Frailty: risk stratification, measurement and outcomes in surgical and critically ill patients.

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February 2020

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Submitted with publication in total fulfilment of the degree of

Doctor of Philosophy

Abstract

Surgical and intensive care populations are ageing worldwide. Frailty, a state of increased vulnerability to stress, is increasingly common in older surgical and critically ill patients. In these cohorts, frailty predisposes to increased complications, mortality, and longer lengths of stay. Implementation of frailty screening can aid case finding, to select patients for more in-depth frailty measurement. This can assist identification of at-risk surgical and critically ill patients, and help identify which areas of health are more affected by frailty in these populations. Using routinely collected hospital data may allow construction of frailty indices, which can accurately and reproducibly measure frailty in granular detail, and help clarify the interplay between age, medical comorbidities, and frailty in individual patients.

Aims of this PhD

1. To review the role of frailty indices in the measurement of frailty in critically ill and surgical populations.
2. Determine which areas of health are adversely affected by frailty in surgical and intensive care patients.
3. Investigate the correlation between the screening Clinical Frailty Scale and multi-dimensional frailty measurement tools.
4. Explore whether frailty can be measured retrospectively from the clinical record.
5. Examine the prevalence and impact of frailty in intensive care unit populations in Australia and New Zealand.
6. To develop and validate a frailty index from medical admission data to measure frailty in surgical and intensive care unit patients.

Phases of research and results

The phases of research to accomplish these aims were:

Phase 1: A systematic literature review was undertaken, assessing the role of frailty indices in the measurement of frailty in intensive care and surgery. Studies were identified through systematic review of MEDLINE, EMBASE, CINAHL databases, including studies which utilised a frailty index containing at least 30 health deficits. Outcomes assessed included mortality, complications, length of stay and discharge location. Study and frailty index quality were assessed, with findings narratively described.

Phase 1 Results (Chapter 2): Thirteen studies utilising frailty indices were identified, nine prospective and four retrospective. Frailty index quality was high in 11 of the 13 studies. Frailty indices identified patients at risk of increased death, surgical complications, increased length of stay, and discharge to residential care. The term "frailty index" was found to be misapplied to a number of measurement tools not fulfilling criteria to be true frailty index scales.

Phase 2: Two concurrent prospective cohort studies were conducted in a tertiary metropolitan hospital, in an intensive care unit and peri-operative department. Adult patients aged ≥ 50 years (ICU) or ≥ 65 years (surgery) admitted between February and June 2017 were eligible for inclusion. Frailty (Clinical Frailty Scale, Edmonton Frail Scale, Frailty Index) were measured at baseline. Outcomes included mortality, discharge to residential care, ICU and peri-operative complications, six-month mortality and residential location.

Phase 2 Results (Chapters 4, 5, 8) : Three-hundred and thirty-six patients were enrolled in a four-month period, 160 ICU patients, 218 surgical patients, with 42 patients in both cohorts. Frailty prevalence (measured via the Edmonton Frail scale) was 36% in ICU patients, and 24% in surgical patients. Mortality in frail patients was higher in both ICU and surgical cohorts (ICU: 24% vs. 9%, $p = 0.010$; surgery = 10% vs. 2%, $p = 0.019$). Patients with frailty

were less likely to be discharged home and more likely to be discharged to in-patient rehabilitation, and to be residing in assisted living facilities at six month follow up.

Phase 3: Based on the results from the cohorts enrolled in Phase 2 above, the Clinical Frailty Scale was compared to the multi-dimensional Edmonton Frail Scale, with agreement measured via Kappa co-efficient, and correlation via Spearman's correlation coefficient. The affected health domains of patients with frailty were compared with those of patients without frailty.

Phase 3 Results (Chapter 4): Clinical Frailty Scale and Edmonton Frail Scales were highly correlated in ICU patients (Spearman correlation coefficient = 0.85; 95% CI, 0.81 to 0.88), with high agreement (kappa coefficient = 0.78; 95% CI, 0.68 to 0.88), and in surgical patients (Spearman correlation coefficient, 0.81; 95% CI, 0.77 to 0.86; kappa coefficient, 0.76; 95% CI, 0.70 to 0.81). Frail patients had worse health status across the full spectrum of frailty domains, in particular functional dependence, malnutrition, and prior hospital admissions.

Phase 4: A secondary analysis of an existing dataset was conducted to examine the feasibility and inter-rater reliability of retrospectively determining a Clinical Frailty Scale from the medical record of critically ill patients. One-hundred and forty-four ICU patients had CFS scores independently assigned by four blinded investigators, with inter-rater agreement between CFS scores examined via quadratic weighted Cohen's kappa coefficients.

Phase 4 Results (Chapter 6): Of 144 enrolled patients, 137 (95%) were able to have a CFS score assigned retrospectively from the medical record. Cohen's kappa coefficient for inter-rater reliability between frailty assessors was 0.67, confirming substantial agreement. Frailty measurement was thus deemed feasible from the ICU clinical record.

Phase 5: A retrospective population-based cohort study was conducted, analysing data from the Australian and New Zealand Intensive Care Society Adult Patient Database. All patients aged ≥ 80 years on admission to ICU between 1 January 2017 and 31 December 2018 were included in the study. The database was interrogated for the Clinical Frailty Scale on admission, with a mixed effects logistic regression fitted to the primary outcome of in-hospital mortality. Secondary outcomes were length of stay (hospital and ICU), re-admission to ICU, and discharge destination (including new chronic care or nursing home admission).

Phase 5 Results (Chapter 7): 15,613 patients aged ≥ 80 years were included from 131 ICUs; 6,203 patients (40%) were frail. Patients with frailty had higher illness severity, and were more likely to be admitted emergently to ICU with sepsis or respiratory failure. Mortality was higher in patients with frailty (17.6% vs. 8.2%, $p < 0.001$; adjusted mortality OR [95% CI] = 1.87 [1.65 – 2.11], $p < 0.001$). Patients with frailty had longer lengths of stay in-ICU and in-hospital, and were more likely to be newly discharged to nursing home/chronic care (4.9% vs. 2.8%, $p < 0.001$).

Phase 6: Based on the results from the cohorts enrolled in Phase 2 above, I developed a frailty index from routine data collected on hospital admission, and tested in both surgical and ICU cohorts. The diagnostic performance of the frailty index against existing frailty tools for both screening (the Clinical Frailty Scale) and measurement (the Edmonton Frail Scale) was assessed. The discriminative ability of the frailty index for mortality was compared to existing risk predictions tools, including the Acute Physiology and Chronic Health Evaluation (APACHE) III score (ICU) and the P-POSSUM score (surgical patients).

Phase 6 Results (Chapter 8): A 36-item frailty index was constructed, able to be completed for all patients. Correlation between Edmonton and Clinical Frailty scales was strong for both ICU and surgical patients. The frailty index had good discriminative ability for prediction of mortality, comparable with the performance of the APACHE-III illness severity score in ICU (AUC-ROC [95% CI] = 0.75 [0.64 – 0.85] vs. 0.80 [0.72 – 0.88]) and the P-POSSUM score in surgery (AUC-ROC = 0.76 [0.61 – 0.91] vs. 0.81 [0.71 – 0.92]).

Conclusions

Frailty is common in critically ill and surgical patients, affecting the full spectrum of health domains, and predisposing to poor outcomes. The Clinical Frailty Scale accurately screens for frailty in these cohorts, is able to be measured retrospectively from the clinical record, and can be used to determine frailty in critically ill patients at a population registry level. Frailty indices derived from routine hospital data are able to measure frailty in the peri-operative and ICU setting; electronic medical records show promise in automating such measurement.

Declaration

This thesis comprises only my original work toward the degree of Doctor of Philosophy.

The contribution by co-authors to jointly-authored works included in this thesis has been clearly acknowledged. Statistical analyses were performed by myself under the guidance of the Melbourne Clinical and Translational Sciences platform at the University of Melbourne.

The thesis length is less than the maximum word limit.

Dr Jai Darvall

Preface

This thesis comprises work carried out by myself as the principal researcher, supervised by two joint supervisors, Professor David Story (Chair of Anaesthesia at the University of Melbourne) and Professor Wen Kwang Lim (Clinical Director of Medicine and Aged Care at the Royal Melbourne Hospital). I also acknowledge the assistance of my co-authors on the six published papers included with this thesis. My input comprised the majority proportion of all aspects of the work. All work contained in this thesis is original. I also gratefully acknowledge the assistance of an Australian Government Research Training Program Scholarship, as well as the Anaesthesia, Peri-operative and Pain Medicine Unit at the University of Melbourne and the Australian and New Zealand College of Anaesthetists, for the provision of a Melbourne Emerging Researcher Scholarship towards completion of this thesis.

Published articles included in this thesis:

1. Darvall JN, Gregorevic KJ, Story DA, Hubbard RE, Lim WK. Frailty indexes in perioperative and critical care: A systematic review. *Arch Gerontol Geriatr*. 2018;79:88-96. doi: 10.1016/j.archger.2018.08.006 (Pages 19 – 41).
2. Darvall JN, Braat S, Story DA, Greentree K, Bose T, Loth J, Lim WK. Protocol for a prospective observational study to develop a frailty index for use in perioperative and critical care. *BMJ Open*. 2019 Jan 9; 9(1): e024682. doi: 10.1136/bmjopen-2018-024682. (Pages 42 – 53).
3. Darvall JN, Greentree K, Braat MS, Story DA, Lim WK. Contributors to frailty in critical illness: Multi-dimensional analysis of the Clinical Frailty Scale. *J Crit Care*. 2019 Aug;52:193-199. doi: 10.1016/j.jcrc.2019.04.032 (Pages 54 – 73).
4. Darvall JN, Boonstra T, Norman J, Murphy D, Bailey M, Iwashyna TJ, Bagshaw SM, Bellomo R. Retrospective frailty determination in critical illness from review of the ICU clinical record. *Anaesth Intensive Care*. 2019 Jul;47(4):343-348. doi: 10.1177/0310057X19856895 (Pages 106 – 117).
5. Darvall JN, Bellomo R, Paul E, Subramaniam A, Santamaria J, Bagshaw S, Rai S, Hubbard RE, Pilcher D. Frailty in very old critically ill patients in Australia and New Zealand: a

population based, cohort study. *Medical Journal of Australia*. 2019 Oct;211(7):318-323. doi: 10.5694/mja2.50329 (Pages 118 – 141).

6. Darvall JN, Loth J, Bose T, Braat S, De Silva A, Story DA, Lim WK. Accuracy of the Clinical Frailty Scale for perioperative frailty screening: A prospective observational study. *Can J Anaesth*. 2020 Jun;67(6):694-705. doi: 10.1007/s12630-020-01610-x. (Pages 74 – 105).

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Acknowledgements

This PhD has been made possible with the staunch support and guidance of a number of people. My two supervisors in particular have been crucial in this endeavour. Professor David Story, as the inaugural Chair of Anaesthesia at the University of Melbourne, was the perfect person to approach when embarking on a PhD in the area of vulnerable elderly surgical patients. More than just his capabilities as a content expert, however, he has always been ready with encouraging and supportive advice, and has been instrumental in navigating University processes. I was also very fortunate that Professor Kwang Lim, as the Clinical Director of Medicine and Aged Care at the Royal Melbourne Hospital, was willing to take me on as a PhD student. His expertise in frailty, as well as his sage advice, calm approach to complex ideas, and guidance through roadblocks, has been pivotal. In addition, my mentor, Professor Kate Leslie, has been a guiding light and source of inspiration in my research career. Her constant advocacy, help and support have made this all possible.

I am very grateful to the Anaesthesia, Peri-operative and Pain Medicine Unit at the University of Melbourne (now Centre for Integrated Critical Care), as well as the Australian and New Zealand College of Anaesthetists, for the provision of the inaugural Melbourne Emerging Researcher Scholarship towards completion of this thesis.

My parents, Jon and Leela, have instilled in me from a young age the great importance of curiosity and learning, this PhD is in no small part due to their continued belief and encouragement. I thank you both, and also my parents-in-law, all four of you have been an endless source of help to us over the years.

Most importantly, I could not have done this work without the unwavering support and encouragement of my wife, Deepa. I embarked on this PhD, quite ambitiously perhaps, with our three small children aged under five years old. My deepest thanks and love to you for the patience, understanding and flexibility this required, and of course to our three wonderful boys, Harvey, Arlo and Leo, who remind me every day how important life away from academic and clinical work is.

I hope that this PhD forms part of a groundswell of change about how we approach patients with frailty in critical illness and surgery. I have greatly enjoyed the process of learning more about these vulnerable groups; it has changed how I practice as a doctor. I hope to continue this process of discovery in the future.

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Chapter 1. Introduction

1.1 Summary

- Frailty is a state of vulnerability to pathophysiological stress, resulting from the accumulation of health deficits over time.
- The two paradigms of frailty are the phenotypic and deficit models, with important differences in construct and measurement.
- Many different frailty measurement tools exist, varying in comprehensiveness and complexity of administration.
- In critically ill and surgical patients, frailty predisposes to complications, increased length of stay, mortality, and functional dependence. Ageing populations in these settings, with commensurate increase in frailty prevalence, pose significant challenges to health services.
- Measurement of frailty in ICU and surgery poses unique challenges; the ideal screening and measurement instruments are not well defined.

1.2 Background

Perhaps the most significant challenge to modern healthcare is that of ageing global populations. By 2050, more than 2 billion people will be aged ≥ 60 years worldwide.[1] In light of this, the concept of patient frailty has become recognised as a clinical entity of importance to clinicians, patients and health systems at large. Frailty prevalence increases with age, especially so in hospitalised cohorts compared with community dwelling populations. Controversy has existed, however, over how to precisely define frailty, which in turn has historically posed challenges for its measurement. A major milestone in harmonising frailty measurement was the 2012 Frailty Consensus Conference, which recommended recognition of six frailty assessment domains: physical performance, gait speed, mobility, nutritional status, mental health, and cognition.[2] The following year, in 2013, the consensus group comprising major international ageing societies agreed on a

definition of frailty as "*a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death*."[3] This operationalised definition makes important distinctions between the related but separate conditions of sarcopenia (loss of skeletal muscle mass and function[4]), and multi-morbidity, and provided for the first time a defined framework within which to progress frailty research.[3] Importantly, despite frailty prevalence increasing with age, it does not equate to ageing, and increasingly frailty is recognised as a condition which can significantly affect younger patients.

1.3 Different paradigms of frailty

Despite the unified definition of frailty above, competing paradigms of frailty still exist, which can be broadly categorised into two models. The phenotypic model, first expounded by Fried in 2001 from a cardiovascular health study of 5300 older adults, conceives patient frailty as a constellation of features across five domains encompassing weight loss, exhaustion, weakness, slow gait speed and low activity.[5] A diagnosis of "frailty" was made if at least three of these five aspects were present. Although convenient and attractive in its simplicity, the lack of granularity in this scale, as well as challenges in measurement in less able populations (those unable to perform a gait assessment, for example, or without access to a dynamometer to measure grip strength) poses challenges.

The alternative "deficit" model proposed by Rockwood in 2005, sees frailty as an accumulation of health deficits, the sum of which contributes to a multi-dimensional risk state.[6] Originally developed from a predominantly community-dwelling cohort of 10,000 older adults enrolled in the Canadian Study of Health and Ageing, the "frailty index" which results from summation of deficits across the range of health (eg. nutrition, comorbid disease, cognitive impairment, functional decline) provides a detailed, granular assessment, and may be considered the most comprehensive model of frailty. Common to both these constructs is the basic understanding above, that a frail state predisposes to increased vulnerability in the face of acute and chronic stressors, with a hallmark being decreased

physiological reserve. There are significant differences, however, in the applicability of the two constructs, particularly with regard to comprehensiveness, and measurement, discussed further below.

1.4 Measurement of frailty

1.4.1 Measurement tools- phenotypic and deficit models

Considering the challenges surrounding frailty definition, and the controversies noted above regarding different paradigms of the frailty condition, it is unsurprising that many different frailty measurement tools have emerged. Early frailty measurement instruments were based around either the phenotypic or deficit model. The Fried scale, the prototypical phenotype measurement scale, measures patient frailty across the five domains listed, with a score of ≥ 3 on this scale denoting frailty.[5] Although relatively straightforward to measure, this does involve the use of a dynamometer, which may not be readily available, and requires the patient to perform a "timed-up-and-go" test.

The deficit model reference measurement tool is the Canadian Study of Health and Ageing frailty index, (CSHA-FI) a 70-item scale that measures health deficits over a range of domains.[6] This in turn is based on a comprehensive geriatric assessment (CGA), and as such requires significant time and resources to complete.[7] The CGA does not measure frailty, per se, however it does provide the granular data required to construct a frailty index. A frailty index is derived by summing the number of health deficits present, and dividing by the number of total possible deficits. Although developed and conceptualised as a continuous scale,[6] a value of ≥ 0.25 (occasionally 0.2) by convention denotes the threshold above which patients are considered frail, with a "ceiling" value of 0.6 reliably observed, above which patients do not survive.[8] Searle et al have summarised the aspects required to construct a frailty index: variables must number at least 30, be associated with health, must cover a range of health systems, must increase in prevalence with age, and must not "saturate" too early in life.[9] Frailty indices constructed in this manner have the major advantage of being

comparable across populations, in that there is no requirement to use the exact same candidate deficits between indices- the frailty index values derived remain valid despite differences in index construct. There are considerable advantages, therefore, to a frailty index, most of all that it represents the most comprehensive construct of frailty across the spectrum of health.

1.4.2 Simplified frailty measures

Based on the limitations in administering these more comprehensive measurement scales, a simplified "Clinical Frailty Scale" (CFS) was developed by Rockwood's team from the original CSHA-FI, which places frailty on an ordinal scale with increasing levels of dependence and functional limitation.[6] The utility of this tool is the accompanying visual depictions of frailty, aiding administration of the instrument. Originally developed as a seven-point scale, subsequently expanded to nine categories, this scale successfully predicts mortality and admission to institutional care, and has since been validated in a range of populations.[10-13] It is, however, perhaps best now known as a "judgement-based tool to *screen* for frailty", selecting patients for whom more granular assessment with a multidimensional frailty *measurement* tool should be undertaken.[14] The CFS can be both dichotomised (not frail: 1-4, frail: 5-9) and also categorised in more detail as originally defined by Rockwood et al (not frail: 1-3, vulnerable: 4, mildly frail: 5, moderately frail: 6, severely frail: 7-9).

The Edmonton Frail Scale measures nine health domains, ranging from cognitive status to functional performance, and as such is considered a multidimensional tool.[15] It is, however, more simple to administer than the CSHA-FI, and a version (the Reported Edmonton Scale) has been developed for use in patients who cannot undergo a functional performance test.[16] It has been found to correlate well with the reference CGA, and has good inter-rater reliability.[15] This scale also measures frailty as both binary (not frail 0-7, frail 8-17) and categorical (not frail: 0-5, vulnerable: 6-7, mildly frail: 8-9, moderately frail: 10-11, severely frail: 12-17).

