis	7 (6)	30.71 (±7.99)	30	17–42	
I don't work for payment	2 (2)	26.00 (±15.56)	26	15–37	
Residential rurality					0.074
Within metropolitan centre	74 (65)	28.27 (±12.21)	30.5	0–44	
Outside metropolitan centre	39 (35)	24.77 (±10.87)	25	0–44	
Current household monthly income (last month)					<$2000 *vs* all else
$<2000	37 (33)	19.89 (±12.31)	19	0–43	<.001*
$2000-$4000	32 (28)	30.06 (±10.67)	31.5	5–44	
$4000-$6000	28 (25)	28.79 (±9.81)	29	4–44	
$6000-$8000	8 (7)	31.63 (±7.93)	35	17–41	
>$8000	8 (7)	37.63 (±6.91)	38.5	22–44	
Other insurances[b]					Insurance[#] vs none
Life insurance	11 (10)	35.64 (±7.16)	38	22–44	.002*
Income Protection insurance	6 (5)	10.33 (±8.33)	10	0–22	
Trauma or critical illness insurance	1 (1)	20.00 (±0)	20	20	
Total and permanent disability insurance	3 (3)	27.34 (±11.36)	26	6–37	
None	92 (81)	27.06 (±11.84)	28	0–44	

HSCT: haematopoietic stem cell transplant.

[a] Kruskall Wallis test were used for ≥2 groups and checked with Mann Whitney U for 2 groups only.

[b] **Life insurance** pays a lump sum upon death, **Income protection insurance** pays part of lost income if the policy holder is unable to work because of illness or injury; **Trauma and critical illness insurance** pays a lump sum if the policy holder suffers a critical illness or serious injury, or; **Total and permanent disability insurance** pays a lump sum if the policy holder becomes totally and permanently disabled because of illness or injury [27].

[*] Significance level of $p < .05$.

COVID-19 pandemic, with a further 17 % unsure of their eligibility status for these payments.

Of concern, delaying or missing medication was a method of saving money by six participants (5%), and a further 10 participants (9%) had delayed or missed medical appointments. Trouble paying a mortgage or utility (phone, gas or electricity) bill was reported by 12 participants (11 %).

Free-text responses yielded other strategies to save money by the cohort: budgeting, eating out less, fewer purchases, staying home more and utilising charity food boxes.

Table 2
Patient factors associated with COST on multivariate analysis.

Variable	Coefficient	Standard error	95 % confidence interval	P value
Age *(vs 18–39)*				
40–65	3.42	2.63	−1.81 - 8.65	.197
>65	9.11	3.19	2.79 - 15.44	.005*
Gender *(vs male)*				
Female	−0.10	1.80	−3.67 - 3.48	.958
Financial dependents *(vs any)*				
None	0.07	2.08	−4.05 - 4.19	.974
Residential rurality *(vs metropolitan area)*				
Outside metropolitan area	0.20	1.89	−3.55 - 3.94	.918
Time since diagnosis *(vs < 1 year)*				
1–2 years	−2.95	2.29	−7.50 - 1.60	.201
>2 years	−3.84	2.40	−8.60 - 0.92	.112
Employment status *(vs working for pay - unchanged status)*				
Unemployed or retired due to diagnosis	−9.47	2.44	−14.31 - -4.62	<.001*
Unemployed or retired before diagnosis (unchanged status)	2.91	2.50	−2.05 - 7.88	.247
Current household monthly income in the last month *(vs $ < 2000)*				
$2000-$4000	2.22	2.66	−3.07 - 7.51	.406
$4000-$6000	3.61	2.81	−1.96 - 9.20	.201
$6000-$8000	6.20	3.50	−0.75 - 13.15	.080
>$8000	8.25	3.04	2.21 - 14.29	.008*
Private health insurance *(vs having no insurance)*				
No insurance	−5.19	1.95	−9.06 - -1.31	.009*

[*] Significance level of $p < .05$.

Table 3
COST financial toxicity grade by disease category.

	Lowest financial burden		Highest financial burden	
Disease category	Grade 0 (none) COST ≥26	Grade 1 COST = 14–25	Grade 2 COST = 1–13	Grade 3 COST = 0
	n (% of the disease category)			
Leukaemia	43 (61)	18 (26)	7 (10)	2 (3)
Lymphoma	5 (39)	3 (23)	4 (31)	1 (7)
Multiple Myeloma	18 (60)	10 (33)	2 (7)	–
TOTAL people	66	31	13	3

3.4. Out-of-pocket (OOP) expenditure

The reported median total OOP expenditure was $100 (AUD) in the past month (range $0-$1,650, mean $224 ± SD $294.31). Table 4 shows OOP cost categories and their respective expenditures. The most common OOP expense was prescription medication (65 %), followed by travel costs (56 %) and non-prescription medication (31 %). Overall, the cohort spent the most on prescription medication ($8291), travel costs related to care ($6700) and allied health expenses ($3032).

OOP expenses and income were used to calculate a ratio to allow for financial outgoings and incoming money. Using Spearman's correlation test, the association between OOP expenses and income ratio and the COST score was significant but demonstrated a weak correlation [28,29] (ρ= -0.3026, p = .001).

4. Discussion

The present study aimed to measure the financial toxicity

Table 4
Cost categories and expenditure in the past month.

Expenditure category	Example	Participants reporting cost category, (% cohort)	Total cohort expenditure	Median per person expenditure (IQR)
Prescription medication	*Any medication prescribed by a doctor, e.g. amoxicillin*	74 (65)	$8 291	$58 (116)
Non-prescription medication	*Any medication available over the counter without prescription e.g. paracetamol*	35 (31)	$2 007	$25 ($80)
Doctor's fees	*Any payable fee not reimbursed*	14 (13)	$1 510	$85 ($100)
Allied health	*Physiotherapy, psychology, diagnostic tests etc.*	19 (17)	$3 032	$100 ($150)
Home-aid devices	*Purchases for home-related to mobility and comfort e.g. grab rails*	3 (3)	$1 100	$250 ($375)
Complementary and Alternative Medicines	*Vitamins, supplements etc. that are not prescribed by a medical professional*	22 (19)	$1 670	$50 ($65)
Well-being activities	*Gym memberships, yoga etc.*	11 (10)	$990	$80 ($90)
Travel costs related to care	*Petrol, parking fees, public transport etc.*	63 (56)	$6 700	$50 ($100)

experienced by patients with haematological malignancies treated in Australia, and therefore within the environment of publicly funded healthcare. We also sought to measure and characterise the most common OOP expenses. Forty-two per cent of our cohort experienced some level of financial toxicity (grade 1, 2 or 3). This estimate is higher than was found in a recent systematic review which examined financial burden in countries with publicly funded healthcare and found between 7 and 39 % of patients experienced financial burden, depending on the country and cancer type [14]. The significant heterogeneity between studies and various methods for measuring financial toxicity has been previously demonstrated [6,14,23,24]; any comparisons drawn in this discussion must be interpreted with caution.

It would be expected that patients in a user-pays healthcare system such as the United States would experience higher levels of financial hardship. It is estimated that between 47 % and 67 % of American haematology patients experience some level of financial hardship after haematopoietic stem cell transplant [30,31]. Arguably, these patients may have exacerbated financial problems as haematopoietic stem cell transplant is one of the most costly medical interventions for this cohort [32]. A cross-sectional study examining financial toxicity in 100 people with multiple myeloma found that 79 % of them exhibited some type of financial toxicity [33]. Knight et al. also found that 58 % of American acute leukaemia patients surveyed exhibited financial hardship [34] and a further investigation into patients with myeloproliferative disease found 39 % of those patients exhibited severe financial toxicity [3]. In comparison, 14 % of our patients exhibited high levels of financial toxicity (COST score <14). Given the differences in health systems, the variation in the prevalence of financial toxicity is not unexpected, but 14 % of people exhibiting this level of financial distress in a publicly funded environment is of concern and may be explained by OOP expenses or lost income [6].

OOP expenses constitute a significant contributor to financial toxicity and health-related debt, and even bankruptcy [35,36]. Most direct healthcare and hospital-related expenses in Australia are covered entirely or heavily subsidised (75 % of the fee) by the Medicare Benefits Scheme (MBS) [37]. Additionally, the Pharmaceutical Benefits Scheme (PBS) allows access to a wide range of subsidised pharmaceuticals [37]. Therefore, it is intuitive that OOP expenses are small for Australian patients. Nevertheless, OOP costs for Australian cancer patients have been previously described [21,22,38,39] and are concurrent with our findings that many of the OOP expenses borne by Australian patients were from medications, consultation fees and travel costs. However, the OOP expenses described by these studies seem to markedly vary by geography, particularly rurality. For example, two studies concentrating on OOP expenses for cancer patients treated at a regional centre in Queensland [40] and one undertaken in Western Australia [21] found much higher travel expenses than the present study. A Canadian study also found that those living further away from treatment centres exhibited higher OOP expenses [41]. In our study, undertaken in the state of Victoria, rurality was not associated with the COST score. This finding is consistent with another Victorian study by McLean et al. [4]. The rurality of Queensland and Western Australia may explain these differences when compared with Victoria, which has several regional centres able to provide cancer care.

Additionally, OOP expenses tend to vary by cancer type. An investigation into Australian men with prostate cancer found their median OOP expenses to be $9205 (±$14,567) in the previous three months [38]. A large study surveying 1919 Australian women with breast cancer found the median OOP costs were approximately $4800 in the first five years after diagnosis. While it is helpful to describe and characterise the OOP expenses borne by patients, there may be additional value to view these expenses in the context of available income or perceived financial burden. For example, we found only a weak association between OOP expenses and COST score ($\rho = -0.3026$, $p = .001$), indicating that the incurred expenses are only a small part of the perceived financial burden.

Of significance is the contribution of work participation to financial satisfaction [42]. We found that 22 % of participants suffered an income loss in the past month and that those participants who were forced to retire or become unemployed due to their diagnosis were more likely to suffer financial toxicity. This is perhaps surprising as Australia has strong workplace leave provisions of four weeks annual leave and ten days sick leave per year (that does not expire) [43]. This provision is in addition to a well-developed social welfare system designed to provide payments for those unable to work due to unemployment, illness or disability [44]. Additionally, one-third of people in our sample who had income protection insurance, trauma or critical illness insurance had not applied to claim on these policies when it is likely they would be eligible to receive payment. Our findings may indicate that individuals do not know their entitlements or there are challenges in accessing these safety nets, and further research should look to investigate this further.

From a clinical perspective, our findings offer several insights. Clinicians can be cognisant of haematology patients potentially at higher risk of financial toxicity in Australia by reviewing the patient chart for red flags; patients of working age, those without private health insurance and patients that have been forced to retire early or have become unemployed due to their diagnosis should be of concern. Clinicians should also be mindful that patients who travel long distances to access care are at higher risk for financial toxicity. There are practical steps clinicians can take to help their patients. Look to reduce OOP expenses by scheduling diagnostic tests and appointments on the same day to reduce travel-related costs. Patients should be informed of schemes designed to provide some reimbursement of excess travel-related costs [45] and the discounted parking available through hospitals [46]. High-risk patients and their families should be referred to social work and organisations such as Cancer Councils (or equivalent) to ensure they

can be assisted in accessing other safety-nets, government services and philanthropic assistance.

The present investigation exhibited many strengths; the study used a validated tool in the Australian cancer population to measure financial toxicity, encompassed a diverse sample across income groups, employment status and geography. However, our study is not without limitations. Patients were recruited from only two specialist health services, our sample size was relatively small and the data was collected during the COVID-19 pandemic. All the participants in this study were subject to various lockdown measures imposed by Governments in Australia in an attempt to quell the pandemic. Whilst we attempted to understand these factors they were difficult to disentangle from evolving social welfare schemes, payments and financial stimulus systems put in place during this time. It is likely that the out-of-pocket expenses reported for travel and parking is an underestimate given that health-services implemented tele-health provisions for patients not requiring clinical procedures and many health resources were re-orientated toward the pandemic effort.

These factors mean that only limited inference can be made from our findings and the results may not be broadly generalisable. Further quantitative investigation should seek to confirm the present findings.

However, of importance is that, this study represents the first investigation of financial toxicity in haematology patients in Australia, who represent a particularly vulnerable group of individuals due to the often intensive and lengthy treatments that markedly impact everyday life. We have identified the presence of financial toxicity in Australian haematology patients and characterised some of the contributing OOP expenses these patients incur. Further efforts are needed to unravel the complexity behind the observed financial burden to mitigate this burden by earlier intervention and to begin advocating meaningfully for patients.

Data availability

Data will be made available on request.

Funding

A PhD stipend for CP was provided through a Monash University Departmental Scholarship.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contribution

Catriona Parker: Conceptualisation, Methodology, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualisation and Project administration.

Darshini Ayton: Methodology, Data curation, Writing - Review & Editing, Visualisation, Supervision

Ella Zomer: Writing - Review & Editing, Visualisation, Supervision

Danny Liew: Writing - Review & Editing, Supervision, Funding acquisition

Catherine Vassili: Data curation, Investigation, Writing - Review & Editing

Chun Yew Fong: Investigation, Writing - Review & Editing

Andrew Wei: Conceptualisation, Investigation, Writing - Review & Editing

All authors read and approved the final manuscript.

Ethics approvals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was given multisite approval by the Alfred Health Human Research Ethics Committee (Project #58355).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Declaration of Competing Interest

The authors report no declarations of interest

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Chapter 8: Quantitative results - Estimating the productivity loss attributable to acute myeloid leukaemia

In this Chapter I present the results of a dynamic life-table modelling study. The study estimated the years of life lost and productivity-adjusted life years (PALYs) lost attributable to AML over the ten-year period from 2020 tot 2029 inclusive. A monetary value in terms of GDP was assigned to the PALYs lost to determine the economic impact of this productivity loss. The findings of this Chapter address objective 3 that sought to examine the societal financial burden attributable to AML. This estimate of economic societal impact is achieved through estimating lost productivity utilising a novel metric; the PALY, which is similar in concept to the QALY. The difference between the PALY and QALY is that the PALY adjusts years of life for productivity loss, rather than impaired health.

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original contributions

Estimating the Productivity Impact of Acute Myeloid Leukemia in Australia Between 2020 and 2029, Using a Novel Work Utility Measure: The Productivity-Adjusted Life Year (PALY)

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QUESTION ASKED: What is the estimated productivity loss attributable to acute myeloid leukemia (AML) on the working population (defined as those age 15-65 years) in Australia between 2020 and 2029?

SUMMARY ANSWER: It is estimated that AML will be responsible for 7,600 years of life lost and 7,337 productivity-adjusted life years lost, amounting to Australian dollars (AU$) 1.43 billion ($971 million in US dollars [USD]) in lost gross domestic product (GDP).

WHAT WE DID: Using published sources, dynamic life tables were constructed to model the Australian working population with and without AML between 2020 and 2029. The model was repeated assuming hypothetically that there were no new cases of AML over this period. The difference between the two model simulations represented the health and productivity impact of AML. Productivity was measured using productivity-adjusted life years (PALYs): a similar concept to quality-adjusted life years, yet adjusts for the productivity loss attributable to disease, rather than impaired health. The constructed model allowed different scenarios to be tested, for example, improvements in survival or return-to-work rates.

WHAT WE FOUND: Over 10 years, lost productivity because of AML in Australia was valued at AU$1.43 billion in lost GDP ($971 million USD). This equated to AU$309,725 ($210,411 USD) in lost GDP per person diagnosed with AML. Improving survival rates by 10% saved an additional 417 life years and 130 PALYs. Refining treatments may affect workforce participation and increasing workforce participation over these 10 years by 10% would provide an estimated 302 additional PALYs valued at AU$58.9 million. Combining both scenarios of improving survival and workforce participation by 10% saved 419 life years, 445 PALYs, and AU$86.6 million.

BIAS, CONFOUNDING FACTOR(S), REAL-LIFE IMPLICATIONS: Model inputs used available published data. There was little available evidence about workforce participation for people with a history of AML or survival data by age and sex more than 5 years postdiagnosis. The model was not able to account for changes in GDP attributable to health care spending because of AML or unpaid work that contributes to GDP. However, incorporation of PALYs into health care assessment may provide a novel approach in considering health care investment for governments and insurers, when assessing financial health resource allocation for treatments and devices. AML represents a significant societal economic burden. This study highlights that even a modest improvement in treatments to reduce morbidity and mortality may translate to a meaningful societal economic benefit.

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ASSOCIATED CONTENT

Data Supplement

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original contributions

Estimating the Productivity Impact of Acute Myeloid Leukemia in Australia Between 2020 and 2029, Using a Novel Work Utility Measure: The Productivity-Adjusted Life Year (PALY)

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abstract

PURPOSE Acute myeloid leukemia (AML) is a rare hematologic malignancy accounting for 0.8% of new cancer diagnoses in Australia. High mortality and morbidity affect work productivity through workforce dropout and premature death. This study sought to estimate the productivity loss attributable to AML in the Australian population over 10 years and to estimate the costs of this productivity loss. Productivity was measured using productivity-adjusted life years (PALYs), a similar concept to quality-adjusted life years, but adjusts for the productivity loss attributable to disease, rather than impaired health.

MATERIALS AND METHODS Dynamic life tables modeled the Australian working population (age 15-65 years) between 2020 and 2029. The model population had two cohorts: those with and without AML. Differences in life years, PALYs, and costs represented the health and productivity impact of AML. Secondary analyses evaluated the impact of different scenarios.

RESULTS Over the next 10 years, there will be 7,600 years of life lost and 7,337 PALYs lost because of AML, amounting to Australian dollars (AU$) 1.43 billion in lost gross domestic product ($971 million in US dollars). Secondary analyses highlight potential savings of approximately AU$52 million if survival rates were improved by 20% and almost AU$118 million in savings if the return-to-work rates increased by 20% on the current estimates.

CONCLUSION Our study demonstrates that even in low-incidence cancer, high mortality and morbidity translate to profound impacts on years of life, productivity, and the broader economy. Better treatment strategies are likely to result in significant economic gains. This highlights the value of investing in research for improved therapies.

INTRODUCTION

Acute myeloid leukemia (AML) is a relatively rare hematologic malignancy, accounting for only 1.1% of all new cancer diagnoses in the United States and approximately 3.7 cases per 100,000 Australians.[1,2] In the United States, approximately 19,940 people in 2020 will be diagnosed with AML, and 11,180 people will die of the disease.[1] There is an increasing incidence with age, and the estimates of 5-year survival are around 28.7% with individual survival estimates greatly influenced by age at onset and cytogenetics.[1-5]

In addition to mortality, the disease-burden and treatment-burden and morbidity have been shown to profoundly affect patients and impair their functioning into survivorship.[6-8]

Contemporary work on the economic impact of AML has primarily focused on treatment- and patient-related costs. The impact of AML on lost productivity has not been examined. The present study sought to estimate the societal economic impact in terms of productivity-adjusted life years (PALYs) for the Australian working-age population over the next 10 years. PALYs are similar in concept to quality-adjusted life years but adjust for productivity loss that is attributable to disease rather than impaired health.[9-13]

MATERIALS AND METHODS

Dynamic Life Table Models

We constructed dynamic life tables to simulate progression of the Australian population of working age (15-65 years) during the period from 2020 to 2029. The life tables were dynamic in that they accounted for people entering and leaving the age bracket over the 10 years, deaths, immigration and emigration, and

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incident AML. The model population comprised two cohorts: those without AML and those with AML (Data Supplement, online only).

Cumulative deaths for each cohort (those with and those without AML) were determined using published mortality rates[14,15] and are described in detail below.