1.4.3 Automated frailty measurement- hospital datasets

More recently, there have been promising developments in using data collected automatically by health services to automate frailty measurement; this has been particularly common in the United States where large administrative and health databases exist. Examples of these scales are the Johns Hopkins Adjusted Clinical Groups (ACG) frailty-defining diagnoses indicator[17,18], the Hospital Frailty Risk Score[19], and the modified frailty index (mFI).[20] These automated scales, being calculated from hospital coding data, necessarily bias towards comorbidity information. Unfortunately, there is comparatively little information regarding other domains of frailty, which results in questionable measurement of true frailty compared to more valid scales. The Hospital Frailty Risk Score, for example, is calculated from the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes, with only fair agreement with the Rockwood CSHA-frailty index (Pearson's correlation coefficient 0·41, 95% CI 0·38–0·47).[19]

The mFI, perhaps the most commonly used of these automated scales in the surgical domain, has been introduced with little validation work at all. Originally designed through mapping variables found within the original CSHA-FI to comorbidities contained within the National Surgical Quality Improvement Program (NSQIP) database in the US, this 11-point scale contains almost exclusively comorbid disease variables (9 of 11) (Table 1.1).[20] There is considerable doubt, therefore, whether these scales (despite being predictive for poorer outcomes in hospitalised populations), are really measuring frailty. More concerningly, recent attempts have been made to simplify the mFI even further. Reducing the 11-variable scale to a 5-variable scale (mFI-5), including only the comorbidities of diabetes, hypertension, congestive heart failure, chronic obstructive pulmonary disease, and functional status, has been performed in an orthopaedic population of > 350,000 patients undergoing hip and knee arthroplasty.[21] Further application of this tool has been made in other surgical populations, including 300,000 colorectal surgical patients.[22] Although predictive of post-operative complications, it is questionable whether this instrument can be referred to as a "frailty index" at all, given that it is measuring just five data points, only one of which is not a medical comorbidity. This is important, as although these simplified scales may indeed be predictive of post-operative outcomes, it is necessary in establishing a proper epidemiological basis for researching and comparing frailty between populations

that such measures do, indeed, measure frailty. As has been emphasised in this section, a frailty tool must be comprehensive, and multi-dimensional.

Table 1.1 Variables contained within the "modified frailty index" (mFI).[20]

Diabetes mellitus	Congestive heart failure
Hypertension requiring medication	Transient ischaemic attack or cerebrovascular accident
Functional status 2 (not independent)	Myocardial infarction
Peripheral vascular disease or rest pain	Cerebrovascular accident with neurological deficit
Chronic obstructive pulmonary disease or pneumonia	Prior percutaneous coronary intervention, prior cardiac surgery or angina
Impaired sensorium	

1.4.4 Automated frailty measurement in primary care

Other healthcare settings have seen more comprehensive implementation of population-level data in deriving frailty indices. The 36-item National Health Service "Electronic Frailty Index" ("eFI") is used in primary healthcare to identify frailty in community dwelling older adults, and given the number and breadth of variables, is a more comprehensive, multidimensional tool than those listed above. Frailty diagnosed with the eFI is associated with admission to hospital and to residential care, as well as with increased mortality.[23] In a further comparison study, correlation between this scale and reference frailty measures ranged from moderate to very strong (Spearman correlation coefficient [ρ] for CSHA-frailty index = 0.68, 95% CI 0.62 – 0.74; for the Edmonton Frail Scale = 0.63, 95% CI 0.57 – 0.69; for the CFS = 0.59, 95% CI 0.49 – 0.65).[24]

The eFI has also been demonstrated to be valid in other primary healthcare jurisdictions, with a recent study demonstrating it is possible to derive an eFI from Australian general practice data.[25] A major advantage in deriving a frailty index in the community setting is that

this measurement is available on admission to hospital, and can thus form useful information in risk stratification and in planning early for recovery from surgery or critical illness. Additionally, without the time pressures and logistic challenges inherent to gathering data during acute hospitalisations, it is likely that frailty so measured is more complete and accurate as a result.

1.5 Importance of ageing populations in surgery and intensive care

The role of frailty in both peri-operative management and critical care has become significant over recent years. This has resulted from the increasing proportion of elderly patients presenting for surgery and intensive care, prompted in turn by ageing global populations. It is estimated that by 2050, the proportion of the world's population aged ≥ 60 years will have more than doubled to over 2 billion people.[1] This has major implications for the case-mix managed in operating theatres and intensive care units (ICUs) worldwide, particularly in more affluent regions. Already, older patients account for upwards of 30% (in some cases, 50%) of all surgical procedures in developed countries.[26,27] Over the coming decades, this proportion will dramatically increase.

Ageing critically ill populations also present a unique challenge for ICUs worldwide, with similar forecasts for many developed countries, despite major differences in health care structures globally. In Scandinavia, for example, both Finland and Norway predict major increases in elderly populations and ICU capacity requirements as a result (Norway, a 30% increase in ICU bed-day requirement by 2025; Finland, a 26% increase by 2030)[28,29]. More dire predictions exist in other countries. In Canada, for example, an 80% increase in patients mechanically ventilated is forecast by 2026, resulting from over one-fifth of the population aged > 65 years by that date.[30] In Australia, over one-quarter of ICU bed-days are projected to be taken up by patients aged > 80 years by 2030.[31] Given these predictions, the role of frailty in the ageing critically ill has also become a pressing issue.

Identification of frail critically ill and surgical patients, then, will become increasingly important in the coming years. This will allow timely involvement of geriatricians, as experts in the management of ageing and frailty, which can potentially provide opportunity to individualise the healthcare of these patients and target interventions at specific health deficits. It can also provide opportunity for goals-of-care discussions, of significant importance in these high-risk populations.

1.5.1 Challenges in frailty measurement in ICU and surgery

There are unique constraints to frailty measurements in surgical and critically ill populations, including an inability to assess functional performance (acute surgical pathology or critical illness leading to mobility impairment and preventing, for example, a timed-up-and-go-test); difficulties assessing cognitive domains (due to sedation, mechanical ventilation, or delirium); and challenges in obtaining accurate an history from patients. There is also a paucity of research validating commonly used frailty scales (such the CFS, Fried scale, or Edmonton Frail Scale) in these settings against accepted, comprehensive tools such as the CSHA-FI. Despite these challenges, a number of studies have assessed frailty and its impacts in these patient groups.

1.6 Studies of frailty in critical illness

Although recognised as a syndrome in community dwelling older adults and in other acute hospitalised populations for at least 20 years, all studies specific to frailty in the ICU have been conducted within the last decade. Indeed, the title of perhaps the first review article identifying frailty as relevant to critical care: *"Frailty in the critically ill: a novel concept"* reveals how unique this condition was considered as recently as 2011.[32] This paper outlined the relevance of the frailty condition to critically ill patients, whilst commenting that most of the then-knowledge base was derived from other surrogate markers such as pre-existing chronic disease, and functional dependence. The benefits of frailty measurement in other populations were listed, with the conclusion*: "Frailty… has not yet been evaluated in the critically ill patient."* This paper also advocated using the CFS for measurement in the ICU.

1.6.1 Early studies of frailty in ICU

The first observational study of frailty was conducted by the same Canadian group. This initial prospective cohort study of 420 patients aged > 50 years across 6 ICUs in Alberta, Canada, was published in 2014, and demonstrated poor outcomes for frail patients, both in-hospital and at longer term follow up in survivors.[10] As defined by a CFS ≥ 5, 30% of this cohort were measured frail, with frailty associated with a doubled risk of one year mortality (32% vs. 16%), and increased functional dependence in survivors of critical illness (71% vs 52%). Longer durations of stay were observed for frail patients, both in-ICU (median [IQR] 7 [4–13] vs. 6 [3–10] days, p = 0.02) and in-hospital (median [IQR] 30 [10–64] vs. 18 [10–40] days, p = 0.02), with an increase in adverse events and hospital re-admission. The same cohort of patients were followed up to examine longer term health related quality of life at six and 12 months; surviving patients with frailty were more likely to have problems with mobility, self-care, usual activities, pain/discomfort, anxiety/depression. This paper concluded that frailty in critical illness was common, with significant implications for survival, length of stay, and quality of life.

A planned sub study of this original cohort examined outcomes in younger critically ill patients (aged 50 – 65 years).[33] This sub study demonstrated that poorer outcomes with frailty were not confined to the older population, with increased one-year mortality (33 % vs. 20 %, p = 0.039) and higher one-year rehospitalisation rates (61 % vs. 40 %; p = 0.02). The authors concluded that frailty measurement should include younger cohorts.

In addition to this initial Canadian work, other groups also published early studies of frailty in critical illness. A small study published in 2014 demonstrated the feasibility of using Fried's criteria for measuring frailty near hospital discharge, although the high "frailty rate" in this study (82%) demonstrates the challenges of separating out true pre-existing frailty prior to the onset of critical illness from the decrement in health resulting from critical illness itself.[34] Concurrently published in 2014, Le Maguet's group in France enrolled 196 patients aged ≥ 65 years across four ICUs, comparing both the CFS and the Frailty Phenotype

with commonly used illness severity scores in mortality prediction.[35] Interestingly, despite significantly greater numbers of co-morbidities and disabilities at baseline in frail patients, illness severity scores (Simplified Acute Physiology Score II [SAPS II]; modified SAPS II [SAPS II without age] score; and Sequential Organ Failure Assessment [SOFA] score) did not differ between frail and non-frail patients. Similarly, sequelae of critical illness and traditional associations with poor outcome (including severe sepsis, septic shock, acute renal failure, vasopressor use, dialysis, and duration of mechanical ventilation) did not differ with frailty status. Despite this, frail patients had significantly higher ICU, hospital and six-month mortalities: among 46 frail patients as diagnosed by a CFS ≥ 5, six-month mortality was almost 60%, twice that of non-frail patients ($p = 0.002$). This study thus demonstrated the importance of chronic co-morbid disease and disability, as distinct from purely acute illness severity, in older patients with frailty.

1.6.2 Registry studies in ICU

Attempts have been made to use large database registries to report on ICU patient frailty. A Brazilian registry study published in 2018 examined outcomes in 130,000 ICU patients admitted to 93 Brazilian ICUs.[36] This study used the mFI, with limitations of this measure previously discussed. Notwithstanding concerns regarding the frailty measurement chosen, this study found that frailty was associated with increased odds of death in-hospital (OR 2.42, 95% CI 1.89–3.08), with decreased likelihood of discharge to home in survivors. Interestingly, treatment intensity (including organ supports such mechanical ventilation and renal replacement therapy) were *more* common in frail patients, in contrast to the studies by Le Maguet and Bagshaw as well as the meta-analysis above. This lends weight to concerns regarding the frailty measure chosen in this study, and whether the predominantly comorbidity-centred mFI is really measuring true frailty across the full spectrum of health. This concern was recently raised by our group in the journal *Intensive Care Medicine*.[37]

1.6.3 Effect of frailty in specific ICU populations

A number of recent studies have gone on to examine the effect of frailty in specific ICU sub-populations. A large registry study published in 2019 examined 88,000 critically ill trauma

patients, also using the mFI, which was nonetheless found to be predictive of both increased rates of complications (34% vs. 18%, $p < 0.001$), and mortality (18.1% vs. 9.7%, $p < 0.001$), with increased rates of discharge to rehabilitation.[38] A 2019 study of 1500 ICU patients with suspected sepsis admitted to two US hospitals demonstrated an increased mortality associated with frailty (adjusted OR, 1.81 [95% CIs, 1.34-2.49]), and an increased odds of discharge to institutional care with increased healthcare costs.[39] In 317 ICU patients with acute kidney injury, an increased association with higher CFS scores was found at 3 and 12 months.[40] After in-hospital cardiac arrest, frailty in 388 Australian patients (as defined by the Hospital Frailty Risk Score) was associated with reduced rate of discharge home (4% vs. 26%; OR 0.13, $P = 0.001$).[41]

1.6.4 Meta-analysis of frailty in ICU

The sole meta-analysis of frailty in ICU was published by Muscedere and colleagues in 2017.[42] Encompassing 10 observational studies, and over 3000 patients, this study examined outcomes associated with frailty in critically ill adults. Notably, the CFS was used as the frailty measure in seven of the 10 included studies, with a frailty index the next most commonly used measurement tool (four of 10 studies). The meta-analysis demonstrated a pooled mortality risk for frail patients of 1.71 (95% CI 1.43 – 2.05, $p < 0.001$), and less likelihood of discharge home (RR 0.59; 95% CI 0.49 – 0.71; $p < 0.001$). No differences were found in pooled analyses for length of stay or treatment intensity (mechanical ventilation, vasoactive medication).

1.7 Frailty in surgery

Frailty in surgical patients has been shown to increase both post-operative complications and mortality.[43] A 2019 systematic review encompassing 2300 surgical patients aged ≥ 60 years across 12 studies demonstrated a risk ratio for post-operative complications of 1.6 (95% CI 1.60 – 2.13) among patients with frailty.[44] Among older surgical patients, the risk imparted by frailty is even greater. A systematic review of 17000 surgical patients aged ≥ 75 years enrolled in 23 studies demonstrated that pre-operative frailty was associated with

increased one-year mortality in all studies (ORs ranging between 1.1 and 4.97), discharge to institutional care, and poorer quality of life.[45] A range of frailty measures were used in the studies included in these reviews, including the Fried score, the frailty index, comprehensive geriatric assessment, and the mFI, among others.

1.7.1 Simplified frailty measurement in surgical patients

The CFS has been successfully administered in surgical populations, including in a Canadian study published this year of 702 non-cardiac surgical patients, demonstrating frailty was associated with death, new disability, and institutional discharge.[46] In an emergency general surgical population, the CFS demonstrated an increasing "dose-response" relationship with risk of death in a 2019 study of 2200 patients, with each increment of CFS score associated with an 80% increase in 90-day mortality (OR 1.80, 95% CI: 1.61–2.01).[12] The Edmonton Frail Scale has also been used in the surgical setting, including in a study of 125 non-cardiac (predominantly orthopaedic) surgical patients. An Edmonton score ≥ 8, denoting frailty, was associated with increased post-operative complications (OR 5.02, 95% CI 1.55 – 16.25), and lower chance of home discharge.[47] Adding the Edmonton score to the EuroSCORE cardiac surgical risk tool was also found to improve mortality prediction in a cohort of cardiac surgical patients aged ≥ 75 years.[48]

1.7.2 Frailty in specific surgical populations

Cardiac surgical patients, often older with considerable comorbid disease, have been the subject of numerous studies investigating the interplay of frailty and outcomes. A 2018 US study reported on 40,000 patients undergoing coronary artery bypass grafting, with a frailty prevalence of 22% (as measured by the Johns Hopkins Adjusted Clinical Groups frailty indicator. Frailty was associated with an increased longer-term mortality (adjusted hazard ratio, 1.20; 95% CI, 1.12 – 1.28).[49] A related population with an even higher frailty prevalence is the trans-catheter aortic valve implantation (TAVI) cohort. A systematic review of 4500 patients across ten studies found objective frailty measures identified patients at much greater risk for late mortality following TAVI procedures (HR 2.63, 95% CI 1.87-3.70).[50]

Oncological surgical patients are at particular risk from the combined effects of frailty and cancer processes. A systematic review of 1000 patients across six studies demonstrated frailty in cancer surgery patients increased the risk of major post-operative complications, and institutional discharge.[51] Vascular surgical patients are also commonly older, with comorbid disease burden and commensurate high frailty prevalence. A study of 129 patients undergoing major vascular surgery demonstrated frailty (as measured by the CFS) was associated with greater risk of institutional discharge (22% vs 6%; P = 0.01), and 30-day mortality (8% vs 0%; P < 0.01).

1.8 Knowledge gaps

Despite the significant progress over the last ten years in frailty research in ICU and surgery, demonstrating the poorer outcomes associated with frailty, there remain significant gaps in the measurement and understanding of frailty in these populations. The most appropriate screening and subsequent measurement (diagnostic) tools for frailty in surgical and ICU patients remain to be defined. Many existing frailty measures have been derived and validated in community dwelling populations; the translation of these to acute hospitalised patients poses unique challenges. Whether candidate screening scales (eg. the CFS) identify frailty with the same precision as granular multidimensional frailty measurement tools is not currently known. The uniquely "data-rich" environment of the operating theatre, and ICU, also lend themselves to contributing large amounts of information on critically ill and surgical patients. Whether routine admission variables in these populations (as distinct from hospital coding or administrative datasets) is able to be combined into a valid, multidimensional and accurate frailty index is not well researched.

Who is best to administer a frailty scoring system in ICU is also not defined. The most comprehensive assessments of frailty are able to be performed by trained researchers, dedicated to collecting this data.[5,7] The busy ICU, however, is not always well resourced for this. Alternative models see a frailty assessment performed by the nursing staff, in conjunction with information gleaned from the patient's next of kin. Limitations exist with this model, however, illustrated by an Australian single-ICU study of 205 patients by Fisher

et al.[52] In this study, only 59% of eligible patients had a CFS collected, with the majority of these (73%) assigned by the nurse in charge without input from the patients' next of kin. This has the potential to introduce bias, as subtleties relating to independence with activities of daily living or activity level may not readily apparent to nursing staff. There also exists a limitation with trained research staff collecting this information- in the study by Bagshaw et al, a large number of patients (840 of 1359 potentially eligible) were either missed, had no consent or were excluded for other reasons.[10]

Given much data gathering in the ICU is done from the medical record rather than from contemporaneous interviews with patients and/or families, work is thus required to determine how feasible routine frailty screening is in the critically ill, and whether perhaps retrospective frailty measurement from the clinical record is feasible. The inter-rater reliability of frailty determined in this manner (versus prospectively, from direct patient interview) also requires exploration.

Which health domains are associated with frailty in surgery and critical illness is not described in the literature. It is likely that certain areas are over-represented (for example, malnutrition and medical comorbidities), but there a lack of current research to guide this understanding. More research is required regarding which domains of health are affected by frailty in ICU and surgical patients, to provide the necessary epidemiological background prior to potential future development of interventions to mitigate against its impact.

Finally, there is a significant lack of large-scale research into frailty prevalence, particularly in critically ill populations. The dramatic increase in frailty research over the last decade has been mainly confined to small, often single centre studies. The few large-scale multicentre studies (> 10,000 patients) published have used questionable frailty measures (such as the mFI), thus leading to uncertainty regarding the true prevalence of frailty in ICU.[21,22,36] The Australasian ICU community has been a leader in addressing this knowledge gap since 2017, at which point the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD) began collecting frailty data using the CFS on admission to ICU.[53]

Similarly to use in other critically ill populations, this scale was operationalised for use in ICUs in Australia and New Zealand by simplifying to an 8-point scale, with removal of category 9 ("terminally ill"). This registry now comprises one of the largest datasets of frail critically ill patients worldwide; to date, however, no analysis of this database has been undertaken.

1.9 Hypotheses

- Frailty in critical illness and peri-operative care affects a wide range of health domains.
- The Clinical Frailty Scale is a valid, feasible screening tool for frailty in these populations.
- Frailty indices are able to be derived from routinely collected hospital data.
- Frailty measurement in the critically ill is possible on a population level.

1.10 Aims of the PhD

1. To review the role of frailty indices in the measurement of frailty in critically ill and surgical populations.

2. Determine which areas of health are impacted by frailty in surgical and intensive care patients.

3. Investigate the correlation between the screening CFS and multi-dimensional frailty measurement tools.

4. Explore whether frailty can be measured retrospectively from the clinical record.

5. Examine the prevalence and impact of frailty in intensive care unit populations in Australia and New Zealand.

6. To develop and validate a frailty index from medical admission data applicable to the measurement of frailty in surgical and intensive care unit patients.