PALYs lived were calculated by applying productivity indices and changes to labor force participation to the estimated years of life lived by each of the cohorts (Data Supplement). PALYs are conceptually similar to quality-adjusted life years but adjust years of life lived for impairment in productivity rather than impairment in quality of life.[9-13] Productivity indices represent the relative productivity of a person and range from zero (completely unproductive) to one (completely productive).[13] PALYs account for presenteeism (nonproductivity while at work), absenteeism (absence from employed work), and dropout from the labor force.

We estimated the years of life lived, PALYs, and costs between 2020 and 2029 for the Australian working-age population for both cohorts (those with and without AML). We then resimulated a hypothetical scenario where we assumed there would be no new cases of AML over this 10-year period. The difference between the two simulations (where the first simulation uses population-based AML data and the second uses a hypothetical scenario of zero AML incident cases) represented the impact of AML on years of life lived, PALYs, and economic costs. The difference between these scenarios is termed the base case, against which all other hypothetical scenarios and sensitivity analyses are compared.

Data Sources

A full description of the model inputs is found in the Data Supplement.

Incidence and mortality. For each year between 2020 and 2029, separate age and sex cohorts with AML were assembled, using age- and sex-specific AML incidence rates for Australia.[16] As historical incidence has remained relatively stable over time,[2] the same incidence rates were applied over the model time horizon. Mortality rates for the AML cohort were based on relative survival rates over the first 5 years.[16] Beyond 5 years, we assumed that the risk of death remained at 5 years after diagnosis from AML, assuming that the risk of death is no better or worse than someone at 5 years since diagnosis and because of relatively small sample sizes and large age brackets available in the published data.[17,18]

Similar to AML incidence, AML mortality data have historically remained relatively constant (and are unlikely to change without revolutionary novel treatments), and therefore, these mortality rates were applied across the model time horizon.

For the non-AML cohort, mortality rates were based on population mortality data.[14] To note, because of the low incidence and low number of AML-related deaths, all deaths in the non-AML cohort were assumed to be equivalent to the general population. All deaths were assumed to occur at the midpoint of each cycle (year).

Productivity indices. The literature regarding the impact of AML on productivity was lacking, with no information on absenteeism and presenteeism, and only limited data available regarding labor-force participation.[19-23] The studies we identified varied in sample size, countries or setting, and treatment received. However, the median ages (approximately early 50s) and estimates on return-to-work were relatively similar across two particular studies.[19,22] They estimated that 41% of people were working just after diagnosis and approximately 46% at 12 months after diagnosis.[19] This peaked at 52% at least 10 years after diagnosis.[22] We, therefore, assumed a workforce participation of 52%, irrespective of age, sex, or time since diagnosis. Thus, the productivity index used for the AML cohort was 0.52, and for the non-AML cohort, we assumed a productivity index of one.

Other data inputs. Other data including population, migration, birth, mortality, employment, and gross domestic product (GDP) were drawn from published sources, and a full description can be found in the Data Supplement.[15,24-28]

Outcomes

The study outcomes were years of life lost (YLL) and PALYs lost to AML, assessed over the 10-year period spanning from 2020 to 2029. These outcomes reflected differences in the modeled progress of the current Australian population (comprising people with and without AML) and the hypothetical situation in which future AML incidence was zero.

To ascribe an economic value to each PALY, we used the 2019 Australian GDP per hour worked.[28] Using labor force participation data and the mean hours worked by age and sex, we were able to estimate the proportional number of equivalent full-time (EFT) workers in each age group and sex category (assuming that full-time workers work 40 hours per week).[29] We, therefore, assumed that the economic value of a PALY was equivalent to the 2019 GDP per EFT, valued at Australian dollars (AU$) 194,955 ($132,442 in US dollars [USD]).

All costs and outcomes were discounted by 5% beyond the first year. Costs were expressed in terms of AU$ and converted to USD on the basis of the 2019 purchasing power parity rate of 1.472.[30]

Scenario and Sensitivity Analyses

Secondary analyses evaluated the impact of different scenarios on AML-related YLL and productivity loss (data sources and summary description are available in the Data Supplement). The first scenario improved the survival rates of AML by 5%, 10%, and 20%, regardless of age or sex. With increasing improvements in oncologic drug therapy, we sought to demonstrate ambitious yet achievable future targets. The second scenario considered increasing the return-

to-work rate of AML survivors by 5%, 10%, and 20%, which may be achieved via multidisciplinary interventions involving physical, psychoeducational, and/or vocational components.[31] The third scenario combined the two scenarios above for each incremental percentage improvement.

To explore the model assumptions and the sensitivity of the model, we added a temporal trend forecasted for GDP and altered the discount rate to 3%. The predicted future Australian GDP per hour worked was modeled using historical GDP values.[32] Therefore, the value of one PALY ranged from AU$197,257 in 2020 to AU$217,982 in 2029 ($134,006-$148,086 USD). We also added a scenario where the value of the PALY was calculated using the 2019 median wage per hour (AU$32.50).[33]

A scenario where the retirement age was increased to 70 years was added, given that many governments around the world are incrementally increasing the retirement age.[34]

Finally, we also recalculated the YLL and PALYs lost, using AML mortality data for 6-10 years, from the work of Luke et al who provided an estimate of relative survival at 10 years postdiagnosis.

Uncertainty in future AML incidence was not included in the analysis for two reasons: first, cancer is a reportable disease in Australia, and the historic rates are considered robust; second, there are no known preventive measures for AML, making it highly unlikely that the rates of disease are able to be markedly changed from preventive, diet, or lifestyle modification initiatives.

RESULTS

Simulating follow-up of the Australian population age 15 to 65 years over a ten-year period, we estimated that there will be approximately 4,617 new cases of AML between 2020 and 2029. Over this period (Table 1), there were 7,600 YLL and 7,337 PALYs lost to AML. This amounted to AU$1.43 billion in lost GDP ($971 million USD), equivalent to AU$309,725 ($210,411 USD) lost GDP per person diagnosed with AML (YLL and PALYs by sex and year are available in the Data Supplement, and undiscounted values are available in the Data Supplement).

The first set of scenario analyses centered on people: improvement in survival rates, workforce participation, and the effect of using estimated survival data at 10 years postdiagnosis (instead of keeping survival the same at 5 years for 6-10 years). Improving survival rates of AML by 20% across all ages and both sexes resulted in 2,550 years of life and 930 PALYs saved, equating to AU$51.6 million ($35 million USD) in GDP (Table 2). Even a modest improvement of 5% in survival demonstrated 207 years of life saved, and 64 PALYs saved, estimated to be worth AU$12.6 million ($8.6 million USD). Improving workforce participation by 20% across all ages and both sexes saved an additional 605 PALYs and AU$117.9 million ($80 million USD). When both 20% hypothetical scenarios were applied simultaneously, there was a saving of approximately AU$179.9 million ($122 million USD) over the next 10 years. The effect of using the estimated survival at 10 years postdiagnosis demonstrated an almost negligible effect on health and economic measures in comparison to the base case.

TABLE 1. Estimated YLL, PALYs Lost and Their Lost Economic Value, Attributable to AML in the Australian Population of Working Age (Age 15-65 years) Over the Next 10 Years (2020-2029)

Outcomes	Simulated Population[a]	Hypothetical Population[b]	YLL or PALYs Lost Because of AML and the Economic Value of PALYs
Years of life			
Men	69,165,838	69,169,904	4,066
Women	69,869,143	69,872,677	3,534
Total	139,034,981	139,042,581	7,600
PALY			
Men	50,189,545	50,194,176	4,631
Women	35,158,680	35,161,386	2,706
Total	85,348,225	85,355,562	7,337
Economic value of PALYs (AU$, billions)			
Men	$9,784.68	$9,785.58	$0.90
Women	$6,854.34	$6,854.87	$0.53
Total	$,16,639.02	$16,640.45	$1.43

NOTE. All costs and outcomes were subject to an annual discount rate of 5%. Costs are expressed in AU$.

Abbreviations: AML, acute myeloid leukemia; AU$, Australian dollars; PALYs, productivity-adjusted life years; YLL, years of life lost.

[a]Includes people with and without AML.

[b]The AML incidence is zero.

TABLE 2. Effect of Person-Centered Scenarios on Years of Life and PALYs Saved in the Australian Population of Working Age (Age 15-65 years) Over the Next 10 Years (2020-2029)

Person-Centered Scenario	Years of Life Saved	PALYs Saved	Value of PALYs Saved (AU$, Millions)
Scenario 1			
Survival rates increased by 5%	207	64	$12.6
Survival rates increased by 10%	419	130	$25.4
Survival rates increased by 20%	2,550	930	$51.6
Scenario 2			
Workforce participation rate increased by 5%	—	151	$29.5
Workforce participation rate increased by 10%	—	302	$58.9
Workforce participation rate increased by 20%	—	605	$117.9
Scenario 3			
Combining scenario 1 and 2 (5% improvement)	207	219	$42.7
Combining scenario 1 and 2 (10% improvement)	419	445	$86.8
Combining scenario 1 and 2 (20% improvement)	855	923	$179.9
Scenario 4			
Using estimated 10-year postdiagnosis survival data[a]	7,696	7,367	$1,440

Abbreviations: AU$, Australian dollars; PALY, productivity-adjusted life year; YLL, years of life lost.

[a]Scenario 4 represents the YLL and PALYs lost because of acute myeloid leukemia when the survival rates postdiagnosis from years 6 to 10 reported by Luke et al[18] are used. In the base case analysis, the survival rates postdiagnosis for years 6-10 are assumed to be the same as at year 5, resulting in 7,600 YLL, 7,337 PALYs lost, and $1,430 million in lost gross domestic product. Therefore, compared with the base case, using the 10-year postdiagnosis survival data from Luke et al[18] resulted in an additional 96 YLL, 30 PALYs lost, and $10 million in lost gross domestic product.

The second set of scenario analyses focused on economic effects: a temporal increase in GDP, a reduced annual discount rate to the WHO standard discount rate of 3%, and increasing the retirement age to 70 years.[35]

Table 3 shows that using a temporaneous GDP increased the estimated GDP lost to AML to be almost AU$1.54 billion ($1.04 billion USD) over the next 10 years. Modeling a reduced annual discount rate led to an additional 9.2% of PALYS lost, whereas increasing the retirement age demonstrated an additional 5.9% of PALYs lost, when compared with the base case (Table 3). Valuating PALYs using the median wage per hour resulted in a loss of AU$99,199 ($67,391 USD) per person over 10 years (compared with the calculated GDP per EFT estimate of a loss of AU$309,725 per person diagnosed over the same time period).

DISCUSSION

Over 10 years from 2020 to 2029, we estimate that among Australians of working age (15-65 years), AML will cause 7,600 YLL and 7,337 PALYs lost, which equates to AU$1.43 billion in lost GDP. Our findings demonstrate that the economic impact attributable to an AML diagnosis is significant, even in a relatively rare cancer predominantly diagnosed in older people.

Previous work undertaken using a PALY outcome measure has used closed cohorts, which were modeled over a working lifetime,[9-13] in contrast to our dynamic method over ten years. Given the significant mortality and work impact on AML, our estimates are suggestive of a potentially higher impact than those estimated for high prevalence conditions such as smoking, diabetes, or hypertension.

For example, Hird et al[13] found that for each person with hypertension, there is an equivalent GDP loss of AU$33,366 ($22,667 USD) over their *working lifetime*. By comparison, we estimated GDP loss over *10 years* per person to be AU$309,725 ($210,411 USD). This is more than a nine-fold difference, and the short time frame for our analysis highlights that even highly prevalent conditions may have a lower productivity impact when compared with rare conditions because of differences in mortality and morbidity.

Our model is largely driven by the increasing incidence of AML with age, and this is highlighted in the scenario analysis that shows lifting the retirement age to 70 years increases the PALY loss by almost 6%. Yet, this is a scenario worth considering; approximately 13% of workers over the age 45 years plan to never retire, and similar to other high-income countries, Australia has a large and growing older population and consideration is being given to increasing the retirement age.[34,36,37] Those age 65 years and older are expected to increase to 22.5% of the population by 2050.[37] The prevalence of cancer survivors is expected to increase because of a combination of an aging population and improved therapies, which will only heighten the societal economic impact in future years.[38]

From an individual perspective, returning to work, whether paid or unpaid, has been shown to improve a sense of

TABLE 3. Effect of Economic-Centered Scenarios on PALYs and GDP Impact During the Working Lifetime (Age 15-65 years) on Years of Life Saved and Productivity Over the Next 10 Years

Economic-Centered Scenario	PALYs Lost Because of AML	Percent Change in PALY Loss Compared With Base Case	GDP Lost (AU$, Million)	Percent Change in GDP Loss Compared With Base Case	GDP Lost Per Person With AML (AU$)
Base case					
	7,600	—	AU$1,430		AU$309,725
Scenario 1					
Modeled temporal trend in GDP	—	—	AU$1,538	+7.6	AU$333,117
Scenario 2					
Annual discount rate reduced to 3%	8,301	+9.2	AU$1,618	+13.1	AU$350,444
Scenario 3					
Increasing retirement age to 70 years old	8,050	+5.9	AU$ 1,569	+9.72	AU$339,831
Scenario 4					
PALY valued using median wage	—	—	AU$458	—	AU$99,199

Abbreviations: AML, acute myeloid leukemia; AU$, Australian dollars; GDP, gross domestic product; PALY, productivity-adjusted life year.

purpose, a resumption of normality and dignity, and is associated with a higher quality of life.[39,40] Additionally, financial burden can result from reduced work and subsequent reduced income, and is linked with lower quality of life and a reduction in survival for patients with cancer.[41,42]

Evidence-based interventions to facilitate return-to-work or other unpaid activities either at a hospital level or by the employer, in conjunction with improvements in current treatments to minimize treatment-related mortality, symptom burden, and morbidity, are therefore urgently needed across all cancers.[31]

PALY estimates can complement traditionally used metrics of burden of disease (such as disability-adjusted life years) by enabling quantification of the broader economic impact of disease. In the short term, these types of data could be useful in assessing research funding proposals and new drug or device listings. For governments tasked with fiscally balancing health care and research expenditure, adopting a productivity perspective helps reframe research funding from an expenditure to an investment.[13]

Yet, previous research suggests that $< 10\%$ of all economic evaluations include an indirect cost estimate although disease-related productivity loss may account for up to 50% of the total cost of illness.[43,44] Therefore, current estimates of the total cost of AML are likely markedly underestimated.

In diseases such as AML, which have no known preventable avenues, quantification of the burden of disease using novel measures such as PALYs, facilitates a break-even investment approach in the longer term, allowing appropriate amounts of government funding to be allocated considering the broader societal disease burden.[45]

We have demonstrated that even small improvements in end points in a relatively rare cancer can lead to significant economic gains. Feasibly, investment in research to improve overall survival can be economically offset by the societal productivity gains alone, and an investment-benefit threshold may be developed.

We acknowledge that our study is not without limitations. Our valuation of productivity loss is likely an underestimation because of limitations to the available data. There was little available evidence about the return-to-work rates for people diagnosed with AML specifically, and we were unable to locate any data on absenteeism or presenteeism. The available data were drawn from overseas and may not be generalizable to the Australian context because of inherent difference in culture, systems, and economies. Normative Australian population productivity data had not been established and, in this model, was likely overestimated among people without AML by assuming that these people had a productivity index of one (were fully productive).

In the analysis, we were not able to account for changes in GDP attributable to health care spending because of AML. Our model did not account for unpaid work that contributes to GDP (eg, personal caring duties), which is particularly important as the incidence of AML increases with age and commonly affects people postretirement. Assuming that the AML death rate for years 6, 7, 8, 9, and 10 years after diagnosis is the same as it is 5 years after diagnosis, may have underestimated the impact of AML on health and productivity measures. However, when the available estimated 10-year postdiagnosis survival data were employed, the difference was minimal with only 96 additional YLL and 30 additional PALYs lost.

Notably, the model used nationally representative incidence and mortality data. As incidence and mortality rates have remained stable over time, we are confident that the projections of the number of people with AML and estimated YLL and PALYs lost are robust.

Finally, although our model has an Australian focus, other researchers are able to substitute their own available inputs into the model to allow for a relevant PALY calculation and valuation for a country and disease of interest.

In conclusion, AML is a rare disease but exerts a significant impact on productivity and the broader economy. Our findings underscore the importance of reducing disease and treatment side effects and improving return-to-work interventions for cancer survivors.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Estimating the Productivity Impact of Acute Myeloid Leukemia in Australia Between 2020 and 2029, Using a Novel Work Utility Measure: the Productivity-Adjusted Life Year (PALY)

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Chapter 9: Discussion, recommendations, future research and conclusions

9.1 Overview

In this thesis, I have demonstrated that the personal and financial impacts arising from AML can be profound for both patients and society. Patients with AML and their families grapple with a life-threatening disease, debilitating treatment and pragmatic concerns about being unable to work and personal finances. The financial burden due to cancer has been well-described in the literature and was estimated to affect 22-73% of cancer patients (140,237,238). Additionally, the diagnosis and treatment modality, being of younger age, lower-income, and female, is associated with a higher likelihood of suffering from financial burden (140). The contemporary literature presents some conceptual challenges around the terminology used and inconsistencies about where and how financial burden contributes to a state of impairment, undoubtedly contributing to considerable heterogeneity in the literature. A shared comprehensive conceptual framework for financial burden is yet to be elucidated, which has contributed to the myriad of terms used interchangeably to describe the financial consequences of cancer, for example, financial toxicity, financial stress, financial hardship, financial distress, economic burden, economic stress, economic hardship, or economic distress (139).

Nevertheless, the literature surrounding the financial consequences of cancer has reported pooled cohorts consisting of many cancer diagnoses, making it difficult to ascertain how particular patient groups are affected. Adding to the complexity in interpretation is that much of the research has been undertaken in the US (140), which adopts a user-pays health care system, a paradigm philosophically and practically different from Australia's health care system (154,155). Therefore, it is challenging to elicit the magnitude of financial issues for patients with

haematological malignancies, specifically those with AML and those treated in health care systems different from the US' user-pays model.

Australian patients with AML are particularly at risk of financial toxicity due to the compounding effect of lengthy hospital stays, the inability to work because of the illness and treatment, and the centralised nature of care requiring some patients to travel for treatment and ongoing monitoring for disease recurrence.

To address these identified research gaps, my research aimed to describe the personal and financial burden caused by AML in Australian adults (aged ≥18 years). The specific objectives were to explore the lived experience of adults with AML, examine the financial burden of AML from the patient perspective, and; investigate the societal financial burden attributable to adults with AML. A mixed-method design incorporating six studies was conducted to meet the aim and objectives.

This Chapter presents the key research findings and an overview of the strengths and limitations of the research. The clinical and policy implications are also described, emphasising the potential avenues for translation into routine clinical care and policy at health-service and government levels for people with cancer. The recommendations for future research to build on these findings are presented.

9.2 Summary of key findings mapped to the thesis objectives

The body of work undertaken in this PhD has provided new information about the personal experience and financial impacts for Australian adults with AML. This information will be of value to those vested in ensuring patient-centred care, including but not limited to; patients and their families, clinicians, healthcare administrators, health advocates, policymakers and insurance

companies. A summary of the PhD objectives, mapped to the corresponding studies and their key findings, are provided in Table 9.