1.11 Thesis outline

1. Introduction

This chapter reviews the definition and different paradigms of frailty, its measurement (including controversies with different measurement scales). This chapter also reviews the literature with respect to frailty impact in ICU and surgical populations, and highlights gaps in the knowledge where further research is required.

2. Systematic review: Frailty indices in perioperative and critical care.

This systematic review was conducted in order to review the role of frailty indices in ICU and surgical patients. It found that frailty indices were able to identify patients with frailty in these cohorts, who had increased risk of death, complications, discharge to residential care, and increased length of stay. "Frailty index" was found to be a term applied to a number of alternative measurement tools questionable in their ability to diagnose frailty.

3. *Protocol for a prospective observational study to develop a frailty index for use in perioperative and critical care*

This chapter describes the protocol developed to conduct two prospective cohort studies in surgery and intensive care at the Royal Melbourne Hospital, between February and June, 2017. It describes the inclusion criteria, data gathered, and outcomes examined.

4. *Contributors to frailty in critical illness: multi-dimensional analysis of the Clinical Frailty Scale*

Frailty in a prospective cohort of ICU patients was found to be common, and associated with poor outcomes including increased mortality in-hospital and at six months. Frailty in critically ill patients affected the full spectrum of health domains, in particular malnutrition, functional dependence and prior hospitalisations. When considered in the same ordinal

categorisations (not frail, vulnerable, mildly frail, moderately frail, severely frail), the CFS and Edmonton Frail Scale had high agreement and correlation.

5. *Accuracy of the Clinical Frailty Scale for perioperative frailty screening, a prospective observational study*

In this prospective cohort study of surgical patients, the CFS and Edmonton Frail scale had similarly strong agreement and correlation, with frailty also represented across the spectrum of health. Increased mortality and decreased rates of home discharge were observed in surgical patients with frailty.

6. *Retrospective frailty determination in critical illness from review of the ICU clinical record*

A retrospective cohort study was undertaken to assess the feasibility and reliability of determining frailty from the clinical record of critically ill patients. Retrospective determination of the CFS was found to be feasible, with acceptable inter-rater reliability in this setting, indicating validity of this approach to frailty screening.

7. *Frailty in very old critically ill patients in Australia and New Zealand: a population-based cohort study*

A retrospective population cohort study of very old critically ill patients in Australia and New Zealand was undertaken, to explore outcomes associated with frailty including mortality, length of stay, and discharge destination. Patients with frailty were found to be more commonly admitted with sepsis or respiratory failure, to be female, to have higher mortality and longer duration of hospital stay, and to be discharged to residential care.

8. *An exploratory development of a frailty index from routine hospital data in perioperative and critical care: a prospective cohort study*

In a prospective cohort study design, a frailty index was able to be formulated for application in ICU and surgical patients. The frailty index was feasible to construct using

routinely collected hospital data, and correlated well with accepted screening and measurement tools. It was found to be predictive for negative outcomes including mortality and institutional discharge.

9. *Discussion and Conclusions*

Routine frailty screening in critically ill and surgical patients is warranted. Frailty in these cohorts affects the full spectrum of health domains, which must be considered in measurement tools. The CFS accurately screens for frailty in these cohorts, can be measured retrospectively from the clinical record, and at a population registry level. Frailty indices derived from routine hospital data feasibly measure frailty in these populations; future research should focus on automating frailty index measurement.

Chapter 2: Frailty indexes in perioperative and critical care: A systematic review.

This chapter is the systematic review published in the *Arch Gerontol Geriatr*. 2018;79:88-96.

Highlights

- Frailty indices, based on health deficits, are a comprehensive mechanism for operationalising frailty in a number of patient populations.
- Although used in a number of other health care settings, frailty indices remain uncommon in ICU/surgical populations.
- Where employed, frailty indices identified patients at higher risk for death, complications and discharge to residential care following critical illness or surgery.
- The term "frailty index" was found in this review to be applied to a number of alternative measurement scales, not fulfilling the requirements for a true frailty index.
- This review highlights the need for further research on the role of frailty indices in these populations, and more rigour in the process of constructing and defining frailty indices.

Key terms: frailty, critical care, postoperative complications, risk assessment

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2.1 Abstract

Background/Objectives: Frail patients are increasingly presenting for both perioperative and intensive care, highlighting the need for simple, valid and scaleable frailty measurement. Frailty indexes comprehensively assess a range of deficits in health, and can incorporate routinely collected data. The purpose of this systematic review was to evaluate the effect of frailty indexes on surgical and intensive care risk stratification and patient outcomes (mortality, complications, length of stay, and discharge location).

Methods: A prospectively registered systematic review was performed. MEDLINE, EMBASE, and CINAHL were searched to identify studies enrolling adult surgical or intensive care patients which used a frailty index. Included studies were those published subsequent to 1990, of any study design, which utilised a frailty index consisting of ≥ 30 health deficits. Primary outcome was mortality; secondary outcomes were complications, length of stay (LOS) and discharge location. Study and frailty index quality were critically appraised by three independent reviewers, with findings narratively described.

Results: 2026 articles were screened, from which nine prospective and four retrospective cohort studies (enrolling 2539 patients) were included. Frailty prevalence ranged between 19-62%; frailty indexes identified patients at risk of increased death [mortality rates ranging between 1.9-73.1%; reported odds ratios (ORs) for death ranging between 1.76-3.09 for frail

vs. non-frail patients], surgical complications (ORs = 1.67-4.4), increased LOS, and discharge to residential care (ORs = 1.9-3.64). The term "frailty index" was found to be applied to a number of alternative measurement scales.

Conclusion: Frail patients are at significantly increased risk in critical illness and the perioperative period. Better standardisation of frailty indexes is recommended.

2.2 Introduction

Growing numbers of older adults will increasingly present for surgical and intensive care unit (ICU) management. During 2015-16 in Australia, a third of both elective surgery and emergency surgery patients were aged over 65 years.[54] In line with global trends, this age group is projected to double in size to 6.8 million Australians by 2040, with those aged 85 years or over tripling in number.[55] Similar increases will be seen in demand for intensive care services for older adults, with significant implications for intensive care provision forecast around the world. This includes Canada (21% of the population aged > 65 years, with an 80% increase in mechanically ventilated patients by 2026)[30]; Finland (26% of the population aged > 65 years, with a 25% increase in required ICU bed-days by 2030)[29]; Australia (an increase in ICU bed-days occupied by patients aged > 80 projected to increase from 6% in 1996 to 26% by 2030)[31]; and Norway (a one-third increase in ICU bed-days required by 2025).[28]

Frailty, a state of vulnerability resulting from a cumulative decline in many physiological systems over a lifetime, is an increasingly important consideration in these patient cohorts. The two accepted paradigms of frailty are a phenotypic construct (Fried et al, 2001) and a deficit accumulation model (impairments in health status, Rockwood et al, 2005), the sum of which contributes to a multi-dimensional risk state.[5,6] Measuring frailty in older adults is increasingly seen as important for risk assessment, as an emerging body of evidence confirms increased perioperative and intensive care morbidity and mortality is conferred by frailty.[10,43] A recent meta-analysis investigating prognostic factors for harm following

elective surgery included over 12,000 patients across 44 studies; frailty and frailty-related factors accounted for almost all the important predictors of adverse outcomes.[56] Frailty in critical illness confers similarly poor outcomes, with a recent Canadian study of 420 patients demonstrating a doubled risk of one year mortality (32% vs. 16%), and increased functional dependence and lower quality of life in survivors.[57] Subsequent incorporation of frailty assessment in these populations has been shown to improve prognostication above existing risk stratification tools.[35,58,59]

The 2010 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in the UK looked specifically at the population of older adults undergoing surgery, finding that whilst frailty was often considered likely to be present, it was not factored into risk assessment. Two specific recommendations were made: "Comorbidity, disability and frailty need to be clearly recognised and seen as independent markers of risk in the elderly"; and "An agreed means of assessing frailty in the perioperative period should be developed and included in risk assessment".[60] Despite consensus guidelines from major organisations calling for routine surgical frailty assessment (including the American College of Surgeons, the American Geriatrics Society and the Association of Anaesthetists of Great Britain and Ireland), this is not yet incorporated into perioperative care.[26,61] Many unknowns persist, therefore, including the prevalence of frailty in these populations, how frailty intersects with standard risk stratification tools, and how best to quantify it.

Frailty measurement is complicated by significant heterogeneity in measurement tools used, as well as reliance on functional testing, which may be difficult or impossible in ICU or surgical populations. A comprehensive approach to operationalizing frailty, without these disadvantages, involves a deficit index, wherein the number of accumulated health deficits are summed, and divided by the total number of possible deficits.[9] This approach has demonstrated consistency and reproducibility across a range of populations, and more importantly, a range of indexes.[62,63] As long as at least 30 variables encompassing a range of systems associated with health status are included, the same health deficits need not be measured across populations, yet the resultant frailty index scores and rate of deficit accumulation are comparable. This approach also has the potential advantage of

incorporating routinely collected patient data, which is then able to be used to automatically generate a frailty index without requiring clinician time or training.[64]

Although systematic reviews of frailty measurement tools in both intensive care and surgical patients exist,[42,43,45] we have not identified any reviews that have specifically examined frailty index application to perioperative or intensive care. We sought, therefore, to perform a systematic review encompassing any study design involving critically ill and surgical patients that utilised a frailty index comprising at least 30-items for risk stratification, with outcomes including mortality (primary outcome), complications, length of stay, and discharge location.

2.3 Methods

2.3.1 Search strategy

A systematic review was conducted of electronic databases including MEDLINE, EMBASE and COCHRANE CENTRAL in January 2018. The search terms used were a combination of both Medical Subject Headings (MeSH) and free text, and is outlined in the Supplementary material. Conference proceedings and reference lists of obtained articles were not systematically searched. Results were limited to English language studies concerning human subjects published after 1990. The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) statement,[65] and the study protocol was prospectively registered with Prospero (http://www.crd.york.ac.uk/PROSPERO/, registration number: CRD42017081336).

2.3.2 Study selection criteria

Included studies were those of any study design published as a full text (including randomized controlled trials, case series, cohort and cross-sectional studies), incorporating a frailty index in the assessment of surgical or ICU patients. Frailty indexes had to accord

with the guidelines published by Searle et al (Supplementary material).[9] Studies were restricted to English language studies published subsequent to 1990. Participants aged 18 years or older undergoing surgery or admitted to an ICU were included, in studies using a frailty index for risk stratification in surgical or critical care. Primary outcome was mortality, with secondary outcomes including length of stay, surgical or in-ICU complications, and discharge location. Studies were excluded if they included fewer than 30 health deficits, or if included deficits only encompassed one area of health rather than a range of health systems. Eligibility assessment was performed in an unblinded manner by two reviewers (JD and RH). Quality of studies was evaluated with an adapted version of the epidemiological appraisal instrument of Genaidy et al.[66] (Supplementary material), classifying studies as low, medium or high methodological quality. In addition, evaluation of the frailty index employed was conducted using the above guidelines (Supplementary material). JD reviewed all included studies, KG and KL reviewed half each such that two reviewers appraised each study. Disparity in study assessment was resolved initially by reaching a consensus score, or if not possible then resolved through adjudication by a third reviewer.

2.3.3 Data extraction and synthesis

Studies were interrogated for population characteristics studied (including age, type of surgery or ICU admission), exposure and outcome variables (primary outcome mortality, secondary outcomes length of stay, complications and discharge location), frailty index composition (including characteristics of included health deficits), and method of data collection. Because of significant heterogeneity in exposures, outcomes, and frailty index composition, meta-analysis of results was not possible. A narrative synthesis was instead performed.

2.4 Results

The search strategy yielded 2026 articles. After screening relevant titles and abstracts and excluding duplicates, 76 full text publications were obtained for further assessment. Of these, 63 articles were excluded, due to being editorials or systematic reviews (12 studies),

conference proceedings (16 studies), involving a non-surgical or ICU population (three studies), utilising frailty measures that were not true multi-dimensional frailty indexes or containing < 30 variables (29 studies), or utilising a full comprehensive geriatric assessment (three studies). 13 studies in total were thus included, enrolling 2539 patients (Figure 2.1).

2.4.1 Study characteristics

Nine of the 13 were prospective cohort and four retrospective cohort studies. Six studies took place in the USA, two in Canada, two in Australia, and one each in Turkey, China and the UK. Individual studies were of moderate size, ranging between 61 and 415 patients, with all but three being single centre in design. Six studies involved general or orthopaedic surgical patients, two studies cardiac surgical patients, one study cervical spinal surgical patients, one study lung transplant patients, one study patients undergoing ventricular assist device insertion, and two studies involved intensive care unit populations (Table 2.1). With the exception of one study involving lung transplant recipients, mean/median patient age was > 60 years in all other studies.

2.4.2 Study/frailty index quality

Study quality was high in six studies, moderate in three, and low in four (Table 2.1). Frailty indexes quality was high (scored ≥ 10/12, Supplementary material) in 11 of the 13 studies.

2.4.3 Outcomes

2.4.3.1 Mortality

Articles included demonstrated increasing frailty index correlated with increased mortality across all populations, with a wide range of mortality rates between 1.9% and 73.1%; reported odds ratios (ORs) for death between frail and non-frail patients ranged between 1.76-3.09 (Table 2.1). The highest mortality was observed in intensive care patients, Zeng reporting an overall 38.7% mortality rate[67], and Kizilarslanoglu demonstrating a 73.1% vs.

45.8% mortality in frail vs. non-frail critically ill elderly patients.[68] Surgical studies reported overall lower mortality, but with greater mortality rates observed in frail vs. non-frail cohorts in emergency and higher-risk surgical populations; Joseph reporting 8.5% mortality vs. no deaths in frail vs. non-frail emergency surgical patients,[69] Krishnan finding 28% mortality vs. no deaths in frail vs. non-frail hip fracture patients,[70] Dunlay reporting mortality of 39.9% vs. 16.2% in left ventricular assist device implantation, Wilson 28.3% vs. 7.1% for lung transplant patients, and Lin 23.4% vs. 6.4% in an intermediate to high-risk surgical cohort. There was also evidence of a quantitative dose-response relationship with mortality and increasing frailty index. Zeng,[67] for example, demonstrated each 1% increase in frailty index in elderly intensive care patients was associated with an increased relative risk ratio for death at 30 days of 1.11 (95% CI = 1.07–1.15), and studies in which the frailty index was defined as a categorical variable also demonstrated progressively increasing mortality risk. Lin, for example, observed 12-month mortality rates in intermediate to high risk surgical patients of 6.4% with frailty index (FI) ≤ 0.25, 15.6% (FI 0.25 – 0.4), and 23% (FI > 0.4).[71] Similarly, Krishnan observed mortality rates of 0% (FI ≤ 0.25), 5.2% (FI 0.25 – 0.4), and 28.1% (FI > 0.4).[70]

In the two intensive care unit studies, incorporation of a frailty index improved mortality risk stratification considerably beyond usual ICU risk scoring methods. In the study by Kizilarslanoglu,[68] frailty index outperformed the Acute Physiology and Chronic Health Evaluation (APACHE) 2 score; this latter score was not found to be predictive of mortality on multivariate analysis. The frailty index used by Zeng performed in isolation at least as well as traditional scales including the APACHE score, Acute Physiology Score, and Palliative Performance Scale, with improvements in mortality prediction gained through the combination of frailty index and conventional ICU scoring tools.[67]

2.4.3.2 Length of stay

Frailty was found to be associated with increasing hospital length of stay (LOS), in cardiac surgery (Jung,[72] hospital LOS 8 vs. 6 days for frail vs. non-frail patients), emergency general surgery (Joseph,[69] hospital LOS 10.0 vs. 6.3 days) and orthopaedic surgery [Cooper,[73] RR

(95% CI) for hospital stay > 5 days = 3.1 (1.4 – 6.8); and Krishnan,[70] 68 vs. 21 days for hip fracture patients] (Table 2.1). Intensive care LOS was also found to be longer with frailty (9 vs. 7 days, Kizilarslanoglu[68]).

2.4.3.3 Surgical complications

A range of surgical complications were found to be associated with frailty (Table 2.1). Post-operative delirium in both elderly general and orthopaedic surgical patients [Lin,[74] OR (95%CI) = 1.67 (1.09-2.56)] and cardiac surgical patients [Jung,[72] 3.26 (1.20-8.82)] was more common with increased frailty index. In the latter study, inclusion of the index improved the performance of the standard EuroSCORE II scale in predicting delirium. Among general surgical patients, Joseph found a major complication rate almost four times higher among frail patients [OR (95% CI) = 3.87 (1.69 – 8.84)], with increased rates of pneumonia, sepsis, urinary tract infections, and return to operating theatre.[69] Saxton, similarly, demonstrated a correlation with frailty index and number (though not severity) of complications.[75]

2.4.3.4 Discharge location

Frailty, as defined by frailty index, was found to increase the likelihood of discharge to non-home location in orthopaedic patients [Cooper,[34] RR (95% CI) = 3.1 (1.4 – 6.8); Krishnan,[70,73] 52.4% of frail vs. 20% of non-frail patients], emergency general surgical patients (Joseph,[69] 58% vs. 40% of non-frail patients), elective cardiac surgical patients [Jung,[72] OR (95% CI)= 3.64 (0.4– 33.45)], and intermediate to high-risk surgical patients (Lin,[71] 10.6% of highly frail vs. 0.9% of non-frail patients) (Table 2.1).

2.5 Discussion

This systematic review has found that studies of frailty indexes in both ICU and surgical cohorts are of predominantly high quality, and are of utility in the identification of frail patients. Frailty indexes were found to correlate with endpoints including mortality (with odds ratios for death ranging between 1.76 - 3.09), length of hospital stay, discharge to non-

home location (between three and ten-times more likely), delirium (ORs ranging between 1.67 - 3.26) and post-operative complications (up to four times more common). This adds significantly to our understanding of the quantification and impact of frailty in the perioperative and critical care setting. There is, currently, no consensus on the best way to measure frailty, especially in these cohorts. Scales incorporating performance based measures (such as the Edmonton frailty scale) have limitations in surgical cohorts, especially emergency patients, and are impossible for critically ill patients to perform.[15] The "deficit" model of frailty may be more useful in these populations, as quantification of health deficits are less confounded by acute illness.[62]

A recent systematic review and meta-analysis examining prognostic factors for adverse events after elective surgery, encompassing 44 studies enrolling more than 12,000 elective surgical patients, has reinforced the role of frailty in this context. Frailty not only predicted adverse outcomes, including post-operative complications [OR (95% CI) = 2.16 (1.29 – 3.62)], non-home discharge and duration of stay, but almost all other variables found to be associated are all considered components of the "deficit accumulation" model of frailty.[56] These included instrumental activities of daily living (IADL) impairment, malnutrition, poor functional performance, poor mobility, cognitive impairment, polypharmacy and depression. As these are all components of a well-constructed frailty index, this study lends weight to the increasing evidence for incorporation of routine frailty measurement into perioperative and ICU care.