Table 3. Summary of key findings by thesis objective and study

Objective	Study undertaken	Key results
To explore the lived experience of adults with AML	**Chapter 4:** Characterising experiences with acute myeloid leukaemia using an Instagram content analysis	• Patients and their support networks are the most frequent group of users on Instagram posting about AML • Instagram could therefore be used to trial a tailored intervention or information dissemination to this group of people. • However, there is an identified gap in health organisations participating on Instagram, representing a missed opportunity for patient and consumer engagement.
	Chapter 5: It doesn't stop at validation: patient-reported outcome measures require ongoing and iterative development	• Derived qualitative themes highlighted the gaps between items of patient importance and the actual topics contained within the most common quality of life instruments used with people with AML. Some themes agreed with the items and some were missing from the instruments. •
To explore the financial burden of AML from the patient perspective	**Chapter 2:** Describing the impact of patient-perceived financial burden in haematological malignancies: a systematic review	• Moderate level evidence indicates that financial burden is prevalent in those suffering haematological malignancies. The prevalence of financial burden was 15%-59%. • From the 20 studies identified, 12 of them were undertaken in the United States. Eleven of the twelve quantitative studies were cross-sectional, and nine qualitative studies were identified.

Objective	Study undertaken	Key results
		• Eleven studies utilised a mixed-haematology cohort. Four studies focused on haematopoietic stem cell transplant patients, four recruited multiple myeloma patients, while two studied patients with chronic lymphocytic leukaemia. Additionally, one study recruited patients with leukaemia or lymphoma of unspecified type, and only one study specifically examined acute myeloid leukaemia and financial burden. • Ten of the twelve quantitative studies utilised unvalidated measures of financial burden. • Out-of-pocket estimates were reported in two studies for patients with multiple myeloma and chronic lymphocytic leukaemia. These studies were undertaken in the United States and identified the expense categories as clinical appointments, prescription medications, non-prescription medications and transport for care. • There was moderate evidence to show the quality of life was worse for patients experiencing financial burden, and one study failed to demonstrate an association between financial burden and reduced overall survival. • Patients implement measures to reduce household expenditure and raise money through liquidating assets, while others sacrifice medical care due to cost.

Objective	Study undertaken	Key results
	Chapter 6: "If I don't work, I don't get paid". An Australian qualitative exploration of the financial impacts of acute myeloid leukaemia	• AML patients experienced financial difficulty in the context of publicly-funded health care. • Reducing or stopping work was perceived as most burdensome to their current and future finances. • Opportunities exist to alleviate financial pressure on patients by abolishing parking fees and ensuring access to social workers to facilitate access to financial aid programs.
	Chapter 7: Do patients with haematological malignancies suffer financial burden? A cross-sectional study of patients seeking care through a publicly funded healthcare system	• 42% of patients experienced some degree of financial toxicity • Protective factors against financial toxicity were being older, having a higher monthly income, having private health insurance and not being forced into unemployment or early retirement due to illness. • One-third of respondents had some income protection insurance, but only two-thirds of these people had made a claim. • 19% of participants had debt accumulation which was reported between $350-$40,000 (median $5000, IQR $11,875) • Delaying or missing medication to save money was reported by 5% of respondents • A further 11% of respondents had trouble paying a mortgage, or phone or utility bill in the past month

Objective	Study undertaken	Key results
		• Out-of-pocket expenses in the past month was between $0-$1,650 (median $100, mean $224±SD $294.31) • The most common OOP expense was prescription medication (65%), followed by travel costs (56%) and non-prescription medication (31%). • In total, the respondents spent the most on prescription medication ($8291), travel costs related to care ($6700) and allied health expenses ($3032)
To examine the societal financial burden attributable to adults with AML	**Chapter 8:** Estimating the productivity impact of a myeloid leukemia in Australia between 2020 and 2029, using a novel work utility measure: the Productivity-Adjusted Life Year (PALY)	• Over the ten-year period of 2020 to 2029 inclusive, 7,600 discounted years of life will be lost attributable to AML. • Over the same period, 7,337 discounted productivity-adjusted life years will be lost attributable to AML. • These losses are valued at AU$1.43 billion in lost gross domestic product

9.3 Objective 1: Exploring the lived experience of adults with AML

Two primary studies addressed objective 1. By employing a qualitative methodology, these studies highlight several novel findings for adults with AML. First, semi-structured interviews with participants revealed that many patients grapple with various health and well-being issues once they finish induction therapy and enter the consolidation phase of their treatment. The following themes were identified from the interviews. The first had an overarching theme of physical outcomes, which included self-described symptoms of fatigue, weakness, pain, changes in taste, vision problems, heart problems and changes in physical appearance. The second identified theme was psychological outcomes with sub-themes of living with uncertainty, awareness of mortality and worry and anxiety for family. An additional theme was termed, life disruptions which included concepts of diagnosis shock and changes in life plans. The final theme, coping strategies, included the sub-themes of why me, the importance of a positive mindset, comparing self to others, beliefs and faith and seeking to restore normality. Many of the reported issues fit within the quality of life framework domains by Ferrans et al., which describes how the symptom experiences affect the individuals functional status and their perception of self and overall quality of life (239). Each domain of the model is influenced by an individuals' characteristics and the characteristics of the environment they find themselves in. The model is particularly relevant to patients with AML. They find their lives drastically changed by extended hospital in-patient stays, intensive clinical monitoring and follow-up, and the physical and psychological changes that come with burdensome chemotherapy and a life-threatening illness.

The literature suggests that people with AML tend to report worsened quality of life during induction therapy and that their quality of life returns to pre-illness levels quickly once the induction therapy is completed (105). Recent literature reported that the most commonly utilised quality of life instruments for AML populations were the 30-item European Organisation for

Research and Treatment of Cancer Quality of Life Questionnaire (240) and Functional Assessment of Cancer Therapy (FACT) questionnaires. The general FACT (FACT-G) core measure contains 27 questions in four domains (physical, social, emotional, and functional). However, it can be supplemented with 17-item leukaemia or a 23-item transplant module (241). The mapping process between the items contained in these instruments and the themes from participants demonstrated some disconnect between the instrument items and the lived experience of people with AML, and thus this disconnect throws into question the present view of resolving quality of life after induction therapy. This finding of disconnect between lived experience and items within these quality of life instruments is supported by a recent systematic review, which sought to identify quality of life instruments used in AML, locate the instruments' validation data, and assess the instruments' psychometric properties (242). The authors found a significant literature gap concerning the validity and reliability of the identified instruments for AML patients, with many of the existing studies exhibiting small sample sizes and a lack of replicated results undermining the confidence in the instruments' ability to have clinical relevance and detect changes in quality of life in the AML patient cohort (242). Salas et al. concluded that more research is needed to determine the most responsive and clinically helpful instrument, particularly in AML patients who relapse, have refractory disease, or respond to treatment. Whilst it is popular (and preferable to allow for inter-study comparison) to utilise generic cancer quality of life instruments, it may be more beneficial to encourage use of a core set of questions and an item bank. A core question set would allow clinicians and researchers to select salient items for the population of interest that are relevant to them at various time points in a patient's treatment, recovery and survivorship journey.

Second, further exploration of the lived experience of people with AML was sought utilising a social media platform. Instagram reports approximately one billion user accounts and represents

a novel avenue to access hard to reach populations and those suffering rarer conditions by virtue of the number of accounts and content volume (198). Younger patients with AML fit this category; the incidence of AML is lower in younger populations, and it is a relatively rare disease overall. These compounding facts make it challenging to recruit younger individuals with AML into research due to fewer individuals. To the best of my knowledge, this is the first investigation attempting to understand the type of AML-related content being posted and who is posting the content. At the time of writing, Instagram has received very little attention from researchers, yet may present an avenue for public health messaging and a glimpse into the lives of populations of interest (243). The Instagram analysis found that AML patients were the most frequent user-type (66% of users) to be posting AML related content and that this was most frequently about their health (31%). This naturally represents an avenue for researchers to investigate lived experiences using extant methods.

Further opportunities exist for engagement with this virtual community to provide credible health information directly to patients, yet only 10% of the posts originated from an organisation. In the era of socially propagated misinformation about health and cancer treatment, it seems remiss of credible organisations to have dismissed such a popular social media platform as an avenue to educate and raise awareness within the public arena. Additionally, Instagram demonstrates improved public engagement compared with Facebook (10), suggesting such information would be consumed and utilised directly by individuals suffering from AML. Foreseeably other such uses exist, such as participant recruitment into clinical and research studies. The issue of patient recruitment, particularly into clinical randomised controlled trials, is a frequently reported problem in both investigator- and industry-sponsored studies, hindering progress in new knowledge, therapies, patient care and outcomes (244–247). A 2018 study in the UK of 151 randomised controlled trials demonstrated that almost half (44%) did not achieve the

target sample size (244). However, a recent review of medical research studies using social media recruitment found social media to be an effective recruitment method (relative to traditional methods) for 12 studies out of 30 (248). Arigo et al. highlight that there is limited evidence about how to best engage with potential participants on social media, which may be hindering using social platforms effectively for recruitment (249). The content analysis featured in this thesis provides a worthy addition to the emerging literature in the field by demonstrating that Instagram can be utilised as a source of meaningful person-centred data regarding AML. The study provided the initial feasibility assessment needed for further research into identifying strategies for public engagement and research participation using Instagram, particularly for difficult-to-access or vulnerable populations.

9.4 Objective 2: Examining the financial burden of AML from the patient perspective

Two primary studies, and a systematic review, addressed objective 2 of this research, focusing on examining the financial burden of AML through the patient lens. Findings from the qualitative study directly informed the data collection instrument used for the quantitative study. The first primary study (featured in Chapter 6) employed a qualitative descriptive study design exploring the patient-perceived financial impact of AML. Four themes were identified; 1)the burden of AML-attributable costs (for example, out-of-pocket expenses); 2) accommodating the AML-impact of paid work (for example, forced early retirement); 3) the consequence of financial strain from AML (for example, utilising savings); and 4) concerns about the future including the familial financial burden (for example worry about depleting financial reserves).

Little international literature has qualitatively examined the lived experience of financial burden due to cancer (250–252), and in Australia, three studies have been published in 2016, 2019 and 2020. The 2016 paper by McGrath sought to examine the out-of-pocket costs for patients

travelling for treatment for haematological malignancies in Queensland, where they found patient expenses could be categorised broadly as travel and accommodation, the costs associated with family and friends during relocation, the costs associated with diagnosis and treatment, and the costs of parking (253). The 2019 paper by Slavova-Azmanova *et al.* focused on provider-patient communication in Western Australia for patients with breast, lung, colorectal or prostate cancer (254). They found that having a doctor aware of costs and the financial situation was beneficial to some patients. In contrast, others experienced significant unexpected expenses (treated in the private system) and were unaware of financial assistance services that could have prevented medication non-adherence and undue stress and worry. The 2020 study by Newton *et al.*, also undertaken in Western Australia in a pooled cancer cohort, found key themes relating to the proximity to treatment (including travel costs and physicians being mindful of appointment scheduling), the effect of continuing employment in coping with out-of-pocket expenses, provider-patient communication about out-of-pocket expenses and utilising financial coping mechanisms (such as financial welfare, utilising savings, and budgeting) (255). Notably, two of these studies were undertaken in Western Australia, where approximately 15% of the population live in outer regional and remote areas, while in Queensland, this figure is 18% (256). These two states' regional and remote populations contrast to Victoria, where only 4% live in outer regional and remote areas (256). Therefore, it may be expected that the source of the out-of-pocket expenses identified in the Western Australian and Queensland studies would be different to those identified in Victoria as we would expect travel costs to be more burdensome. However, this qualitative study also found travel and parking costs for Victorians with AML to be frequently discussed by participants in the interviews as burdensome, which adds further evidence to this expense category being a financial burden for cancer patients in Australia no matter the state of residence.

The financial assistance schemes available for patients travelling from rural areas (such as the Victorian Patient Transport Assistance Scheme (150)), and the advocacy work undertaken in Victoria in 2017 to reduce hospital parking costs for cancer patients (257–259) is discussed in the manuscript presented in Chapter 6. However, there is still an opportunity to alleviate some of the financial burden surrounding out-of-pocket travel and parking expenses for patients with cancer through health service or government policies in 2021 and beyond.

Furthermore, congruence between the findings in this study and the literature was present regarding the role of paid employment, accessing welfare or government supports, and the mechanisms used by patients to cope with the financial burden. Given the similarities between the coping mechanisms observed in Chapter 6 and those observed in other cancer types in Australian studies (260), there are likely systemic and/or common contributors that lead to similar coping mechanisms in all cancer patients.

Chapter 6 additionally undertook a novel mapping process of a patient-reported outcome measure, the COmprehensive Score for financial Toxicity (COST) and provides researchers with some surety that this instrument developed in the US has relevance for the Australian population. Since this research was undertaken, Durber et al. have undertaken a formal validation study of this instrument in Australian cancer patients (216).

The findings of the qualitative study in Chapter 6, and the systematic review findings of Chapter 2, informed the survey instrument to measure the magnitude of out-of-pocket expenses incurred by patients. The survey instrument was complemented by the validated financial toxicity measure (COST instrument). In the quantitative cross-sectional study presented in Chapter 7, which included leukaemias, lymphomas, and patients with multiple myeloma, the median out-of-pocket expenditure was $100 (AUD) in the past month, ranging between $0 and $1,650. Prescription

medication and travel expenditure were the most frequently reported cost categories that broadly aligned with the systematic review findings in Chapter 2. Allied health out of pocket expenses were also notable and may suggest that patients have ongoing health issues addressed outside the tertiary health system (once discharged from hospital). For example, treatment for haematological malignancies are associated with marked physical deconditioning often requiring an exercise physiology or physiotherapy intervention, not always reimbursed by the public system or private health insurance (261). Additionally those with private health insurance have been shown to have higher out of pocket expenses compared to those without private health insurance (262). Almost 50% of the sample in Chapter 6 reported having private health insurance, which may partially explain high allied health out of pocket expenses.

The findings in Chapter 7 demonstrate a broad range of out-of-pocket expenses and illuminate the sources of the financial burden for haematological patients.

A 2021 systematic review of Australian cancer patients financial burden also found a large variety of reported out-of-pocket expenditure in the literature that varied by cancer type, with medications and travel also frequently noted as financially burdensome by some studies (260). For Australian patients with breast cancer and lymphoedema annual out-of-pocket costs were on average $977 per year (263), while patients with prostate cancer experience average out-of-pocket costs for their treatment of $11,077 (209). These expenses are considerably higher than patients with haematological malignancies, and may partly be explained by the centralised nature of care in tertiary public health services for many haematology treatments. It is estimated that approximately 54% of Australians with cancer are treated in the private system (264) and these patients more commonly experience higher out-of-pocket expenses (260).

The study presented in Chapter 7 demonstrated that 42% of respondents exhibited financial toxicity (as measured by the COST instrument), with people with AML who were older than 65

years, had a higher income and maintained employment were less likely to experience financial toxicity. The proportion of patients exhibiting subjective financial toxicity in this study (42%) was higher than that reported by a recent systematic review of financial toxicity in cancers in publicly funded healthcare systems (7-39% of cancer patients) (151), yet less than reported in a small study of 106 AML patients in the US (54% using the COST instrument) (265). The prevalence found in Chapter 7 did align with the prevalence identified with the systematic review in Chapter 2 (15%-59%). These variations are likely due to different measurement instruments, varying cancer types, a vague concept of financial burden and within the context of distinct healthcare systems. The financial burden experienced by those with haematological malignancies may also be exacerbated by the often protracted treatment trajectories, causing poor functioning (physical and psychological) due to the disease and the treatment side-effects. This can lead to loss of employment or early retirement in those of working age as evidenced by the findings in Chapter 7 and may also partially contribute an explanation of the higher prevalence of financial burden in these patients.

In the Chapter 7 study, private health insurance was independently associated with higher (better) COST scores indicating less financial toxicity, even when adjusting for confounders such as income. This finding is at odds with other Australian studies undertaken in prostate cancer (209), neuroendocrine tumours (262) and mixed cancer cohorts (128,266). It may be that aspects of treatments for these other cancer types can be partially (or fully) undertaken in the private health care sector where many patients experience inadequate health care coverage (262) and out-of-pocket costs double those treated in the public health care system (209). Unravelling the relationship between private health insurance status and the likelihood of financial burden for various cancer types will be important in the future to identify those at risk of financial toxicity.

Such information is often documented in a patient's hospital record and may serve as a helpful proxy marker for whether a patient should be more formally screened for financial burden.

Additionally, there may be other patient groups that are at higher risk of financial burden outside the scope of this PhD. For example, older single women (aged 60 years and older) are the fastest-growing group of homeless people in Australia (267), with 30% living in permanent poverty (268). Unexpected out-of-pocket expenses for this cohort may be financially crippling. Furthermore, those suffering multiple chronic conditions or more than one-lifetime cancer event may also be particularly susceptible to financial toxicity due to the compounding effect of out-of-pocket expenses and possible reduced income due to an inability to work. The effects of unexpected out-of-pocket expenses flow onto the wider household impacting carers and family members, particularly in cases of severe financial toxicity and bankruptcy (which affected an estimated 9% of cancer survivors in the US (269)) (270,271). These financial ramifications may continue for those left behind long after the patient with cancer has died.

Chapter 7 reported that 71% of respondents indicated they undertook strategies to financially cope with their illness such as using their savings (47%), borrowing money from family or friends (16%) and using credit cards to cover expenses (12%). There were 19% of people who accumulated debt, $350-$40,000 (median $5000, IQR $11,875). The free-text responses revealed other savings strategies, such as budgeting and eating out less and fewer purchases.

In Chapter 7, there was additional evidence of medication non-adherence (5% of the sample) and compromising care by missing or delaying appointments (9%). The reported rates were lower than that identified in the systematic review reported in Chapter 2 (up to 19% of patients delaying or missing medications), which may be explained by the substantially higher medication

costs passed to patients in the American health care system. These findings align with a newly proposed model of the economic consequences of cancer treatment by Newton et al. where our findings fall under the objective measures of financial toxicity and contribute to a change in consumption and subjective measures of financial toxicity (such as distress, quality of life, indebtedness, health outcomes and non-adherence) (25).

9.5 Objective 3: Investigating the societal financial burden attributable to adults with AML

Direct costs for the treatment for AML are substantial and primarily driven by inpatient stays, treatments and procedures. They also vary greatly by treatment modality and country (31,272). For example, relapsed or refractory disease is estimated to be the most costly (US$439,104 per patient) compared with standard induction therapy (US$198,657 per patient) (272), and similar patterns of cost exist in European estimates (273–275). However, much less is known about the indirect costs of AML, which limits cost-effectiveness analyses from a societal perspective (31). Examining the financial burden of AML from a societal perspective using lost productivity represents a novel method to monetarily value the impact of this disease and provides a new dimension from which to assess the cost-effectiveness of therapies under consideration by funders tasked with balancing fiscal concerns with treatment efficacy.