2.5.1 Utility of frailty indexes

Whilst providing a comprehensive overview of deficits across a range of systems associated with health status, collecting information for and calculating a frailty index can be time consuming. As such, frailty indexes have been criticized as too complex for use as a screening tool.[76] One major advantage over other frailty measurement scales, however, is the potential for integration of already-collected patient data. With the increasing role of electronic medical records within health services this has the added advantage of rapid, automatic inclusion of patient information, without the disadvantage of other frailty scales

that may require specific data collection with concomitant time burden and training requirements. In thus reducing clinician or researcher time required, a frailty index derived in this manner is more likely to be adopted and maintained in clinical practice.[64] The studies included in this review varied in this aspect of ease of data collection and integration. The full 70-point index from the Canadian Study of Health and Ageing, as used by Saxton et al, was the most comprehensive but the least automated frailty index reviewed, with multiple data points requiring specific researcher time to collect. In contrast, the 32-point deficit index used by Wilson et al comprises data commonly collected on admission for all patients, including independence with IADLs, exercise and ambulatory capacity, as well as a standard inclusion of medical comorbidities. A similar index should be capable of being calculated from data collected routinely for perioperative and critically ill patients on hospital admission, thus enhancing prospects of "routine" frailty screening.

The source and veracity of information used in a frailty index may also vary. Although ideally obtained directly from a patient, in many circumstances (such as emergency surgery or within the intensive care unit), this is not possible. The study by Kizilarslanoglu,[68] for example, involved information gathering from ICU patients' next of kin or caregivers, thus accuracy of data may have been reduced compared to collection from patients themselves. This, however, is a common methodological issue with ICU studies. One advantage of a frailty index over other frailty measurement scales in this regard is that any error in the subjectivity of certain data points (particularly, for example, due to a relative being critically unwell in an ICU) is diluted across a range and larger number of deficit counts.

2.5.2 The term "frailty index"

One of the ongoing barriers to implementation of frailty measurement is the heterogeneity of tools available. In screening studies for eligibility, this review identified significant variability in the application of the term "frailty index". Many studies examined in this review lacked breadth in deficit assessment, utilised an index comprising too few variables, or measured patient attributes unrelated to frailty. Past literature has emphasised the importance of a frailty index containing at least 30 variables, in order to accurately measure

the complexities of a "failing system". An index with too few variables, particularly those containing around 10 or less, is inherently unstable.[9] This requirement for a frailty index to contain ≥ 30 variables has become accepted in the frailty literature,[77] with exclusion of those containing less deficits commonplace.[78] Furthermore, Searle et al have provided guidance on the five important determinants of variables to be used in constructing a frailty index,[9] which have also become the accepted standard in the subsequent literature by which frailty indexes are measured.[79,80] In brief, deficits should: 1. Be associated with health status, 2. Increase in prevalence with age 3. Not saturate too early 4. Cover a range of systems and 5. If used serially on the same population, variables must remain constant.

The most commonly utilised frailty measure in the surgical literature screened in this review, for example, was the "modified frailty index" (mFI).[81] Derived from mapping 11 variables contained within the NSQIP database to items contained within the original 70-item Canadian Study of Health and Aging Frailty Index, it has the advantage of rapid derivation and automated calculation. Although purportedly a multidimensional frailty measurement, however, this scale does not actually represent a comprehensive overview of the many domains of frailty but rather comprises an over-representation of medical comorbid disease. Nine of the 11 variables are medical comorbidities, with only "altered sensorium" and "functional status- not independent" incorporating assessment of other deficits. There is thus a significant under-representation or outright lack of assessment of important frailty domains such as cognitive impairment, communication, mood and behaviour, continence, nutrition and medications. When considering the criteria for construction of a frailty index above, and in keeping with many similar "frailty indexes" identified in this review (such as the Gronigen frailty indicator,[82] the Multidimensional Frailty Score,[83] and the Johns Hopkins Adjusted Clinical Groups frailty indicator[18]), the mFI should not be regarded as a robust frailty index measure. As such, it and other scales did not warrant inclusion in this systematic review. It is hoped that future studies involving frailty indexes in these and other populations will better standardise deficit number and type for inclusion, allowing for both more robust individual studies but also to assist synthesis and meta-analysis of pooled data, which was not possible in this review.

2.5.3 Strengths and limitations of the review

Strengths of this review include a strict definition of frailty index according to an accepted definition, with both face and construct validity. A further strength is the inclusion of all ICU and surgical admission types, as well as not restricting patient inclusion based on an age cut-off (as frailty is not solely found in elderly patients, particularly in critically ill and surgical populations). Limitations of this review include confining search strategy to English language only publications. Meta-analysis of results was also not possible due to marked heterogeneity of populations studied, and variability in the primary outcomes of individual studies. We did not conduct a formal assessment of publication bias, due to the small number of studies included and absence of meta-analysis. We note, however, that evaluation of publication bias is problematic in reviews containing small numbers of studies, due to lack of power, and in reviews of non-randomized studies, due to confounding.[84] We were also unable to stratify results based on different study designs, as all were cohort studies.

2.5.4 Implications for practice

As surgical and ICU populations become increasingly older and more complex, frailty indexes hold promise in improving outcomes for this cohort. With better identification of frail patients presenting for surgery and to ICU, clinicians may be able to enhance various aspects of acute care. This may include more informed discussions with patients and their families, targeting increased monitoring or postoperative resources to at-risk patients, or potential future interventions aimed at preventing or attenuating the outcomes identified in this review. Interventions such as specific rehabilitation after surgery or critical illness, or prehabilitation prior to surgery, may hold promise in improving outcomes.[85] Indeed, the benefit of comprehensive geriatric assessment in reducing the exact negative outcomes identified in this review (postoperative complications, increased length of stay, non-home discharge) has been recently demonstrated in a high risk vascular surgical population.[86] Future research is required to determine whether such interventions can specifically benefit frail ICU and other surgical cohorts.[87]

2.6 Conclusions

Frailty indexes are of utility in both identifying and risk stratifying frail patients in surgical and critically ill populations. Increasing frailty index scores were found in a variety of surgical and ICU settings to increase the risk of post-operative complications, discharge to residential care, increased length of stay, and mortality. Further research is required to determine whether improved patient outcomes result from incorporating frailty indexes into routine surgical and ICU care. Better standardisation of frailty indexes used in future studies in this area is also required, which will both enhance comparative research and improve the potential for future interventions for these frail cohorts.

Acknowledgements

The authors would like to acknowledge Ms Smaro Lazarakis for assistance with literature searching.

Conflict of interest

All authors disclose there are no conflicting interests.

Author contributions

Study concept and design: JD, WL, RH, DS

Data acquisition: JD, KG, WL, RH

Data analysis: JD, KG, WL

Preparation of manuscript: JD, WL, KG, RH, DS

Funding

This work was supported by the Australian and New Zealand College of Anaesthetists (Emerging Researcher Scholarship for the first author).

Table 2.1: Characteristics of the 13 included studies

Study (sample size)	*Population, age, study design*	*Quality*	*Location, setting*	*Frailty prevalence*	*Mortality (primary outcome)*	*Secondary outcomes/frailty prevalence*	*Frailty index deficit count*	Frailty index appraisal score
Cooper et al (2016)[73] (n = 415)	Orthopaedic surgery, > 70 years, prospective cohort study	High	Two tertiary hospitals, USA	41%	Not reported	Frail patients had longer LOS [RR (95% CI) = 3.1 (1.4-6.8) for hospital stay > 5 days; 24% of all frail patients) and discharge to institutional care [RR (95%CI) = 1.9 (1.4-2.5); 79% of frail patients).	42	12/12
Dunlay et al (2014)[88] (n = 99)	Left ventricular assist device implantation, mean age 65 years, retrospective cohort study	High	One tertiary hospital, Minnesota, USA	62%	39.9% frail patient mortality vs. 16.2% for non-frail (hazard ratio for death 3.09, 95% CI 1.40 – 7.48)	Increasing FI correlated with increased rehospitalisation [hazard ratio (95%CI) = 1.42 (0.98-2.06)].	31	12/12
Freiheit et al (2016)[89] (n = 374)	Patients undergoing cardiac surgery or medical treatment for coronary	Moderate	One tertiary hospital, Alberta, Canada	38.5%	Not reported	Initial improvement in frailty index, then deterioration after 6 months. Younger patients (< 75 years)	53	11/12

	artery disease, mean age 71 years, prospective cohort study					undergoing coronary artery bypass grafts or percutaneous coronary intervention saw sustained frailty reduction.		
Joseph et al (2016)[69] (n = 220)	Emergency general surgical patients, mean age 76 years, prospective cohort study	High	One tertiary surgical centre, Arizona, USA	32%	8.5% vs. 0% for non-frail patients	Frail patients had more major complications [OR (95% CI) = 3.87 (1.69-8.84)], discharge to non-home location (58% vs. 40% non-frail) and longer hospital LOS (10.0 vs. 6.3 days).	50	12/12
Jung et al (2015)[72] (n = 133)	Elective cardiac surgical patients, mean age 71 years, prospective cohort study	Moderate	One tertiary hospital, Winnipeg, Canada	45.9%	Low overall mortality: 2.8% for frail patients vs. 0% for non-frail.	Frail patients had more post-operative delirium [OR (95%CI) = 3.26 (1.20-8.82)], major adverse events [OR = 3.52 (0.38-32.45)] and discharge to institutional care [OR = 3.64 (0.40-33.45)], and longer LOS (8 vs. 6 days).	35	10/12
Kizilarslanoglu et al (2016)[68]	Intensive care unit patients, median age 71 years,	High	One university hospital ICU, Ankara, Turkey	21.3%	73.1% in-hospital mortality	Frail patients had longer ICU LOS (9 vs. 7 days)	55	12/12

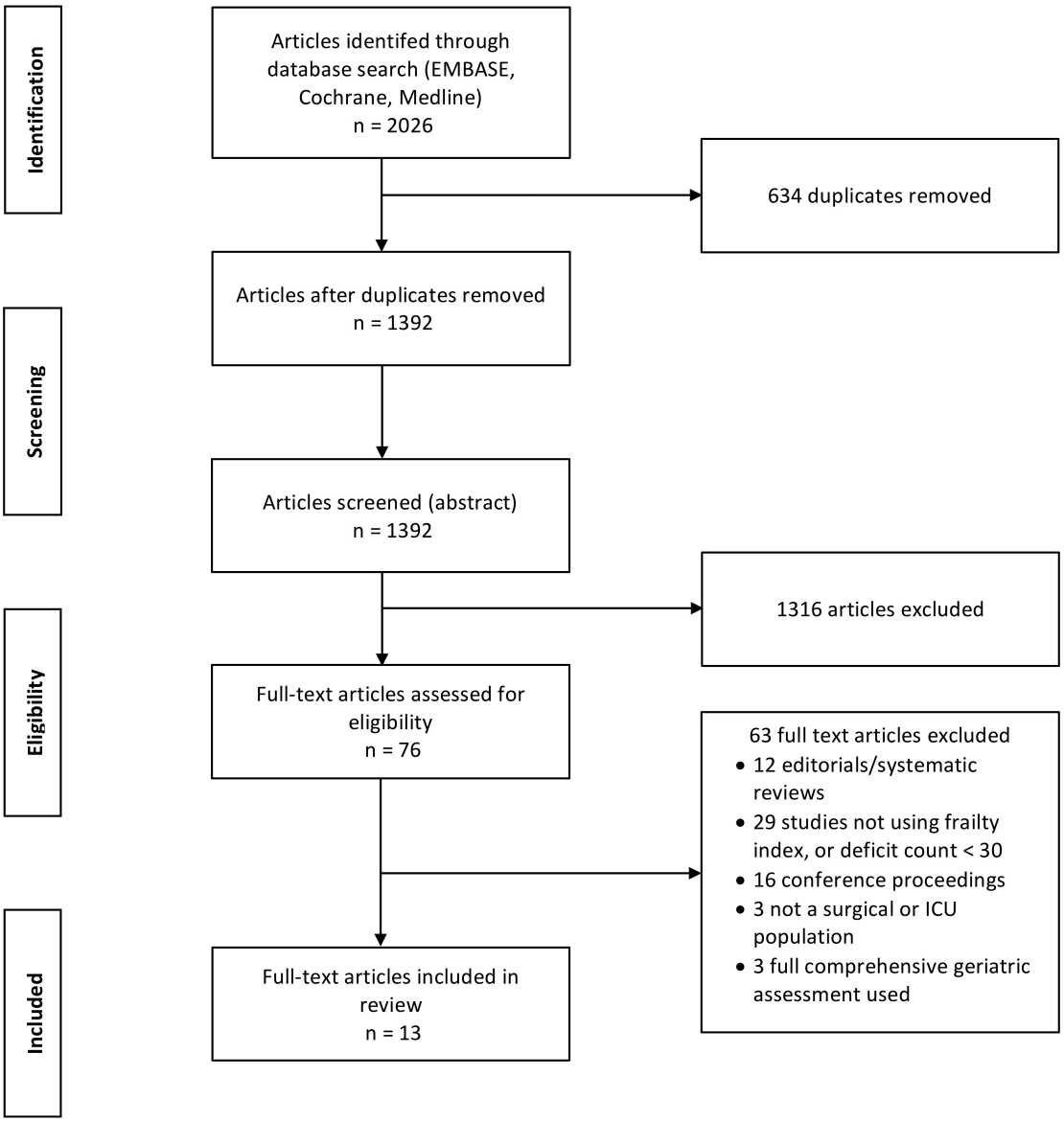
(n = 122)	prospective cohort study				(84.6% six-month mortality) for frail patients vs. 45.8% (55.9% six-month) for non-frail patients.			
Krishnan et al (2011)[70] (n = 178)	Hip fracture patients, median age 81 years, prospective cohort study	Low	One university hospital, Cardiff, UK	68.5%	In-patient mortality 28.1% in high frailty group (FI > 0.4), 5.2% in intermediate frailty (FI 0.25 – 0.4) and 0% in non-frail patients.	Mean LOS in high FI group (FI > 0.4) = 68 days vs. 21 days for non-frail patients. 6.3% of highly frail patients had returned home at 30 days vs. 41.3% of intermediate frail patients, and 80% of non-frail patients.	51	10/12
Lin et al (2016)[74] (n = 208)	Surgical or orthopaedic patients, mean age 79 years, prospective cohort study	Moderate	Four acute care hospitals in Queensland, Australia	Not reported	Low overall mortality (1.9%), higher for frail patients [OR (95%CI) = 1.76 (1.19-2.59)]	Baseline and inpatient FI were predictive of inpatient delirium [OR (95%CI) = 1.67 (1.09-2.56)] and composite adverse outcomes [OR (95%CI) = 1.54 (1.00-2.37)].	56	12/12
Lin et al (2017)[71] (n = 246)	Intermediate to high-risk surgery (vascular, intraperitoneal,	High	One tertiary hospital in Queensland, Australia	19.1%	Mortality at 12 months 23.4% in high frailty group (FI > 0.4),	Increased new admission to residential care (10.6% highly frail vs.	55	12/12

	intrathoracic, head and neck, prostate, orthopaedic), mean age 79 years, prospective cohort study				15.6% in intermediate frailty (FI 0.25 – 0.4) and 6.4% in non-frail patients.	7.8% intermediate frail vs. 0.9% non-frail), and hospital readmission (61.7% vs. 48.9% vs. 33.9% respectively 34%).		
Miller et al (2018)[90] (n = 61)	Adult patients with cervical spine deformity, mean age 58 years (non-frail), 62 years (frail), retrospective cohort study	Low	Multiple centres (number not specified) in USA	55.7%	Not reported	Increased major complications, OR (95%CI) = 4.4 (0.6-32), p = 0.14 for frail and 43 (2.7-684), p = 0.01 for severely frail patients.	40	9/12
Saxton et al (2011)[75] (n = 226)	Elective general surgical patients, mean age 61 years, retrospective cohort study	Low	One tertiary hospital, Detroit, USA	Not reported	Not reported	A dichotomised frailty index > 0.12 predicted postoperative complications [OR (95%CI) = 2.71 (1.08-6.78), p = 0.14, and correlated with poorer pre-operative quality of life.	70	11/12
Wilson et al (2016)[91] (n = 102)	Lung transplant recipients, median age 57 years, retrospective cohort study.	Low	One tertiary hospital, Minnesota, USA	45%	Mortality at 12 months 28.3% in frail patients vs. 7.1% in non-frail patients,	Increased (non-significant) hospital length of stay after transplantation [median (IQR) 14 (8–	32	6/11

					adjusted HR (95% CI) for death = 2.24 (1.22–4.19; p=0.009	18.3) days vs 10.5 (7.3–16] days, p=0.26)].		
Zeng et al (2015)[67] (n = 155)	Geriatric intensive care unit patients, median age 83 years, prospective cohort study	High	One specialised geriatric ICU, Guangzhou, China	Not reported	Overall mortality at 300 days = 38.7%, relative risk ratio (95% CI) for 30-day death with each 1% increase in FI = 1.11, 1.07-1.15.	No other outcomes reported.	52	11/12

LOS = length of stay, OR = odds ratio, HR = hazard ratio, FI = frailty index

Figure 2.1: PRISMA flowchart of literature search



Supplementary material

Search strategies for Medline, EMBASE and Cochrane Central

Medline/EMBASE:

1	exp Critical Illness/ or exp Intensive Care Units/ or exp Critical Care/
2	(icu or intensive care or critical care or intensive therap* or critical* ill*).mp.
3	1 or 2
4	exp general surgery/
5	surgery.fs.
6	exp Surgical Procedures, Operative/
7	(surg* or perioper* or peri oper* or neurosurg*).mp.
8	4 or 5 or 6 or 7
9	3 or 8
10	exp Frail Elderly/ and exp Geriatric Assessment/
11	(frail* adj4 (assessment* or index* or risk* or protective factor* or asset* or indice* or measur* or scale* or tool*)).mp.
12	10 or 11
13	9 and 12
14	limit 13 to (english language and yr="1990 -Current")

Cochrane Central:

ID	Search
#1	icu or intensive care or critical care or intensive therapy or critical illness
#2	surgery or perioperative or peri operative or neurosurgery

#3 #1 or #2

#4 frailty index or frailty assessment or frailty risk or frailty protective factor or frailty asset or frailty indices or frailty measurement or frailty scale or frailty tool

#5 #4 and #3 Publication Year from 1990 to 2018

Criteria for frailty index inclusion (from Searle et al[9])

1. The variables must be deficits associated with health status.

2. A deficit's prevalence must generally increase with age.

3. Chosen deficits must not saturate too early.

4. The deficits that make up a frailty index must cover a range of systems.

5. If a single frailty index is to be used serially on the same people, the items that make up the frailty index need to be the same from one iteration to the next.

Epidemiological Appraisal Instrument (adapted from Genaidy et al[66])

Score <33 = low quality, 33–35 = moderate quality, >35 = high quality

(scoring 0 = absent, 1 = partial, 2 = present)

1. Is the hypothesis/aim/objective of study clearly defined?

2. Are all the exposure variables clearly described?

3. Are the main outcomes clearly described?

4. Is the study design clearly described?

5. Is the source of the subject population (including sampling frame) clearly described?

6. Are the eligibility criteria for subject selection clearly described?

7. Are the participation rates reported?

8. Are the characteristics of study participants described?

9. Have characteristics of subjects lost after entry or not participating from eligible population been described?

10. Are important covariates and confounders described?

11. Are statistical methods clearly described?

12. Are main findings clearly described?

13. Does the study provide estimates of random variability for outcomes or exposures?

14. Does the study provide estimates of statistical parameters? 15. Are the exposure variables reliable?

16. Are the exposure variables valid?

17. Are outcome measures reliable?

18. Are outcome measures valid?

19. Is there adequate adjustment for covariates and confounders in analysis?

20. Can study results be applied to the eligible population?

Frailty Index Assessment

(scoring 0 = absent, 1 = partial, 2 = fully. Total score out of 12)

1. Are the deficits included well associated with health status?

2. Do the deficits included increase in prevalence with age?

3. Do the deficits included not saturate too early with age?

4. Do the deficits included cover a range of health systems?

5. Is the frailty index feasible to collect?

6. Is the frailty index clinically useful?

Chapter 3. Protocol for a prospective observational study to develop a frailty index for use in perioperative and critical care

This chapter is the protocol paper published in the *BMJ Open.* 2019 Jan 9; 9(1): e024682 (Appendix 1.) (Lightly edited for headings and formatting consistency).

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Keywords: frailty, critical care, post-operative complications, risk assessment

This work was carried out in the Royal Melbourne Hospital, Melbourne, Victoria, Australia.

3.1 Abstract

Introduction

Frailty is of increasing importance to perioperative and critical care medicine, as the proportion of older patients increases globally. Evidence continues to emerge of the considerable impact frailty has on adverse outcomes from both surgery and critical care, which has led to a proliferation of different frailty measurement tools in recent years. Despite this, there remains a lack of easily implemented, comprehensive frailty assessment tools specific to these complex populations. Development of a frailty index using routinely collected hospital data, able to leverage the automated aspects of an electronic medical record, would aid risk stratification and benefit clinicians and patients alike.

Methods and analysis

This is a prospective observational study. 150 intensive care unit (ICU) patients aged ≥ 50 years and 200 surgical patients aged ≥ 65 years will be enrolled. The primary objective is to develop a frailty index. Secondary objectives include assessing its ability to predict in-hospital mortality and/or discharge to a new non-home location; the performance of the frailty index in predicting post-operative and ICU complications, as well as health-related quality of life at six-months; to compare the performance of the frailty index against existing frailty measurement and risk stratification tools; and to assess its modification by patients' health assets.

Ethics and dissemination

This study has been approved by the Melbourne Health Human Research Ethics Committee. Dissemination will be via international and national anaesthetic and critical care conferences, and publication in peer-reviewed literature.

3.2 Introduction

Frailty is increasingly recognised as a clinical entity of importance to clinicians, patients and the health system at large. In particular, the relevance of patient frailty to perioperative and critical care is growing, as older adults comprise an increasing proportion of patients presenting for surgery and to intensive care units (ICUs) worldwide. Over the next decade, adults aged > 65 years will account for more than one-quarter of all ICU admissions in many countries, and up to half of all surgical patients.[29-31,54,58] In the largest ICU study to date[10], frailty was associated with almost twice the odds of mortality and new functional dependence, and in the largest meta-analysis of post-surgical complications (encompassing over 12,000 surgical patients across 44 studies) frailty was perhaps the most important predictor of adverse outcome, with more than doubled odds of post-operative complications.[56] In the almost-decade since the 2010 UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) examined older adults undergoing surgery, the recommendation that "An agreed means of assessing frailty in the perioperative period should be developed and included in risk assessment" remains unfulfilled.[60]

Frailty can be described as either a phenotypic construct (criteria such as exhaustion, weakness, low activity or weight loss are present), or as a deficit model (risk accumulates due to impairments in health-related domains such as medical comorbidities, cognition, mood and behaviour, communication, sensorium, continence, nutrition and medications).[5,6] Although various frailty measurement tools have been devised, these can be of limited use in the ICU or surgical setting. Performance based measures, for example, such as "timed-up-and-go" tests or grip strength assessment are impossible for mechanically ventilated or acutely unwell patients to perform.[92] Similarly, assessments including subjective questions requiring patient input may not be possible in this cohort, with potential for error when information is derived from surrogates.[52] Conversely, the perioperative and ICU environments are incredibly data-rich, with much information collected routinely for all admitted patients. Particularly in the era of electronic medical records, this has the potential to allow automated data integration and rapid derivation of relevant risk stratification scores.

In addition to potential automated calculation, a frailty index based on accumulated deficits has other advantages. As described by Searle et al, frailty indices demonstrate reproducibility across different populations, despite differences in composition related to which individual health deficits are present in a particular index.[9] As such, as long as certain prerequisites regarding candidate deficits are met (at least 30 deficits should be included, they should be associated with health status, increase in prevalence with age, not saturate too early, cover a range of systems and remain constant if intended for repeated use in the same population), subtle variation in terminology or specific data collected between health services for use in a frailty index do not matter.

The objective of this study, then, is to develop a frailty index, based on accumulated health deficits, that is able to be incorporated into routine hospital management of ICU and surgical patients.

3.2.1 Aims

The primary aim of this study is to develop a frailty index based on accumulated health deficits, using routinely collected hospital data, enabling rapid and easily scaleable assessment of surgical and ICU patients' frailty. Secondary aims are to assess the performance of the frailty index in predicting in-hospital mortality and/or discharge to a new non-home location, post-operative and ICU complications, as well as health-related quality of life at six-months; to compare the performance of the frailty index against existing frailty measurement and risk stratification tools; and to assess its modification by patients' health assets (protective factors that support health and wellbeing).

3.3 Methods

3.3.1 Study Design

This study is designed as a prospective, single centre cohort study, with follow up period six months post-discharge.

3.3.2 Study Setting

This study will be conducted at the Royal Melbourne Hospital (RMH), Melbourne, Australia, a tertiary metropolitan hospital that admits over 2000 intensive care patients and with a surgical volume of over 25000 operations annually. Enrolment and follow-up are expected between February 2017 and December 2018.

3.3.3 Inclusion and exclusion criteria

Patients are eligible if they:

- Are aged ≥ 65 years on admission for any surgery (emergency or elective), or
- Are aged ≥ 50 years on admission to the ICU for any indication;
- Provide written informed consent (or the Person Responsible in the event of incapacitation).

Patients are ineligible if they:

- Are non-English speaking (or the Person Responsible is non-English speaking).
- Are admitted to the ICU or operating theatre for reasons of organ retrieval.

3.3.4 Data collection (routine for all patients)

Baseline demographics: Pre-operatively (surgical patients) or on admission to the ICU (ICU patients): age, gender, height, and weight will be collected.

Surgical data: Operative type (surgical speciality)/severity (defined according to the P-POSSUM scoring system), blood loss, and American Society of Anesthesiology (ASA) score will be recorded.

ICU data: Routine ICU data collected (relating to the entire ICU admission episode) will include mechanical ventilation, renal replacement therapy, cardiac arrest, inotropes/vasoactive infusions, Acute Physiology and Chronic Health Evaluation (APACHE) III illness severity score, and presence of any limitations to medical treatment.

Other hospital data: Routine data recorded on admission for RMH patients (and common to most health services) will be used to generate a frailty index, consisting of 36 health deficits (Table 3.1). Data will be derived from the falls risk assessment and management plan (RMH form designation: form IP8L), Malnutrition risk assessment and management plan (IP63C), Pressure injury prevention plan (IP8G), Daily nursing care plan (IP8F), Nursing admission and assessment (IP8). Chosen deficits increase in prevalence with age, and encompass a range of systems associated with health status.

3.3.5 Data collection (additional, by study investigators)

Additional admission data: The Katz Index of independence in activities of daily living, and Charlson comorbidity score will be collected, with information added to the frailty index (Table 3.1) below. Data related to surgical risk stratification will be collected, including the P-POSSUM Score[93], albumin and lactate (where available), and will be compared with the frailty index for prediction of secondary outcomes listed.

Other frailty measurements: The Clinical Frailty Score[6] and the Edmonton Frailty Score[15] will both be collected. For patients that are unable to perform the "Timed Up and Go Test" component of the latter scale (eg. emergency surgical or mechanically ventilated ICU patients), a Reported Edmonton score will be derived.[16] Data collected represents the health status of the patient prior to the onset of acute illness.

Health Asset Data: The health assets index developed by Gregorevic et al[94] will be used, with data collected including educational level, family proximity, financial means, social

engagement and psychosocial wellbeing (representing patients' baseline state prior to hospital admission).

3.3.6 Outcomes

Endpoints collected will include in-hospital mortality (primary outcome); length of stay (time in days between either admission to the intensive care unit and discharge from hospital, or surgical operation and discharge from hospital); discharge destination (including new non-home discharge, including assisted living facility, rehabilitation or other acute hospital location); post-operative/ ICU complications (acute myocardial infarction, cardiac arrest, sepsis, acute pulmonary oedema, deep venous thrombosis, pulmonary embolism, stroke/transient ischaemic attack, wound infection, unplanned return to operating theatre, unplanned ICU/HDU admission) (all secondary outcomes). The outcome assessors will have access to frailty information collected.

Six-month follow up: Health-related quality of life (EQ-5D scale), place of residence (home, residential care facility, hospital) and Clinical Frailty Scale will be recorded. A scripted telephone text will be used, proven feasible and valid in both geriatric populations and ICU survivors.[95,96] In addition, we believe this study will be the first to administer the Clinical Frailty Scale by telephone, thus will provide an assessment of its feasibility through this modality.

3.3.7 Statistical analyses

We will calculate a frailty index score for each patient with 80% or more non-missing health deficit scores.[97] A frailty index score will be derived for each patient as the sum of the deficit scores divided by the total number of non-missing deficit scores thus ranging from 0 (no deficits) to 1 (all deficits). Patients with a frailty index score ≥ 0.25 will be considered frail.[62] A histogram and descriptive statistics of the frailty index scores will be provided for the entire patient sample and by surgical/ICU patients, gender, and age. Mean frailty index scores will be plotted versus age for all patients and by surgical/ICU status. A linear

regression analysis of the frailty index on age will be performed and by surgical/ICU status to obtain the rate of accumulation of health deficits over age, in case of positive skewness the frailty index scores may be log transformed before analysis. A random sampling procedure using 80% of frailty index items without replacement will be used and repeated several times to investigate the impact of an individual item on the rate. This approach has been successfully used in similar studies of frailty indices.[64]

A logistic regression model will be fitted to the outcomes of in-hospital mortality (primary outcome), discharge to a new non-home location, in-hospital mortality or discharge to a new non-home location, post-operative and ICU complications, including in the model the frailty index, surgical/ICU status, gender, and age. Receiver operating characteristic (ROC) curves and the area under the ROC curves will be obtained to assess the ability of the model to discriminate between two classes of these outcomes. Health-related quality of life at 6 months, whereby death will be coded as 0, will be analysed with a linear regression model using the explained variation to evaluate overall model performance. Anticipating about 5% missing quality of life data, we will use multiple imputation to explore the sensitivity of the results to underlying missing data assumptions. We will obtain Spearman's rank correlation between the frailty measurement tools (the frailty index, Edmonton and Clinical Frailty Scales) on admission and between the frailty index and risk stratification tools (APACHE for ICU and P-POSSUM for surgery). Each patient's score will be categorised into frail, vulnerable and non-frail (reference); for the frailty index (frail ≥0.25, vulnerable 0.2-<0.25, non-frail 0-<0.2), Edmonton (frail ≥8, vulnerable 6-7, non-frail 0-5) and Clinical Frailty Scale (frail ≥5, vulnerable 4, non-frail 1-3). We will examine the difference in the strength in association between each categorised frailty scale and the outcomes using the models described earlier. Furthermore, we will obtain the measures listed above to compare the ability of the models to predict these outcomes between the three categorised frailty tools and to predict in-hospital mortality between the frailty index and risk stratification tools. Modification of the effect in frail versus non-frail patients by health assets for outcomes (death, new non-home discharge location, and post-operative and ICU complications) will be examined for the frailty index using interaction tests.

3.3.8 Sample size

A convenience sample of 200 surgical and 150 ICU patients from a single hospital is planned. Based on comparative literature (including a systematic review and meta-analysis of over 8000 surgical patients, and the largest multicentre study of ICU frailty), we assume that 20% of surgical patients and 30% of ICU patients, combined about 24%, will be frail.[10,98] We will be able to obtain a 95% confidence interval of +/- 4.4% around the prevalence of frailty of 24% with a sample size of 350. In addition, we anticipate an in-hospital mortality of 5% in surgical patients (based on the pooled mortality rate in the meta-analysis above) and 21% in ICU patients, overall about 10%. Assuming the odds of in-hospital mortality of frail patients is 3.5 times than that of non-frail patients (based on pooled odds ratios from previous systematic reviews[45,98]) and in-hospital mortality is 6.8% in those who are not frail, the power to detect this effect with a sample size of 350 patients is 87% (two-sided 5% alpha).

3.4 Patient and Public Involvement

The development of the study design was informed by patient centred endpoints- rather than just assessing mortality, new residential care admission, post-operative and post-ICU complications are outcome measures of importance to patients. Similarly, assessment of quality of life (and potential decrement in quality of life) is also patient-centred. During the consent process, patients or their Person Responsible are given verbal and written information that study results are available to be disseminated to them. A written summary of the study findings will be provided in this instance. Specific patients were not however formally involved in the study design.

3.5 Ethics and Dissemination

Ethics approval for this study has been granted by the Melbourne Health Human Research and Ethics Committee (20 January 2017, HREC/16/MH/321). Results from this study will be published in a peer-reviewed medical journal.

3.6 Discussion

The importance of routine frailty assessment in the perioperative and ICU setting has been emphasised by various organisations, including the American College of Surgeons, the American Geriatrics Society and the Association of Anaesthetists of Great Britain and Ireland.[26,61] Given this pressing need for an easily implementable and valid frailty assessment tool, various scales have been developed. One such frailty measure, the "modified frailty index" (mFI), has the advantage of using automatically collected variables from the US National Surgical Quality Improvement Program (NSQIP) database. Unfortunately, only 11 items are contained in this index, with the majority (nine) representing medical comorbidities, thus it can perhaps be more accurately described as predominantly a "comorbidity" scale.[81] The Groningen frailty scale, although encompassing a wider range of health deficits, numbers only 15 deficits in total.[82] A third proposed scale, the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses indicator, only comprises 12 items and includes criteria such as "poverty" and "barriers to access to care" which may more accurately be described as absent health assets, rather than deficits contributing to frailty per se.[18] More recently, frailty indices in non-surgical/ICU specific populations have been developed using other health databases such as Medicare claims-based data,[99] or the interRAI assessment system, which aids the comprehensive geriatric assessment of older hospitalised inpatients.[64]

This study will thus provide a comprehensive and timely assessment measure of frailty, and its importance in an increasingly elderly surgical and critically ill population. Although routinely collected data does vary slightly between health services, potentially limiting generalisability, conducting sensitivity analyses will allow for individual variable effect to be assessed. As this group poses new challenges for anaesthetists, intensivists, surgeons, peri-operative physicians, and health services alike, derivation of an automated frailty index using routine hospital data has the potential to revolutionise risk stratification, and improve outcomes, as the prevalence of frailty increases dramatically in coming years.

Authors' contributions

JD: was involved in study design, protocol drafting and manuscript preparation

DS: was involved in study design, protocol drafting and manuscript preparation

SB: was involved in study design, protocol drafting and manuscript preparation

KG: was involved in protocol drafting and manuscript proofing

JL: was involved in protocol drafting and manuscript proofing

TB: was involved in protocol drafting and manuscript proofing

KW: was involved in study design, protocol drafting and manuscript preparation

Funding statement

This work has been partially supported by an Emerging Researcher Scholarship for the first author by the Australian and New Zealand College of Anaesthetists, from a grant from Dr Peter Lowe.

Competing interests statement

All authors declare no competing interests

Table 3.1: Frailty Index (from routine data collection)

1	Falls in last 12 months	0 = no, 1 = yes	
2	Dementia diagnosis	0 = no, 1 = yes	
3	Altered cognition	0 = no, 1 = yes	
4	On four or more medications, at least one affecting CNS/CVS	0 = no, 1 = yes	
5	Vision impairment	0 = no, 1 = yes	
6	Hearing impairment	0 = no, 1 = yes	
7	Assistance with transferring	0 = no, 1 = yes	
8	Assistance with mobilising	0 = no, 1 = yes	
9	Assistance with toileting	0 = no, 1 = yes	
10	Assistance with bathing	0 = no, 1 = yes	
11	Assistance with dressing	0 = no, 1 = yes	
12	Postural hypotension/dizziness	0 = no, 1 = yes	
13	Bowel incontinence	0 = no, 1 = yes	
14	Urinary incontinence	0 = no, 1 = yes	
15	Eating poorly?	0 = no, 1 = yes	
16	Lost weight without trying?	0 = no, 0.5 = 1-10 kg, 1 = > 10 kg	
17	Pressure injury- current or past	0 = no, 1 = yes	
18	Neuropathic foot disease	0 = no, 1 = yes	
19	Problems managing at home prior to admission	0 = no, 1 = yes	
20	Often feels sad or depressed?	0 = no, 1 = yes	
21	Requires assistance with eating?	0 = no, 1 = yes	
	Charlson Comorbidity Data		
22	Ischaemic heart disease	0 = no, 1 = yes	
23	Congestive heart failure	0 = no, 1 = yes	
24	Peripheral vascular disease	0 = no, 1 = yes	
25	Cerebrovascular disease	0 = no, 1 = yes	
26	Hemiplegia	0 = no, 1 = yes	
27	Chronic lung disease	0 = no, 1 = yes	
28	Connective tissue disease	0 = no, 1 = yes	
29	Peptic ulcer disease	0 = no, 1 = yes	
30	Chronic liver disease	0 = no, 1 = yes	
31	Diabetes	0 = no, 1 = yes	
32	Leukaemia/lymphoma	0 = no, 1 = yes	
33	Malignant tumour	0 = no, 1 = yes	
34	Metastatic cancer	0 = no, 1 = yes	
35	Moderate/severe kidney disease	0 = no, 1 = yes	
36	Moderate/severe liver disease	0 = no, 1 = yes	
		TOTAL =	

Chapter 4. Contributors to frailty in critical illness: multi-dimensional analysis of the Clinical Frailty Scale

This chapter is the study published in *J Crit Care*. 2019 Aug;52:193-199. (Lightly edited for headings and formatting consistency).

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Keywords: frailty, critical care, risk assessment

Declarations of interest: none

4.1 Abstract

Purpose: Frailty in critical illness is common and associated with poor outcomes, however little is known about contributing factors. We compared the Clinical Frailty Scale (CFS) with a multi-dimensional validated tool, the Edmonton Frail Scale (EFS), and investigated which health domains are affected by frailty in ICU.

Materials and methods: This prospective cohort study enrolled patients aged ≥ 50 years admitted between February - June 2017, comparing the CFS and EFS using Spearman correlation and Kappa coefficients, assessing frailty status across health domains, and examining outcomes including mortality.

Results: 160 patients were enrolled, 33.8% were frail. Frail patients had greater in-hospital and six-month mortality [25.9% vs. 8.5%; adjusted OR (95% CI) = 3.31 (1.17, 9.39), p = 0.024; and 40.4% vs. 17.3%; OR (95% CI) = 2.84 (1.18, 6.83), p = 0.020 respectively]. CFS and EFS scales were highly correlated [Spearman correlation coefficient = 0.85 (95% CI 0.81 to 0.88)], with high agreement [kappa coefficient = 0.78 (95% CI: 0.68 to 0.88)]. Frail patients had worse health status across the spectrum of frailty domains, in particular functional dependence, malnutrition, and prior hospital admissions.

Conclusions: Frailty in the critically ill affects a range of health deficits, adequately measured via the CFS.