The study presented in Chapter 8 presents a significant economic picture by highlighting the profound loss of income and years of life attributable to AML. Returning to work after a cancer diagnosis can be challenging due to personal or disease-related factors, employment attributes and contextual factors, including family, social and cultural considerations (276). After a cancer diagnosis, return to work rates vary in the literature and are estimated to be between 39 to 93% of cancer survivors returning to work 1-2 years after diagnosis (277–279). In Australia, it is

estimated that 46% of cancer survivors are unable to return to employment after a cancer diagnosis (219), and 67% change their employment status following diagnosis (266). For AML, where incidence is highest in age groups older than retirement age, it would seem productivity loss should be minimal. However, little is known about the return to work rates for working-age people with AML. One Canadian study estimated that 46% of people diagnosed with AML were working 12 months after diagnosis, and in a longitudinal study undertaken in Sweden (125), they observed this rose to just 52% at ten years after diagnosis (137). Undoubtedly, ongoing physical and psychological effects from the disease and treatment are significant contributors to the return to work rate estimates (280). However, a Danish registry-based cohort study found that suffering acute leukaemia was significantly associated ($p<0.001$) with a reduced likelihood of return to work compared with other haematological malignancies (136). Chapter 7 reports that 37% of study participants were unemployed, with an additional 26% forced into unemployment or early retirement due to their diagnosis. Placed in the context of our findings presented in Chapter 8, where we estimate 7,600 discounted years of life lost and 7,337 discounted PALYs lost (valued at $1.43 billion in lost GDP) over ten years; acute leukaemia is burdensome at all levels - personal, system and societal. While the findings of this study are economically non-trivial, the estimation likely underrepresents the actual value owing to a lack of data available estimating the amount of unpaid work undertaken by Australians. This is true for those of working age and post-retirement, where many individuals take on caring duties for grandchildren and spouses and volunteer their time in the community.

9.6 Financial burden: the missing domain of patient-centred care

It is difficult to disentangle the health and well-being or quality of life impacts and symptoms described by the participants in our studies presented in Chapters 5-7, given the associations between quality of life and financial burden in the literature (281–283). These concepts are intrinsically linked, and while the quality of life is a well-accepted component of patient-centred care, financial burden is yet to be viewed with the same level of importance within the context of the Australian publicly funded healthcare system. This research represents an important step in furthering the agenda for health services and policymakers concerned with supporting best practice patient-centred care.

The Therapeutic Goods Administration (TGA) in Australia considers the quality, safety and efficacy of new therapeutic agents and devices in Australia (284). Schubert explained that simply being approved for use increases the likelihood that the treatment is used without consideration of the costs passed on to the patient (285). Meanwhile, the Pharmaceutical Benefits Scheme Advisory Committee (PBAC), which considers drugs approved by the TGA (sometimes in parallel with the TGA process), assesses the clinical efficacy and cost-effectiveness of these therapeutics before making a recommendation as to which drugs are subsidised by the Australian Government (284,285). However, there is concern that the lengthy application and assessment processes may leave patients either without access to novel agents or with access and large out-of-pocket expenses (284). Putting this into the context of AML, there has been little evolution of standard treatment for AML since the 1970s (164). However, since 2017, there have been nine approvals by the Food and Drug Administration for new therapeutic agents for AML (272). Whilst a number of these drugs are still undergoing trials in Australia, their eventual submission to the TGA for full approval and PBAC for financial subsidy may leave some patients needing

these agents with the ability to obtain them, but without subsidy from the Australian Government resulting in out-of-pocket costs for these medications (286). Of course, this issue is exacerbated by the high-costs of novel agents imposed by their commercial sponsors, who justify these on the basis of lengthy and costly drug development (287).

Therefore, the findings of this thesis is of paramount importance to aid in the understanding of the current personal and societal financial burden, before the landslide of new agents are seeking approvals from the TGA and PBAC. The findings presented allow health providers, health services, policy makers, advocacy agencies and governments to anticipate the financial effects of the evolving treatment landscape.

9.7 Strengths and limitations

The methodological strengths and limitations were described for each study presented in Chapters 2, 4, 5, 6, 7 and 8. Below are the major strengths and limitations of the overall PhD research program.

One of the significant strengths of the presented research is the novelty, as evidenced by five manuscripts accepted for publication at the time of writing and a further manuscript currently under review. Too often, researchers shy away from rarer health conditions like AML, favouring those with many sufferers, for which it is easier to recruit large, diverse samples (288). However, small incremental gains in evidence over time can improve the understanding of disease and enhance patient-centred and clinical outcomes. For example, 50 years ago, a diagnosis of childhood acute lymphoblastic leukaemia meant almost certain death, but now the 5-year survival rate is >90% (289) due to small incremental gains in evidence over time contributing to improved patient outcomes. In the same way, this research contributes an incremental gain in

understanding the personal and financial burden of AML in Australia, which will be important in improving patient and clinical outcomes.

More specifically, the qualitative study examining the financial burden of AML is a novel contribution to the literature. The qualitative studies utilised broad inclusion criteria, with purposive sampling, which generated a sample of patients with AML of varying disease experiences, disease severity, socioeconomic backgrounds, family situations and different age groups, discussing their health and well-being concerns and financial experiences. Although qualitative research does not seek to be generalisable, the sampling method employed resulted in a diverse sample.

The quantitative study (arising from the qualitative investigations) examining financial toxicity using the COST instrument in haematological patients is the first time this has been attempted in Australia in this population and examining some of the cost drivers, including work. The productivity loss assessment in the Chapter 8 provides a novel metric for health economic evaluations and a new paradigm through which to view the burden of AML. Furthermore, the presented method allows updated data to be easily entered to update the model as new evidence becomes available. Additionally, it allows data inputs to be changed for disease type or data sets from various countries to allow for inter-disease or inter-country comparisons.

Finally, the Instagram study (Chapter 4) presents a novel method and avenue of investigation into the patient experience, while the mapping exercise presented in the Chapter 5 study highlights the challenges in working with rarer populations and utilising validated instruments in research. Together, this mixed-methods research design takes advantage of the strengths and

accounts for the weaknesses in the individual study designs allowing for a more complete and rigorous understanding of the personal and financial burden of people with AML in Australia

However, the presented research is not without its limitations. Due to AML being a rarer disease, with a high disease burden, there is a limited population to approach for research participation at any given time. Whilst it was not intended that our qualitative investigations focused on men, more men than women did participate in the qualitative research. The addition of more women may have allowed a more complete capture of the health and well-being and financial experiences of AML. This may have been specifically relevant for financial experiences as evidence suggests that being female is associated with a worsening financial burden (290). Nevertheless, this was partially remedied in the quantitative examination of financial toxicity, where 47% of the sample were women.

Importantly, this study was undertaken during the COVID-19 pandemic, during which out-of-pocket expenses may have been underestimated for travel and parking, as health services in Victoria moved to telehealth consultations for outpatient appointments. More broadly, the out-of-pocket expenses, work impacts, and financial toxicity measures may not be representative of 'usual' times, given the unprecedented restrictions in Victoria on business operations and people's movement during the COVID-19 pandemic. While the research tried to account for this by asking questions about the impact of the COVID-19 pandemic, the impact was obfuscated by constantly evolving restrictions and government financial incentives.

Estimating productivity loss due to AML (Chapter 8) utilised the best available population data-sets and literature to input into the model. However, it could not account for the resulting economic stimulus resulting from the health service usage of those suffering AML. Additionally,

the model did not account for unpaid work, such as child-minding or carer duties, or volunteer work, and therefore our estimation of productivity loss is likely an underestimation. Finally, for the Instagram study in Chapter 4, the criticism of this social media platform is that it is a curated environment that may not reflect the spectrum of real-life experiences is acknowledged. Because of the possible curation of posts, the analysis was careful not to take an interpretative approach. Additionally, the identity, diagnosis, sex or country of origin of the posts analysed could not be verified. Lastly, none of the included research considered clinician experience, opinion or recommendation, which will be an essential view to capture in future work.

9.8 Recommendations arising from the research

The key finding from this research is that some patients with AML experience financial toxicity in Australia, even though they are treated within an environment of universal healthcare where their treatment costs are largely covered. Because of Australia's universal healthcare system, the issue of financial burden for patients with AML has been largely ignored. Therefore, the following recommendations have been made based on the findings of the research:

1. **Clinician consideration of potential financial impacts on AML patients**

   Ideally, all patients would be formally screened for financial burden using a validated scale, as per the recommendations for distress in cancer. However, pragmatically, it will be essential to identify the patients most at risk for financial burden (Chapter 7) and concentrate in the first instance on ensuring these people are captured and assisted. From this thesis' findings, we understand that those of younger age (≤65 years), lower incomes, holders of private health insurance, or forced into unemployment or early retirement are

at a higher risk of financial toxicity. This is particularly pertinent when considered in context with the findings of Chapter 2 (systematic review), where there is some evidence that financial toxicity may reduce medication adherence. Literature from other cancers has also found associations between financial toxicity and poorer survival outcomes. Medication non-adherence reported in the literature is also supported by the quantitative findings in the study presented in Chapter 7.

Additionally, clinicians should be mindful of grouping appointments where possible to reduce travel and parking costs, provide prescriptions covered by the PBS, and enable generic prescription filling (Chapters 6 and 7). Additionally, providing referrals for diagnostic tests at public facilities (versus private facilities where out-of-pocket expenses for patients are often incurred) should be prioritised, but at a minimum, informing patients of any potential out-of-pocket expenses to be transparent and open a cost dialogue between provider and patient (ergo informed financial consent) (291).

To aid the uptake of this approach, the findings of this research have been published in peer-reviewed literature, presented at conferences or departmental meetings (where possible in the COVID-19 pandemic) and will be disseminated through other mechanisms as opportunities arise.

2. The development of referral pathways in our health system for financial assistance

Hospital policies should reflect financial services and assistance available to patients. For example, some patients interviewed in the Chapter 6 study were unaware of the reduced parking rates available to them, which implied the information was inconsistently supplied to patients. Hospitals should work with parking providers to provide reduced rates for patients and assist in disseminating reduced parking cost information through

flyers in the parking facilities and on the wards where eligible patients and families frequent. Additionally, in the Chapter 6 study, some patients found the social work service inadequate or had a lengthy wait for an appointment, likely reflective of an overstressed system where there is evidence of too few social workers for the population (292). Access to social workers should be prioritised for those most at risk for financial toxicity and there is emerging evidence to support this suggestion (177). Social workers (or possibly through the implementation of administrative patient navigators or case managers (293)) could be better linked and have access to Centrelink and philanthropic agencies to better assist their patients with direct links to these supports. Additionally, there may be a role for community-based general practitioners if they could be supported with the correct information due to their implicit role in person-centeredness, trusted and enduring patient relationships (294).