4.2 Introduction

With ageing critically ill populations worldwide, frailty has emerged as one of the major challenges for modern intensive care. In Australia, it is forecast that by 2030, patients aged > 80 years will account for 26.3% of all admission to intensive care units (ICUs), with similar trends seen in other countries [29-31]. Frailty, a syndrome characterised by diminished physiological reserve against external stressors, has a prevalence of over 40% in critically ill patients aged > 80 years, and is associated with twice the odds of mortality and new functional dependence [10,100]. The two paradigms of frailty are the physical phenotypic model, with criteria including exhaustion, weakness, weight loss, and decreased physical activity (with much self-reported); and the deficit model with accumulating "deficits", or impairments across a range of health-related areas [5,6]. Various measurement tools have been devised for both models, examples of the former (phenotypic) being the Fried score, and the latter (deficit) scoring system the 70-item Canadian Study of Health and Aging Frailty Index (CSHA-FI), in-turn based on a comprehensive geriatric assessment [6]. Due to the complexity in administering such an exhaustive tool, particularly in the ICU, various simplified scales have been devised. The Clinical Frailty Scale (CFS) simplifies the frailty index above into a judgement based nine-item categorical scale, able to be measured at the bedside for rapid frailty screening [6], and which correlates with increased mortality, adverse events and functional dependence in ICU survivors [10,35]. Expert consensus, however, is that such screening tools should be used to identify patients for whom more in-depth frailty assessment is indicated, using for example the CSHA-FI, or other multidimensional tools [3,15].

A major as-yet unmet challenge in frailty assessment in the ICU is quantification of which areas of health frailty affects. It is not known whether, for example, medical comorbid conditions or malnutrition contribute more towards frailty in the critically ill than do cognitive impairment, continence, or physical performance- all of which contribute to the frailty syndrome. There is a distinct lack of studies utilising multi-dimensional assessment tools encompassing the spectrum of health domains, resulting in a lack of granularity around the interplay between frailty and critical illness. There is a particularly pressing need to investigate this, as a number of automated "frailty scales" have recently been adopted, based on their ability to be constructed quickly using large patient databases [36,81].

Unfortunately, these scales are often not validated against existing, gold standard frailty measures, and can be too narrowly focused on one area (for example, medical comorbidities), thus failing to capture the multi-dimensional state that is frailty [37].

Accordingly, we conducted a prospective cohort study to examine factors contributing to frailty in the critically ill through the Edmonton Frail Scale (EFS) [15,16], a multi-dimensional frailty assessment measure shown to be valid and reliable in a range of different populations when used by non-geriatricians, and compare this to the most utilised frailty assessment tool in ICU, the CFS. Our primary hypothesis was that the EFS and CFS would be strongly correlated in a critically ill population. Secondarily, we hypothesised that differences between frail and non-frail patients could be observed in the individual EFS domains assessed, and further that these differences would translate to detrimental outcomes for frail patients such as increased mortality, length and stay and new non-home discharge, as observed in overseas cohorts.

4.3 Methods

4.3.1 Study design and population

We performed a prospective cohort study in the Royal Melbourne Hospital Intensive Care Unit (RMH ICU), Melbourne, Australia, a tertiary metropolitan ICU that admits over 2000 intensive care patients annually. Approval was gained from the Melbourne Health Human Research and Ethics Committee (20 January 2017, HREC/16/MH/321). Patients aged ≥ 50 years on admission to the ICU between February 1st and June 30th, 2017, were eligible for enrolment after written informed consent from either the patient or their surrogate in the event of incapacity. Patients who were non-English speaking, or admitted to the ICU for reason of organ retrieval, were excluded. A convenience sample of non-consecutively admitted patients were enrolled, based on availability of study investigators to screen and consent eligible patients during the day (although patients could be admitted to the ICU at any time).

4.3.2 Study data

Demographic data including age, gender, height, weight, comorbidities as defined by the Charlson comorbidity score, and residential location were recorded, along with admission diagnosis, presence of limitations of medical treatment on admission, and illness severity scores [Acute Physiology and Chronic Health Evaluation (APACHE) III-J and Simplified Acute Physiology Score (SAPS) 2]. ICU treatment intensity was measured, including mechanical ventilation, inotropes/vasoactive infusions, and continuous renal replacement therapy. Pre-illness frailty and all study assessments were measured by one of two study investigators [KG (medical student) or JD (specialist intensivist)] through interviews with the participants or surrogates using the Reported Edmonton Frail scale [16], which adjusts the original EFS scale to allow for reported physical performance in patients unable to perform the "timed-up-and-go" (TUG) test, with scores for individual frailty domains recorded. These frailty domains are general health, functional independence, cognition (clock drawing test), social supports, medication use, nutrition, mood, continence, and self-reported performance (ability to perform housework, walk up stairs, walk one kilometre). In the event of patient confusion, or an abnormal score on the clock drawing test, collateral history from patients' surrogates was sought. Pre-illness frailty was defined as the baseline patient state prior to the onset of acute illness precipitating hospital admission. The baseline Katz index of independence in activities of daily living, and the judgement-based Clinical Frailty Score (which, as with the EFS, is designed to rank the severity of frailty, with anchoring descriptions for each item based on burden of illness, physical activity, motivation, and functional independence) were measured [6], with data collected also defined as the health status of the patient prior to the onset of acute illness. Outcome data included in-hospital mortality (primary outcome); length of stay (time in hospital and time in ICU), readmission to ICU, discharge destination (including non-home discharge, assisted living facility, rehabilitation or other acute hospital location); (all secondary outcomes). Six-month mortality was established by contacting patients or their next-of-kin by telephone, with patients lost to follow-up censored at last contact.

4.3.3 Statistical analyses

All enrolled patients were included in the analysis set. Comparisons between frail and non-frail patients were performed using Chi-square or Fisher's exact tests for binary or categorical data, two-sample t-tests for normally distributed data and Wilcoxon rank-sum test otherwise, with results reported as counts (%), means [standard deviation (SD)] or median (25^{th} – 75^{th} percentile) respectively. Correlation between the continuous Edmonton and Clinical Frailty scales was assessed using Spearman correlation coefficient and agreement using Kappa coefficients for binary (not frail: CFS 1-4, EFS 0-7; frail: CFS ≥5, EFS ≥8) and ordinal categories (not frail: CFS 1-3, EFS 0-5; vulnerable: CFS 4, EFS 6-7; mildly frail: CFS 5, EFS 8-9; moderately frail: CFS 6, EFS 10-11; severely frail: CFS ≥7, EFS ≥12), the latter using quadratic weighting. Logistic regression was performed on death and re-admission to obtain the odds ratios and corresponding 95% confidence intervals (CIs) of the association with frailty status. Length of stay was transformed into natural logarithms before linear regression analysis due to its approximate lognormal distribution, providing geometric mean ratios (GMR) and 95% CIs. In addition to fitting unadjusted models, we fitted adjusted models which included age, sex, admission source, Charlson comorbidity score, and APACHE 3 score. All statistical analyses were performed using STATA 14.1 (College Station, TX, USA).

4.3.4 Sample size

We calculated that a sample of 160 participants would obtain a 95% Clopper-Pearson binomial confidence interval (CI) of 23% - 38% around an estimate of frailty prevalence of 30%, based on a systematic review of 3030 ICU patients across ten studies with a pooled frailty prevalence of 30% [42]. With a sample size of 160, the power to demonstrate that the spearman correlation coefficient between the EFS and CFS was at least strong (0.80), when assuming a correlation of 0.90, was >95% (two-sided alpha 5%) [101].

4.4 Results

4.4.1 Participants

During the 4-month recruitment period there were 511 patients aged ≥ 50 years admitted to the ICU, a total of 160 patients were consented and enrolled (Figure 4.1). There were no differences between included and non-included eligible patients in baseline demographics, age, illness severity scores, mechanical ventilation, or limitation of medical treatment on admission. Mean (SD) age of the included cohort was 70 (10) years, with 145 (91%) of patients residing at home prior to the onset of critical illness (Table 4.1). Reported EFS and CFS scales were able to be completed for all patients in the analysis set. Apart from 45 patients who were unable to perform the clock drawing test due to sedation or decreased consciousness, all other data was complete. Frailty was diagnosed in 58 patients [36.3%, 95% CI (28.8, 44.2)] using the EFS, and 54 patients [33.8%, 95% CI (26.5, 41.6)] using the CFS, respectively. 57 (35.6%) of patients required some data gathering from interviews with their surrogates, with no statistical difference between frail (37.9%) or non-frail patients (34.3%) in requirement for surrogate input. 156 (98%) of patients or their families were able to be contacted at 6 months and had follow-up data recorded. Compared to non-frail patients, frail patients were older and less likely to be residing at home, with higher comorbidity scores, less independence with activities of daily living, and higher APACHE 3 and SAPS 2 scores (Table 4.3). Frail and non-frail patients had similar intensity of treatment in ICU, with no difference in mechanical ventilation, renal replacement therapy or vasoactive/inotrope infusions. Despite no differences in limitation of medical treatment on admission, frail patients were more than twice as likely to have limitations instituted in the ICU (48.1% vs. 21.7%, p = 0.001).

4.4.2 Agreement between Edmonton and Clinical Frailty Scales

Patient numbers were similar in each frailty category, as scored by either scale (Figure 4.2). Spearman correlation coefficient between the continuous scale CFS and Edmonton scale was 0.85 (95% CI 0.81 to 0.88), suggesting “high” correlation. When considered as either dichotomised (frail vs. non-frail) or categorical variables (non-frail, vulnerable, mildly frail, moderately frail, severely frail), kappa coefficients were 0.78 (95% CI: 0.68 to 0.88) and 0.79 (95% CI: 0.75 to 0.83) respectively, suggesting good agreement.

4.4.3 Frailty domains

Frail patients demonstrated significantly poorer health status across the full spectrum of Edmonton frailty domains (Table 4.4). Domains with considerable magnitude of difference were functional dependence (48.3% of frail vs. 2.0% of non-frail patients requiring help with 5 – 6 activities, $p < 0.001$), malnutrition (53.5% vs. 26.5% of non-frail patients, $p = 0.001$), and reported performance (> 80% of frail patients unable to perform across all three domains of housework, stair climbing and walking 1km vs. 25.5%, 21.6% and 33.3% of non-frail patients respectively, $p < 0.001$). Frail patients were also more likely to report issues with mood (63.8% vs. 20.6%, $p < 0.001$), and over half (55.2%) of the frail cohort described their health as "poor" compared with only 5.9% of non-frail patients ($p < 0.001$). 43.1% of frail patients reported > 2 hospital admissions in the year prior to onset of critical illness, compared with 10.8% of non-frail patients ($p < 0.001$).

4.4.4 Outcomes

In-hospital mortality was three times greater for frail patients, as measured via the CFS [25.9% vs. 8.5%; adjusted OR (95% CI) = 3.31 (1.17, 9.39), $p = 0.024$], with six-month mortality also higher [40.4% vs. 17.3%; OR (95% CI) = 2.84 (1.18, 6.83), $p = 0.020$] (Table 4.3). Readmission to ICU did not vary depending on frailty status, nor did ICU or hospital length of stay [median (IQR) 2.7 (1.5 – 4.9) vs. 3.0 (1.4 – 4.8) days, $p = 0.557$; and 14.6 (8.9 – 21.8) vs. 11.2 (7.7 – 22.1) days, $p = 0.607$ respectively]. Frail patients were less likely to be discharged home (34.5% vs. 55.9%) and more likely to be discharged to in-patient rehabilitation (32.8% vs. 20.6%, $p = 0.004$). Both frailty scales were comparable in estimating magnitude of association with death, re-admission, and length of stay in both unadjusted and adjusted models (Table 4.3).

4.5 Discussion

4.5.1 Key findings

This study has demonstrated that in measuring frailty in critically ill patients, the CFS and EFS are highly correlated and in high agreement. This study also provides novel insights into the health domains disproportionately affected by frailty in an ICU cohort, particularly greater functional dependence, poor mood, malnutrition and poorer physical performance. We have also demonstrated that frail critically ill patients in an Australian context have similarly poor outcomes to overseas cohorts, with mortality three times higher in-hospital and twice as high at 6-month follow-up, with reduced odds of discharge home in frail survivors of critical illness.

4.5.2 Relationship to prior literature

We observed a comparable proportion of frailty in our cohort (36%) to similar studies utilising the CFS; 33% in Bagshaw et al's Canadian study of 421 critically ill patients [10] and a 30% pooled prevalence in the largest systematic review of frailty in critical illness encompassing over 3000 patients [42]. Fewer patients in our cohort required input from the next-of-kin to derive data (36%) compared with other studies, such as 69% in Le Maguet et al's study of 196 French ICU patients [35]. This was perhaps related to differences in availability of data-collectors in our study, who may have been able to return at a more convenient time to derive data from patients themselves. Similar to these two previous studies (Bagshaw and Le Maguet), we observed worse health outcomes among frail critically ill patients. In-hospital mortality (24.2%) was slightly less than the 32% observed in Canada and 50% in France, although this latter study was restricted to patients aged ≥ 65 years, perhaps explaining the higher mortality found. Compared to Bagshaw et al's population, we found no significant differences in limitations of medical treatment on admission, perhaps related to the high proportion of surgical patients in our cohort. Subsequent limitation of medical treatment once in the ICU, however, was more than twice as common in our frail cohort, likely related to clinical deterioration in this higher-risk group.

Prior literature has demonstrated the challenges in comparing results of different frailty scales, a 2017 review of 35 different frailty scores demonstrating significantly differing degrees of agreement between scales in a longitudinal study of over 5000 older community

dwelling participants [102]. Aguayo et al, in this review, thus cautioned against comparing or pooling results generated from using different frailty scales, which should not be assumed to be interchangeable. Accuracy among the different scales was found to be highest, however, for multidimensional frailty assessment tools, such as the EFS examined in our study. The strong agreement between the EFS and CFS found in our study is also likely due to differences in study design, with data collection faithful to the original scales and no missing data (versus considerable imputation of missing data and "tailoring" of variables in Aguayo et al's study), as well as a higher event rate (frailty prevalence 36% in our cohort vs. 11.5% of men and 17.7% of women frail as defined by a comprehensive geriatric assessment in the latter study).

An interesting target for future research would be to further extend our findings to comparison with the criterion standard deficit-model reference frailty scale, the 70-item CSHA-FI [6], or indeed the multidimensional gold standard comprehensive geriatric assessment, recognising the major challenges in applying these scales to data collection in an ICU population. Future research could also seek to confirm our observations regarding health status in individual frailty domains in a larger, ideally multi-centre, study. To date this literature is lacking, thus making our study unique in the granularity of data regarding frailty in critical illness. A final, ambitious, goal of future research should be to identify intervenable targets for frailty in a critically ill population. Our study provides insights into particular areas of difference in frail patients (namely functional dependence, mood, malnutrition and physical performance); whether these domains are potentially modifiable once critical illness has supervened, or are fixed markers of poor prognosis, requires future research.

4.5.3 Implications of study findings

The findings of this study imply that the CFS is a valid measurement tool for frailty in the critically ill, compared with a multi-dimensional tool, the Edmonton Frail Scale. This is an important finding, as the CFS is rapidly becoming the dominant tool for frailty measurement in critical illness. This study also implies that both scales are measuring similar frailty

thresholds. Of 10 discrepant patients scored frail on the Edmonton scale but non-frail via the CFS, all scored only one point lower than the threshold for frailty (score = 4, "vulnerable" or "pre-frail"). Furthermore, this study illustrates certain aspects of health deficits which may disproportionately affect frail critically ill patients, in particular malnutrition, functional dependence and physical performance, and aspects which may not differ, such as social support, medication adherence and continence (although small patient numbers make these conclusions less certain). This may allow identification of targets to potentially modify the effect of frailty in intensive care, although there is rarely a "window" prior to the onset of critical illness for such interventions compared to, for example, the elective surgical setting. There may, however, be opportunity to target concerning frailty domains in the convalescent period for survivors of critical illness, if identified through such a multidimensional assessment process. An important finding of this study is that frailty in an ICU population affects the full spectrum of health domains. This implies that "frailty" assessment tools derived from database registries, particularly of automated coding data, are likely to be over-simplistic. One example, the "Modified Frailty Index" (mFI), encompasses 11 variables from the National Surgical Quality Improvement Program (NSQIP) database. This has recently been found in a study of over 130,000 ICU patients to be predictive of increased mortality and length of stay [36]. When examined, however, nine of the 11 variables are simply medical comorbidities, with little assessment of other frailty domains such as physical performance, mobility, nutritional status, cognition or mental health. With increasing utilisation in the literature, ICU clinicians and researchers alike should exercise caution in the application of such scales to measurement of patient frailty. Future studies should seek to validate such scales against accepted frailty measures in both critically ill and non-ICU populations.

4.5.4 Strengths and limitations

Strengths of this study include the inclusion of both medical and surgical patients from a tertiary, referral ICU setting, enhancing the generalizability of our findings, as well as the completeness of data collection. A further strength is demonstration of the feasibility of conducting a Reported Edmonton Frail Scale in the ICU environment, which did not present major challenges or add burden in interviewing either patients or surrogates, although this

was not formally assessed. A final strength is that study investigators were not specialist geriatricians, nor full-time research personnel. The ability to conduct frailty assessments via either scale at the bedside by clinicians is thus likely generalizable to other ICU settings.

Limitations include the single-centre design which may reduce the external validity, as well as the fact that the same unblinded investigators were involved in assessment of both the CFS and the Edmonton scales, potentially introducing bias into measurement. We consider this unlikely, however, considering that included and non-included eligible patients were similar in demographics and illness severity at baseline, and that assignment of both frailty scores are based on defined, quantifiable criteria (eg. level of independence with ADLs, physical performance, and medical conditions). We also note that all other studies comparing frailty scales have used similar methodology, without data collectors blinded to either the alternative scale or other demographic data.[10,35] A further limitation is the reliance on input from patients' next of kin in one-third of the cohort, potentially introducing a source of bias into frailty measurement. This is, however, a common methodological challenge in the assessment of frailty in ICU. Although the Reported Edmonton scale relies on subjective measures of physical performance, subject to potential recall bias by either patients or their next-of-kin, it is more feasible in the ICU than traditional functional assessments (such the 'timed-up-and-go' tests or grip strength measurement) that are impossible for the majority of critically unwell patients to perform. Finally, assessment of the cognitive domain in the ICU environment is challenging, with one-quarter of our study cohort unable to complete the clock drawing test mainly due to sedation and mechanical ventilation. Even for patients that could complete this component, measurement may potentially be confounded by acute conditions separate from pre-morbid cognitive status, such as delirium, which may have resulted in an overestimation of frailty. This is a common challenge in the assessment of cognition in the critically ill, and is hard to overcome, although future research could explore potential further modification to the Reported Edmonton Frail Scale to more accurately assess the cognitive domain in the ICU environment.

4.6 Conclusions

This study demonstrates the validity of the CFS as a frailty measurement tool in the critically ill, compared to the Edmonton multi-dimensional scale. It also confirms the poorer health outcomes experienced by frail patients in critical illness. Finally, this study has shown that frailty in critical ill patients affects the full spectrum of health domains, which should be accounted for in any measurement of ICU frailty.

Table 4.1. Baseline demographics of study participants

Variable	Total N = 160
Age (years), mean (SD)	70.4 (10.3)
BMI (kg/m^2), median (IQR)	29.0 (25.0-32.4)
Male, n (%)	70 (43.8%)
Admission Source, n (%) Home Acute hospital Assisted living	 145 (90.6%) 11 (6.9%) 4 (2.5%)
Admission type, n (%) Medical Surgical	 100 (62.5%) 60 (37.5%)
Charlson Comorbidity Score, median (IQR)	2 (1-4)
ADL Function (Katz), n (%) Dependent (0 – 2) Partially Dependent (3 – 4) Independent (5 – 6)	 8 (5.0%) 9 (5.6%) 143 (89.4%)
APACHE 3, mean (SD)	70 (24)
SAPS2, mean (SD)	40 (14)
Limitation of medical treatment on admission, n (%)	17 (10.6%)

SD = standard deviation; IQR = interquartile range; ADL = activities of daily living; APACHE = Acute Physiology and Chronic Health Evaluation; SAPS = Simplified Acute Physiology Score

Table 4.2. Baseline demographics and interventions in ICU of study participants, according to Edmonton and Clinical Frailty Scales

Variable	Edmonton frailty scale (N = 160)			Clinical Frailty Scale (N = 160)		
	Frail N = 58	Not Frail N = 102	p-value	Frail N = 54	Not Frail N = 106	p-value
Baseline characteristics						
Age (years), mean (SD)	73.2 (9.3)	68.8 (10.4)	0.008	74.0 (9.5)	68.5 (10.2)	0.001
BMI, median (IQR)	28.9 (24.5 – 32.7)	29.2 (25.6 – 32.2)	0.618	28.9 (24.5-32.1)	29.2 (25.2-32.6)	0.508
Male, n (%)	29 (50.0%)	41 (40.2%)	0.229	28 (51.9%)	42 (39.6%)	0.140
Admission Source, n (%) Home Acute hospital Residential care	 46 (79.3%) 9 (15.5%) 3 (5.2%)	 99 (97.1%) 2 (2.0%) 1 (1.0%)	 <0.001	 43 (79.6%) 7 (13.0%) 4 (7.4%)	 102 (96.2%) 4 (3.8%) 0 (0.0%)	0.001
Admission type, n (%) Medical Surgical	 38 (65.5%) 20 (34.5%)	 62 (60.8%) 40 (39.2%)	 0.552	 38 (70.4%) 16 (29.6%)	 62 (58.5%) 44 (41.5%)	0.142
Charlson Comorbidity Score, median (IQR)	3 (2-4)	1 (0-3)	<0.001	3 (2-4)	2 (0-3)	<0.001
ADL Function (Katz), n (%) Dependent (0 – 2) Partially Dependent (3 – 4) Independent (5 – 6)	 8 (13.8%) 7 (12.1%) 43 (74.1%)	 0 (0%) 2 (2.0%) 100 (98.0%)	 <0.001	 8 (14.8%) 8 (14.8%) 38 (70.4%)	 0 (0.0%) 1 (0.9%) 105 (99.1%)	<0.001
APACHE 3, mean (SD)	78 (25)	66 (22)	0.004	79 (24)	66 (22)	<0.001
SAPS2, mean (SD)	43 (14)	38 (13)	0.037	43 (13)	38 (13)	0.010
Limitation of medical treatment on admission, n (%)	9 (15.5%)	8 (7.8%)	0.130	9 (16.7%)	8 (7.5%)	0.077
Interventions in ICU						
Mechanical ventilation, n (%)	27 (46.6%)	56 (54.9%)	0.310	25 (46.3%)	58 (54.7%)	0.313
Renal replacement therapy, n (%)	5 (8.6%)	7 (6.9%)	0.758	5 (9.3%)	7 (6.6%)	0.541
Vasoactive medication, n (%)	37 (63.8%)	60 (58.8%)	0.536	32 (59.3%)	65 (61.3%)	0.801
Limitation of medical treatment instituted in ICU, n (%)	28 (48.3%)	21 (20.6%)	<0.001	26 (48.1%)	23 (21.7%)	0.001

SD = standard deviation; IQR = interquartile range; ADL = activities of daily living; APACHE = Acute Physiology and Chronic Health Evaluation; SAPS = Simplified Acute Physiology Score

Table 4.3. Outcomes by frailty status, Edmonton and Clinical Frailty Scale

Outcome	Frailty	N (%)	OR (95% CI) Unadjusted	P value	OR (95% CI) Adjusted*	P value
In-hospital mortality	Edmonton					
	Frail	14/58 (24.1%)	3.29 (1.32, 8.18)	0.010	2.96 (1.04, 8.46)	0.043
	Not Frail	9/102 (8.8%)	Reference		Reference	
	CFS					
	Frail	14/54 (25.9%)	3.78 (1.51, 9.42)	0.004	3.31 (1.17, 9.39)	0.024
	Not Frail	9/106 (8.5%)	Reference		Reference	
Re-admission to ICU	Edmonton					
	Frail	7/58 (12.1%)	1.42 (0.50, 4.03)	0.512	1.46 (0.45, 4.80)	0.531
	Not Frail	9/102 (8.8%)	Reference		Reference	
	CFS					
	Frail	7/54 (13.0%)	1.61 (0.56, 4.57)	0.376	1.88 (0.56, 6.27)	0.305
	Not Frail	9/106 (8.5%)	Reference		Reference	
6-month mortality	Edmonton					
	Frail	21/57 (36.8%)	2.62 (1.25, 5.51)	0.011	2.37 (0.98, 5.73)	0.056
	Not Frail	18/99 (18.2%)	Reference		Reference	
	CFS					
	Frail	21/52 (40.4%)	3.24 (1.53, 6.86)	0.002	2.84 (1.18, 6.83)	0.020
	Not Frail	18/104 (17.3%)	Reference		Reference	

OR = Odds Ratio; CI = Confidence Interval *Adjusted for age, sex, admission source, Charlson comorbidity score, and APACHE 3 score.

Table 4.4. Frailty domains according to both frailty scales

Variable	Edmonton frailty scale (N = 160)			Clinical Frailty Scale (N = 160)		
	Frail n = 58	Not Frail n = 102	p-value	Frail n = 54	Not Frail n = 106	p-value
General Health *(Number of hospital admissions in past year)*						
0 admissions	9 (15.5%)	59 (57.8%)	< 0.001	10 (18.5%)	58 (54.7%)	< 0.001
1-2 admissions	24 (41.4%)	32 (31.4%)		21 (38.9%)	35 (33.0%)	
>2 admissions	25 (43.1%)	11 (10.8%)		23 (42.6%)	13 (12.3%)	
General Health *(In general, describe your health)*						
Good – excellent	9 (15.5%)	70 (68.6%)	< 0.001	11 (20.4%)	68 (64.2%)	< 0.001
Fair	17 (29.3%)	26 (25.5%)		16 (29.6%)	27 (25.5%)	
Poor	32 (55.2%)	6 (5.9%)		27 (50.0%)	11 (10.4%)	
Functional Independence *(Number of activities requiring help*)*						
0-1	11 (19.0%)	90 (88.2%)	< 0.001	3 (5.6%)	98 (92.5%)	< 0.001
2-4	19 (32.8%)	10 (9.8%)		21 (38.9%)	8 (7.5%)	
5-8	28 (48.3%)	2 (2.0%)		30 (55.6%)	0 (0.0%)	
Cognition *(Clock drawing test**)*						
No errors	10 (25.0%)	46 (60.5%)	< 0.001	10 (28.6%)	46 (57.5%)	0.015
Minor spacing	7 (18.0%)	14 (18.4%)		8 (22.9%)	13 (16.3%)	
Other errors	22 (56.4%)	16 (21.1%)		17 (48.6%)	21 (26.3%)	
Social support *(Can you count on someone to meet your needs?)*						
Always	46 (79.3%)	92 (90.2%)	0.092	47 (87.0%)	91 (85.8%)	1.000
Sometimes	7 (12.1%)	8 (7.8%)		5 (9.3%)	10 (9.4%)	
Never	5 (8.6%)	2 (2.0%)		2 (3.7%)	5 (4.7%)	
Medication use *(Five or more different prescription medications*)						
No	6 (10.3%)	48 (47.1%)	< 0.001	7 (13.0%)	47 (44.3%)	< 0.001
Yes	52 (89.7%)	54 (52.9%)		47 (87.0%)	59 (55.7%)	
Medication use *(Do you forget to take prescription medications?*)						
No	44 (75.9%)	85 (83.3%)	0.250	41 (75.9%)	88 (83.0%)	0.283
Yes	14 (24.1%)	17 (16.7%)		13 (24.1%)	18 (17.0%)	
Nutrition *(Have you recently lost weight, with clothing looser?)*						
No	27 (46.6%)	75 (73.5%)	0.001	28 (51.9%	74 (69.8%)	0.025

Yes	31 (53.5%)	27 (26.5%)		26 (48.2%)	32 (30.2%)	
Mood *("Do you often feel sad or depressed?")*						
No	21 (36.2%)	81 (79.4%)	< 0.001	21 (38.9%)	81 (76.4%)	< 0.001
Yes	37 (63.8%)	21 (20.6%)		33 (61.1%)	25 (23.6%)	
Continence *(Do you have a problem with losing control of urine?)*						
No	37 (63.8%)	82 (80.4%)	0.021	36 (66.7%)	83 (78.3%)	0.111
Yes	21 (36.2%)	20 (19.6%)		18 (33.3%)	23 (21.7%)	
Self-Reported Performance *(Can you perform heavy housework?)*						
No	52 (89.7%)	26 (25.5%)	< 0.001	51 (94.4%)	27 (25.5%)	< 0.001
Yes	6 (10.3%)	76 (74.5%)		3 (5.6%)	79 (74.5%)	
Self-Reported Performance *(Can you walk stairs to second floor?)*						
No	47 (81.0%)	22 (21.6%)	< 0.001	45 (83.3%)	24 (22.6%)	< 0.001
Yes	11 (19.0%)	80 (78.4%)		9 (16.7%)	82 (77.4%)	
Self-Reported Performance *(Can you walk one kilometre?)*						
No	52 (89.7%)	34 (33.3%)	< 0.001	46 (85.2%)	40 (37.7%)	< 0.001
Yes	6 (10.3%)	68 (66.7%)		8 (14.8%)	66 (62.3%)	

***** Activities of daily living assessed: meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications.

** 19 frail and 26 non-frail patients were unable to perform the clock drawing test.

Figure 4.1: Study flow diagram

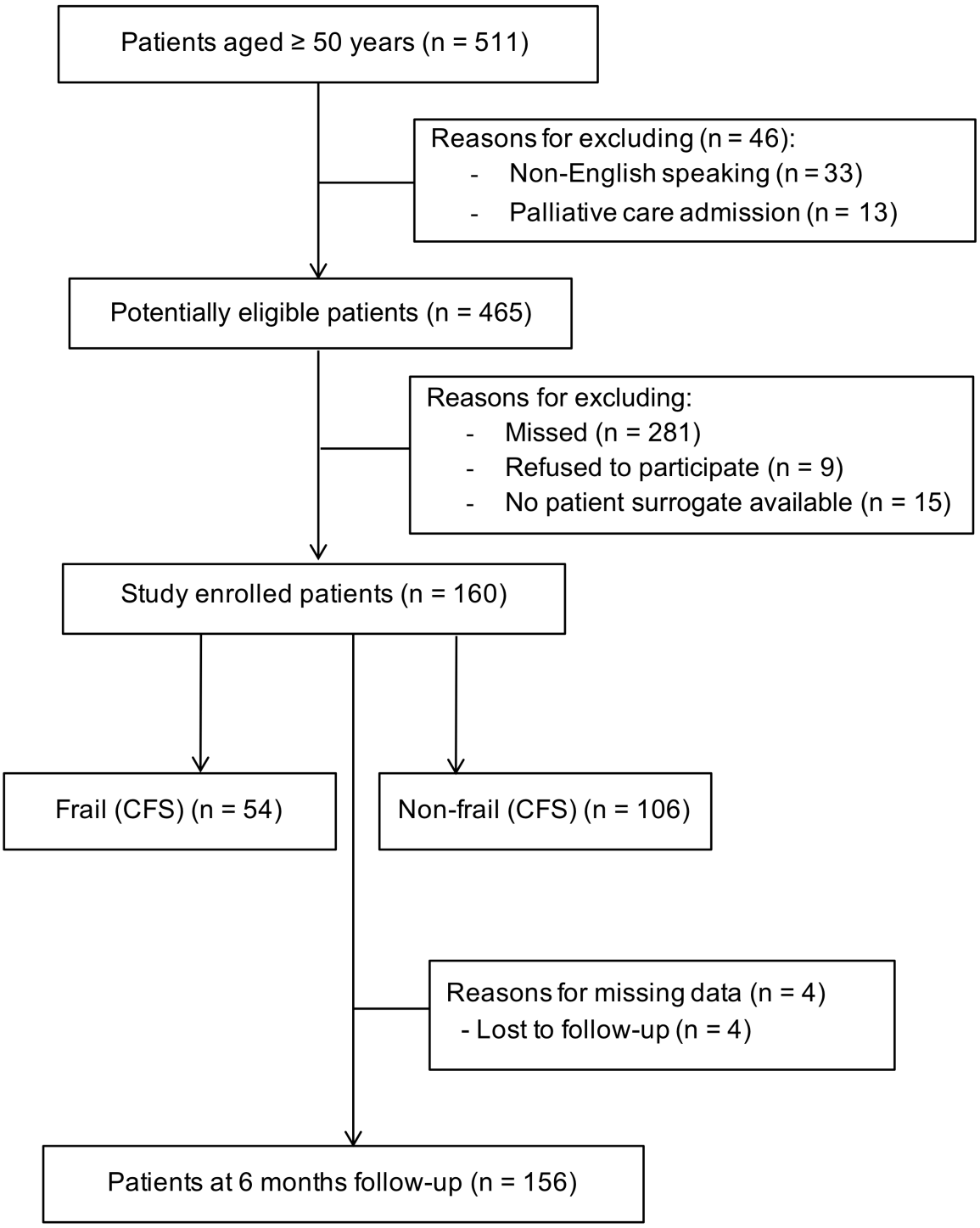
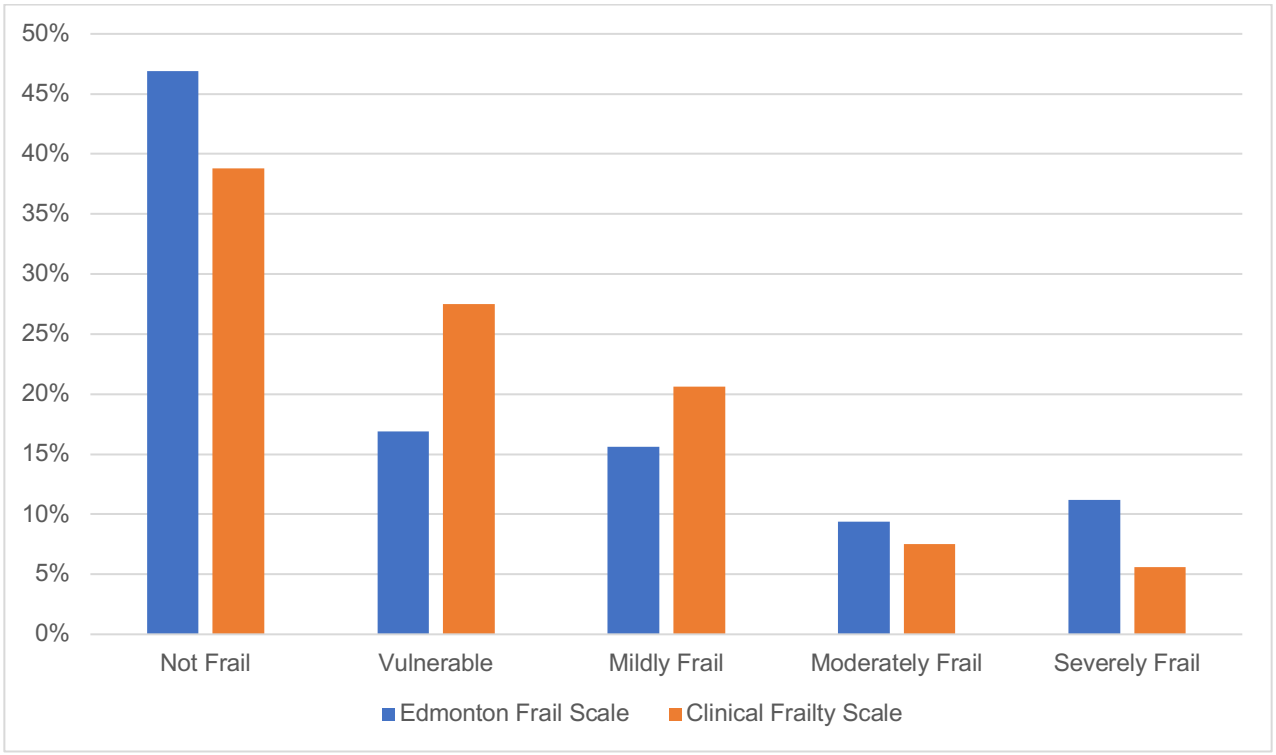


Figure 4.2: Frailty status of study participants at baseline



Chapter 5. Accuracy of the Clinical Frailty Scale for perioperative frailty screening: A prospective observational study

This chapter is the study published in the *Canadian Journal of Anesthesia*. 2020 Jun;67(6):694-705. (Lightly edited for headings and formatting consistency).

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Keywords: frailty, perioperative care, risk assessment

Funding:

This work was supported by an emerging researcher scholarship from the Australian and New Zealand College of Anaesthetists.

Declaration of interest

The authors declare no conflicts of interest.

5.1 Abstract

Purpose: Perioperative frailty increases postoperative complications, mortality, and new functional dependence. Despite this, routine perioperative frailty screening is not widespread. We aimed to assess the accuracy of the Clinical Frailty Scale (CFS) as a screening tool prior to anesthesia, and to determine which domains of health are affected by frailty.

Methods: In a prospective, single-centre observational study we enrolled 218 patients aged ≥ 65 years undergoing elective and emergency surgery. The screening performance of the CFS was compared with the Edmonton Frail scale, including the effect in individual frailty domains, and outcomes including discharge location and mortality.

Results: The median [IQR] age of the enrolled subjects was 74 [69 – 80] years and 24% of the patients were frail. The CFS and Edmonton scales were highly correlated (Spearman correlation coefficient, 0.81; 95% CI, 0.77 to 0.86), and in substantial agreement (kappa coefficient, 0.76; 95% CI, 0.70 to 0.81), with an area under the receiver operating characteristic curve of 0.91 (95% CI, 0.86 to 0.94) indicating excellent discrimination for the CFS in predicting frailty status based on the Edmonton scale. Frail patients had higher 30-day mortality (odds ratio, 5.26; 95% CI, 1.28 to 21.62), and were less likely to be discharged home. Frail patients had poorer health throughout frailty domains, including functional dependence (42% of frail vs. 4% of non-frail patients; $P < 0.001$), malnutrition (48% vs. 19%, $P < 0.001$) and poor physical performance (12% vs. 47%, $P < 0.001$).

Conclusion: The Clinical Frailty Scale is a valid and accurate tool to screen for perioperative frailty, which encompasses the spectrum of health-related domains.