3. **Advocacy and community engagement to streamline services and improve policies**

Partnership opportunities exist between researchers, community and philanthropic organisations (such Cancer Voices Australia, Leukaemia Foundation or Cancer Council Victoria) and health services to advocate the Federal Government tasked with providing government welfare and the State Government tasked with patient transport assistance to improve timely access to financial support for AML patients. Some patients interviewed in the Chapter 6 study and others who provided a free-text response in the Chapter 7 survey expressed frustration with the bureaucratic processes required to access government support, particularly when unwell and experiencing a reduced ability to cope and comprehend essential matters.

Currently, no specialist pathway exists for patients and their families with cancer to contact Centrelink or access these supports, and some financial assistance programs are complex for cancer patients to qualify for access (295). The government should consider emergency payments for those in difficult circumstances, such as the compounding effects of unemployment and illness.

There are more passive supports available. For example, some patient information flyers are currently available for patients from organisations such as Cancer Council. It may be prudent to ensure these are regularly reviewed for the inclusion of emerging evidence and contain pathways for financial assistance. One of the key challenges will be facilitating uptake and utilisation of these existing resources. Understanding why patients do not access available financial assistance mechanisms (Chapter 6 and Chapter 7) will be important for future research. General practitioners may have a role in supporting patients with financial worries. However, more broadly, strategies to address cost-related health literacy and resources for all health professionals will need to be addressed (294).

4. Measures of financial toxicity included in clinical registries and clinical trials

To fully capture the extent of financial toxicity resulting from a cancer diagnosis in our community (population-level data), the data needs to be more routinely captured. This could be facilitated through current data collection capabilities, such as disease-specific clinical registries or through the Household, Income and Labour Dynamics in Australia (HILDA) survey. Clinical trials may also present novel avenues to collect such data that could be incorporated with health economics metrics such as those used in the Chapter 8 study, particularly in industry-sponsored studies, from which a submission to PBAC for drug reimbursement will likely be made.

9.9 Future research directions and conclusions.

In the future, it will be important that the present research is confirmed through replication and reproducibility -- a pillar of scientific evidence. The carers and family members of those with AML will need to be considered in future research to understand the long-term impact of financial burden on their lives, even after the death of a loved one. It will be essential to examine the impact and adequacy of the current systems in place for those suffering AML and financial toxicity to understand how it can best be altered to serve the people it seeks to assist. Interventions need to be co-designed and robustly assessed to help those most in need. The perspectives, attitudes and commitment of clinicians working at the interface between patients, medicine, health services and governments will be critical for any intervention or policy change to come about.

Finally, through a mixed-methods approach, this thesis has provided a rigorous and thorough investigation into the personal and societal financial burden of AML. The presented research has provided novel findings to contribute to a growing body of patient-centred evidence that the personal and financial burden of AML is profound for some patients and societally burdensome. The results from this thesis can raise awareness about this issue and stimulate further research that could be leveraged through advocacy activities for meaningful supports for patients.

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Appendix A

Systematic review search strategy developed for Medline (and modified for the other included databases)

Step	Search terms
1	exp neoplasms/
2	(tumo?r* or carcinoma* or metasta* or oncolog* or cancer* or malignan*).mp.
3	1 OR 2
4	(Family budget or Household budget or household expense* or household expenditure* or household budget or financial budget).mp.
5	(financ* adj2 vulnerab*).mp.
6	(financial toxicity or financial burden or financial distress or financial stress or financial impact or financial worry or financial worries or financial sacrifice*).mp.
7	(economic burden or economic stress or economic distress or income stress or income distress or budget impact or budget stress or budget distress or money stress or money distress or money worries or money worry).mp.
8	hardship.mp.
9	out-of-pocket.mp.
10	(bankrupt* or financial insolvenc* or credit payment* or mortgage payment* or borrowing money).mp.
11	(financ* adj3 treatment*).mp.
12	(financ* adj3 therap*).mp.
13	(medical debt or debt burden or going into debt or mortgage debt or debt stress or debt distress).mp.
14	(medical care cost* or medical treatment cost* or cancer care cost* or cancer treatment cost*).mp.
15	exp "Cost of Illness"/
16	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17	16 AND 3
18	limit 20 to (english language and yr="2000 -Current")

Appendix B

Systematic review quality appraisal scores for each identified study

Author	**Year**	**Country**	**Study design**	**JBI score**
Abel *et al*	2016	USA	Cross-sectional	87.5%
Abelda *et al*	2019	USA	Cross-sectional	100%
Bala-Hampton *et al*	2017	USA	Cross-sectional	62.5%
Buzaglo *et al*	2017	USA	Cross-sectional	62.5%
Fenn *et al*	2014	USA	Cross-sectional	75%
*Goodwin *et al*	2013	USA	Cross-sectional	75%
Gupta *et al*	2018	USA	Cross-sectional	87.5%
Hamilton *et al*	2013	USA	Cross-sectional	87.5%
Head *et al*	2018	USA	Qualitative	80%
Huntington *et al*	2015	USA	Cross-sectional	100%
Jella *et al*	2021	USA	Cross-sectional	75%
Khera *et al*	2018	USA	Cohort	75%
McGrath	2015	Australia	Qualitative	70%
McGrath	2016	Australia	Qualitative	70%
McGrath	2016	Australia	Qualitative	70%
McGrath	2016	Australia	Qualitative	70%
Paul *et al*	2013	Australia	Cross-sectional	87.5%
Parsons *et al*	2019	Canada	Qualitative	80%
Tan *et al*	2017	Malaysia	Qualitative	70%
Wang *et al*	2016	China	Qualitative	70%

Appendix C

Additional supporting quotations for the systematic review narrative synthesis

Themes	Sub-themes	Illustrative quotes
Out-of-pocket expenditure(253)	Travel and accommodation	We were paying double costs you know $60 every trip for train trips to and from the airport.
		The cost when (name of partner) use to fly back to keep her job over the Saturday and Sunday and to make sure everything was right at home…. She was doing that to keep her work going and the family going.
		Like I have ended up with heaps of tolls and fines driving through… so stressed and time is so… well you have so much going on.
		You don't know how long you're going to be there (in hospital) and you leave the ward just to get out of there to get something to eat. You spend quite a bit of money there to start with.
		You've got two lots of food and you've got the kids up here and then I've got grocery bills down there. And that's more expensive as you've got two households really.
	Caring for family and friends	Like we had someone looking after (child's name) if we weren't there and … and (being delayed to pick up child) that is another cost.
		Oh, yeah, his mobile phone bill went up the roof (increased). He was up here and I was down there.
		I would end up shouting (paying for) them lunch because I felt, you know, they were giving up there time.
		We rented a house and it only got stayed in a few months (only got stayed in a few months so you had to pay all that rent for nothing) yes.
	Diagnosis and treatment	So in relation to the cancer treatment the out of pocket which did hit us the most was when I had my stem cell and my bone marrow transplant. I had to pay for a bit of out of pocket.
		A couple of the pills were $35 and that and you get a few bottles of them and you get three bottles of them and it is $130.
		When you're an outpatient you get quite a pharmacy bill. I had quite a pharmacy bill. We were quite out of pocket. I think in the taxes it was about $1300 medical expenses.
Relying on others for financial support:	Not needing financial assistance from others(296)	No need to borrow money off family and friends.
	Aware of family members that could	Well, I would have family I could respond to but at this stage I haven't thought about it because I haven't needed… I have family but don't need to ask.

Themes	Sub-themes	Illustrative quotes
	be called upon for financial assistance(296)	Yes, I have that help. I have (relatives) in mind that would gladly help me out if I was stuck … so that is a big buffer
	Received assistance from family or friends(296–298)	My mother gave me some money to pay for a bill and my sister said if we got desperate she would give us a loan of some money and my mother kept giving us some money when she could. I talk to my daughter and she helps us out a lot too because she paid some bills when we couldn't afford to.
		Yes, I did. My mother did all the grocery shopping. So it saved me from having to dip into my savings but it ate into her savings as well.
		Yes and we had the car payment as well which my parents paid off for us. We were well supported.
		I have had to rely on gifts from family and friends to keep from filing bankruptcy. Each year my co-pays increase and covered prescriptions decrease which put additional burdens on my budget. I have very little savings and rely on credit cards when I have unexpected expenses.
		Our daughter gave us her tips and we had friends who collected money and gave us a couple of Visa cards.
Familial or household impacts	Financial coping mechanisms(298–300)	Yes, you max that out (credit card) and you never catch up
		Yes, we have to use the credit card quite a lot. Usually for food, the one thing that cannot wait. You have to have it. It is a worry.
		"I had only just started at my new job. I had just been there 4 months. . . . So not any sick leave or rec leave . . . nothing. It was at a bad time, that didn't even pay my mortgage. It really ate into my savings. Because I had no sick leave or anything."
		I sold all my jewelry that my grandma gave me."
		I was earning $420 a week and I leased my car because I got it back on tax every year so I had a brand new car every year and I had money to buy things. Now I live on less than $300 a fortnight because (described hematological condition and treatment). I have had to shut down my business, move out of the house, and sell the business. I am thinking of going into bankruptcy, that is the bottom line. I have so many tiny unpaid things.
	Responsibility to others(297,301)	"The stress... I mean the financial impact... is really stressful. [And now that there are younger people being diagnosed as] young as... mid 40s... this even plays a bigger role... Because they have to stop their work and some are trying to go to work and because of the stress of the financial impacting young children and all of that"
		We have a son going to college & we cannot help with tuition.
Barriers to care due to cost(298,302)	Unable to afford care	Most of the people in village who always fall sick could not go to the hospital, this is the problem. Finance. Now, finance is really needed. We want to go to the hospital, there's no vehicle, vehicle got to pay, that is difficult. Go once can, second time can, third time cannot go already because of insufficient finance.
		"I really debated my last treatment which was photopheresis and I quite doing it because it was so expensive."