5.2 Introduction

By 2050, the proportion of the global population aged ≥ 60 years will more than double, reaching 2.1 billion people.[1] In high-income countries, this older cohort already accounts for 30 – 50% of all surgical procedures, a proportion which is increasing.[27,103,104] As a result, the syndrome of increased vulnerability to external stressors known as frailty has emerged as a major area of importance. In older surgical patients, the prevalence of frailty is as high as 40-50%.[105] Preoperative frailty also doubles the risk of surgical complications, and leads to increased mortality and length of stay, posing unique challenges for anesthesiologists, surgeons, and health services.[56,98] There are two "paradigms" of frailty – i.e., the phenotypic model (based on five criteria: exhaustion, weight loss, weakness, and decreased physical activity[5]), and the deficit model which conceptualizes frailty as an accumulation over time of "health deficits", or impairments across the spectrum of health.[6] The phenotypic model is attractive in its simplicity, however the deficit model is likely a more comprehensive and multidimensional representation of frailty.

Given this evidence of increased harm, preoperative frailty screening is necessary. Although recommended by the 2010 United Kingdom National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in older surgical patients that stated that "an agreed means of assessing frailty in the perioperative period should be developed and included in risk assessment", this is not yet commonplace.[60] The challenges are complex and logistical. Comprehensive frailty measurement instruments, such as the 70-item frailty index, require significant time to perform and are thus impracticable prior to anesthesia.[6] Other frailty measurement scales require time, training, and functional testing of patients, constraining widespread uptake.[15] Numerous prior studies have investigated more simple frailty instruments in surgical patients in order to find the optimal scale in the perioperative context. For example, a 2016 North American study of 415 orthopedic patients measured the 5-item frailty phenotype scale, demonstrating only moderate concordance with the reference frailty index (weighted Kappa = 0.42; 95% confidence interval [CI], 0.36 to 0.49).[73] A promising much simplified instrument is the 9-point Clinical Frailty Scale (CFS). This scale enables rapid frailty screening incorporating a range of areas known to be affected by frailty without the requirement for specific geriatric expertise or functional testing; in other

populations it has been shown to be reliable and accurate.[6,10] It also requires considerably less time to administer compared with other multidimensional frailty measurement tools. The CFS has been examined in surgical populations, including a 2018 study of 702 patients undergoing elective non-cardiac surgery, where it was found predictive of death, new disability, and institutional discharge.[46] However, its application in anesthesia and surgery compared to other more validated frailty tools requires further work.

Accordingly, we aimed to test the CFS as a frailty screening tool in a cohort of elective and emergency surgical patients. In particular, we hypothesized that the CFS would have excellent accuracy for frailty prediction and be strongly correlated and in agreement with the Edmonton Frail Scale, a well-researched, commonly used and studied, multi-dimensional frailty scale that is too detailed to be applied as a widespread screening tool. We secondarily hypothesized that frailty would affect the full range of health domains in surgical patients and be associated with detrimental postoperative outcomes including increased mortality and complications.

5.3 Methods

This was a prospective, observational cohort study in the perioperative department of the Royal Melbourne Hospital, and formed a complementary, concurrent investigation to our previously published study in 160 critically ill patients.[106] The protocol for this frailty research program has previously been published.[107] Ethics approval for this study was issued by the Human Research and Ethics Committee of Melbourne Health (20 January 2017, HREC/16/MH/321). Patients aged ≥ 65 years presenting for either elective or emergency surgery between February 1st and June 10th, 2017 were eligible. Written consent was obtained from either the patient, or their next-of-kin if incapacitated.

Patients who were non-English speaking or presenting for endoscopy procedures were excluded. A convenience sample of patients was enrolled around availability of investigators; only the first operation during the hospitalisation was included. Patients were

identified from the elective pre-admission anesthetic clinic, or the emergency operating room list. Perioperative data collected included age, sex, height, weight, Charlson comorbidity index, Katz index of independence in activities of daily living,[108] residential location prior to admission, P-POSSUM surgical risk score,[93] and surgical subspecialty.

Frailty was defined as the state of the patient in the two weeks prior to admission to hospital (elective surgery) or prior to onset of acute illness (emergency surgery) to be consistent with past definitions[62]; it was preoperatively collected by one of three study investigators. Treating medical teams were blind to patient data collected for this study. Prior to commencement of data collection, all assessors were trained in the measurement of the CFS by the lead investigator, who has been specifically trained in the derivation of the CFS score, with ongoing supervision of randomly selected patients throughout the study period. Illness severity, functional ability and social independence were assessed via using the free-text descriptions of these domains contained within the CFS tool. The Edmonton Frail Scale quantifies frailty across nine areas: general health, independence, cognition, social supports, medication, nutrition, mood, continence, and function. If the "timed-up-and-go" test was not possible, a Reported Edmonton Frail Scale was conducted which assesses three areas of reported performance (ability to perform heavy housework, walk up two floors of stairs, walk one kilometre unaided), with a total score of 18 vs. 17 for the original scale.[16] In the case of abnormal cognition (e.g., delirium or confusion), history from patients' next-of-kin was obtained; this surrogate history was also used to determine frailty status using above definitions if required. Following collection of the Edmonton frailty scale data, the CFS was also measured preoperatively, which is judgement-based around illness severity, functional ability, and social independence. [6] The Edmonton frailty scores were subsequently aggregated and the total score assigned after all data collection was complete.

The primary outcome was agreement and correlation between CFS and Edmonton scales (as described below). Secondary outcomes included: 30-day mortality, hospital length of stay, postoperative complications (acute myocardial infarction, cardiac arrest, tracheal reintubation, acute pulmonary oedema, deep venous thrombosis, pulmonary embolus, stroke, wound infection, acute kidney injury, unplanned need for re-operation, unplanned

admission to the intensive care unit [ICU], all the definitions of which are listed in electronic supplemental material [ESM]); discharge status at postoperative day 30 (i.e, home, assisted living facility, rehabilitation, other acute hospital, or not discharged); and residential location at six-months postoperatively (i.e., home, acute hospital, assisted living facility). Outcomes were measured at 30 days postoperatively by investigators not blinded to study data, although the Edmonton frailty scores were aggregated subsequent to all data collection being completed.

5.3.1 Statistical analysis

Continuous data were summarised using mean (standard deviation [SD]) or median [interquartile range (IQR)] in the case of skewed data. Binary and categorical data were summarised as frequencies and percentages. We compared baseline characteristics, health outcomes, and health domains of patients with and without frailty using Chi-square or Fisher's exact tests, two-sample t-tests, and Wilcoxon rank-sum tests as appropriate. Univariable and multivariable regression models were also fitted to secondary outcomes, the latter adjusting for age, sex, admission source, Charlson comorbidity index and emergency/elective surgery. Binary variables with more than one patient were analysed using Firth logistic regression to obtain the estimated odds ratio (OR) and 95% confidence interval (CI).[109] The estimated median difference and 95% CI between patients with and without frailty regarding hospital length of stay (in days) were obtained from bootstrapped quantile regression with 5000 replications. Discharge location was analysed using multinomial logistic regression, yielding the estimated relative risk ratio and 95% CI. Spearman correlation coefficient was used to measure correlation between Edmonton and CFS scales, with inter-rater agreement assessed using Cohen's kappa between dichotomized (not frail: CFS 1-4, Edmonton 0-7; frail: CFS ≥5, Edmonton ≥8) and ordinal categories (not frail: CFS 1-3, Edmonton 0-5; vulnerable: CFS 4, Edmonton 6-7; mildly frail: CFS 5, Edmonton 8-9; moderately frail: CFS 6, Edmonton 10-11; severely frail: CFS ≥7, Edmonton ≥12), the latter via quadratic weighting due to the increasing clinical importance of higher CFS categories. Kappa coefficients were categorized using the scale of Landis and Koch.[110] A Firth logistic regression model was fitted to frailty defined via the Edmonton scale using the ordinal CFS as a predictor to obtain the area under the receiver operating characteristic

curve (AUCROC) and its exact binomial 95% CI. The AUCROC was categorized using the general guidelines of Hosmer, Lemeshow, and Sturdivant.[111] Sensitivity and specificity were also calculated guided by the optimal cut-point according to the highest Youden index. We included all enrolled patients in the analyses with the exception of the analysis of residence location at follow-up which was restricted to patients admitted from home. In addition, we performed separate analyses to examine differences between the whole dataset, and subgroups according to whether patients were admitted to the ICU or not (and hence included in our previous report).[106] No adjustment for multiple testing was performed. STATA 15.1 (College Station, TX, USA) was used for statistical analyses.

5.3.2 Sample size

A sample size of 200 was calculated to have power >99% (two-sided alpha of 5%) for the Spearman coefficient between the Edmonton and CFS scales to be at least strong (0.80), assuming a correlation of 0.90[101]. A sample of 200 participants was also calculated to produce a 95% Clopper-Pearson binomial confidence interval (CI) of 15% to 26% around a frailty prevalence estimate of 20%, based on a meta-analysis encompassing more than 8000 surgical patients, thus providing acceptable CIs around likely frailty prevalence for this sample size.[98]

5.4 Results

5.4.1 Baseline demographics

Two-hundred and eighteen patients were enrolled during the 4-month recruitment period, 118 (54%) undergoing elective and 100 (46%) emergency surgery (Figure 5.1). Forty-two patients (19%) were admitted to the intensive care unit following surgery, and were included in the previous published analysis.[106] Median [IQR] age of patients was 74 [69 – 80] years, 99 (45%) of patients were female, with 195 (89%) residing at home prior to surgery. Compared with non-included eligible patients undergoing identical surgical operations in the study period, included patients were of similar age (74 [69 – 80] years vs. 74 [70 – 80]

years for non-included patients; *P* = 0.51), with an increased median [IQR] hospital length of stay (5 [2 – 13] days vs. 4 [1 – 9] days; *P* = 0.005). Frailty scales were completed for all included patients; reported physical performance was used for 107 (49%) patients who were unable to perform the timed-up-and-go test. A further 28 (13%) patients had incomplete cognition (clock-drawing) tests due to decreased conscious state, all other data was complete.

5.4.2 Comparison between frailty scales

Fifty-two patients (24%; 95% CI, 18 to 30%) were measured as frail using the Edmonton scale, compared with 61 (28%; 95% CI, 22 to 34%) via the CFS (Figure 5.2). The Spearman correlation coefficient comparing the continuous CFS and Edmonton was 0.81 (95% CI, 0.77 to 0.86), indicating a "high" correlation. The kappa coefficient comparing the dichotomised CFS and Edmonton was 0.65 (95% CI, 0.54 to 0.77), and comparing ordinal scales was 0.76 (95% CI, 0.70 to 0.81), both indicating substantial agreement. The AUCROC of the CFS when predicting frailty according to the Edmonton scale was 0.91 (95% CI, 0.86 to 0.94) indicating excellent to outstanding discrimination. A CFS cut-point of "vulnerable" (CFS = 4) captured all but one patient with frailty, as scored by the Edmonton scale, for a sensitivity of 98.1% (95% CI, 89.7% to 100%) and specificity of 54.8% (95% CI, 46.9% to 62.5%). A CFS cut-point of "mildly frail" (CFS = 5) had the highest Youden index for a sensitivity of 80.8% (95% CI, 67.5% to 90.4%) and specificity of 88.6% (95% CI, 82.7% to 93.0%). Agreement, correlation, sensitivity and specificity of the CFS were similar when considering subgroups of patients admitted and not-admitted to the ICU (Supplementary Tables 5.1 and 5.6).

5.4.3 Outcomes

Compared to patients without frailty, those scored as frail had higher Charlson comorbidity scores, less functional independence, less likely to be living at home, with higher P-POSSUM scores (Table 5.1). These associations with frailty persisted when considering the previously unreported subgroup of 176 patients not admitted to ICU (Supplementary Table 5.2). After adjusting for potential confounders, mortality at 30 days was higher in patients with frailty using the Edmonton scale (9.6% vs. 1.8%; OR, 5.26; 95% CI, 1.28 to 21.62). Any

postoperative complications were more common with frailty using the Edmonton scale (OR, 3.67; 95% CI, 1.84 to 7.30), in particular, any unplanned admission to the intensive care unit (OR, 4.54; 95% CI, 1.83 to 11.26), and unplanned return to the operating theatre (OR, 6.20; 95% CI, 2.09 to 18.38). The median [IQR] hospital length of stay was longer in patients with frailty (9.0 [5.0 – 14.6] vs. 3.0 [1.0 – 9.0] days; mean difference, 2.52; 95% CI, -0.66 to 5.69 days). When considered via the CFS, patients with frailty were more commonly discharged to assisted living or rehabilitation (23 [38%] frail vs. 23 [15%] non-frail) compared to home (29 [48%] frail vs. 118 [75%] non-frail; relative risk ratio, 2.66; 95%CI, 1.15 to 6.13). At six-month follow-up, excluding five patients who were lost to follow-up and 33 patients who had died, eight of 41 surviving patients with frailty (20%) were living in an assisted living facility, compared with five of 134 surviving patients without frailty (4%), as measured via the CFS. The relative change in the odds of living in an assisted living facility at follow-up, for frail patients compared to non-frail patients (as measured via the CFS) admitted from home was 1.74-fold (95% CI, 0.37 to 8.16).

5.4.4 Frailty domains

Across the spectrum of Edmonton scale domains, patients diagnosed with frailty had significantly worse health; the magnitude of discrepancy in health status was similar whether assessed via the Edmonton and CFS scales (Table 5.3). Frailty was associated with significantly worse malnutrition (48% vs. 19% patients, $P = 0.001$), medication usage (92% vs. 45% of patients taking five or more medications, $P < 0.001$), higher functional dependence (42% vs. 4% of patients; $P < 0.001$), and lower physical performance (12% vs. 47% of patients able to perform a timed-up-and-go test in ≤ 10 seconds, $P < 0.001$). Patients with frailty also had considerably more hospital admissions in the year prior to surgery, compared with patients without frailty ($P < 0.001$). When separately considering subgroups of patients admitted and not admitted to ICU, demographics were similar apart from higher median [IQR] P-POSSUM mortality risk in ICU-admitted patients (9.4% [6.2 – 20.1%] vs. 3.9% [2.5 – 8.1%]; $P < 0.001$) and more emergency surgery (25 [59.5%] vs. 75 [42.6%]; $P = 0.048$) (Supplementary Table 5.3); findings with frailty across domains remained, although analyses were constrained by small numbers in the ICU-admitted cohort (S 4 and 5).

5.5 Discussion

5.5.1 Main findings

In a single-centre prospective cohort study, we found strong correlation and agreement between the CFS and the Edmonton Frail scale in a surgical population. Furthermore, the CFS demonstrated a strong ability to discriminate between people identified as having, or not having, frailty based on the Edmonton scale. This study also demonstrates that frailty in surgical patients measured by the CFS affects the full spectrum of health, including functional dependence, medication use, physical ability, and nutrition. Consistent with the larger perioperative literature, surgical patients with frailty also had considerably worse postoperative outcomes, with increased complications, higher mortality, and reduced discharge home after surgery.

5.5.2 Implication of study findings

It is ten years since the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) recommendation to include frailty screening in surgical risk assessment for older patients.[60] However, there remains a major gap in perioperative frailty screening. The Association of Anaesthetists of Great Britain and Ireland, the American College of Surgeons, and the American Geriatrics Society all similarly emphasise the importance of perioperative frailty measurement.[26,61] The Edmonton Frail scale has been applied in a variety of surgical cohorts, where it has been found predictive of postoperative complications, increased length of stay, and inability to be discharged home after surgery.[47] It also has good inter-rater reliability, and correlates well with a comprehensive geriatric assessment.[15] There are significant challenges, however, in its widespread application as a screening tool to a surgical population. Half of our cohort, for example, could not undergo the timed-up-and-go test, with a further 13% unable to undergo clock-drawing cognitive assessment due to decreased conscious state. There is also a time and training requirement, which presents challenges in a busy preoperative assessment clinic, as well as the emergency surgical setting. Due to these challenges, the Edmonton scale has limited scope for widespread

deployment in an unselected population at risk for frailty. The CFS thus presents a convenient, easy to deploy screening tool devoid of many of these constraints. The CFS has been well studied in the perioperative literature, and has been demonstrated to be both feasible. In the study by McIsaac et al, it was rated by anesthesiologists as easy to use, useful, and beneficial to patient care, and taking mean (SD) of 44 (40) seconds to administer,[46] and was associated with poor outcomes in surgical patients. The AUCROC of 0.91 and high degree of correlation between the CFS and Edmonton scales found in this study supports its role as a screening tool in surgical patients. This study also implies that the threshold for frailty measured by both the CFS and Edmonton scales is similar. Nine of 10 divergent patients (Edmonton frail, CFS non-frail), had a CFS score = 4 ("vulnerable"), only one point less than the frailty cut-point of 5. Similarly, 18 of 19 patients scored frail via the CFS and non-frail with the Edmonton scale had an Edmonton score of 6-7 ("vulnerable"), just less than the frailty cut-point score of 8. This indicates that the CFS adequately selects patients for further assessment with a more detailed, granular multidimensional frailty measure such as the Edmonton scale. Although the highest Youden index was seen for a CFS ≥ "mildly frail" (CFS = 5), we advocate that this screening cut-point should be a CFS ≥ 4, which would have captured in our cohort all but one Edmonton-scored patient with frailty. This also represents an appropriate balance between specificity and sensitivity; patients selected at this point will likely have Edmonton scores achieving or very near the "vulnerable" threshold, and will likely also benefit from formalised frailty measurement. This formalized assessment is obviously less applicable to emergency surgical patients. In this population, the finding of significantly increased mortality and post-operative complications with frailty (as with other studies) may instead prompt more attention to a shared-decision making process for frail patients.

A major finding of our study was that perioperative frailty affects a wide range of domains of health, with screening able to identify particular areas in which health deficits are over-represented in frail surgical patients. This included functional dependence, medication use, physical performance, and malnutrition, and concurs with our recent study into the areas of health affected by frailty in critical illness.[106] This is a significant finding, as it implies that follow-up frailty measurement following a screening process must be comprehensive,

particularly given recent trends to use hospital databases to construct so-called "frailty" measures. Although these rapid scales are easy to derive, there may be a significant bias towards medical comorbidities, and comparatively little information contained regarding other equally important domains of frailty. For example, the "modified frailty index" (mFI), an automated frailty measure derived from coding data which has seen numerous publications in the surgical literature, is almost entirely a comorbidity measure.[20] It may therefore fail to capture the complex multidimensional state that is frailty, and risk over-simplifying this complex condition to the detriment of future research and potential development of interventions for frail surgical patients.[2,37]

More recent examples of better-designed electronic frailty indices exist. The "eFI", derived and validated in primary-care setting datasets in the UK, is a 36-item frailty index that captures a wide range of health deficits.[23] It is able to predict mortality, hospitalisation and nursing home admission, but has not been tested in the perioperative setting. A more recent surgical-specific index, the "perioperative frailty index" (pFI) has been developed by McIsaac's group using population-based health administrative data in Canada.[112] This index comprises 30-items, and in over half-a-million surgical patients was shown to correlate with postoperative death and institutional discharge. In this new era of electronic health records, electronic frailty indices thus represent an extremely useful approach to measuring frailty, however must be comprehensive across the spectrum of health.

The finding of specific health domains that are disproportionately affected by frailty may also help identify areas that are potentially modifiable perioperatively. For example, the emerging interest in preoperative physical training ("prehabilitation") may potentially be able to improve physical performance prior to surgery in frail patients. Limited research has demonstrated this potential, with ongoing studies in this area.[113,114] Preoperative nutritional support may also be able to reduce the malnutrition seen in surgical patients with frailty.[115,116] More research is needed to determine whether these or other interventions can translate to better postoperative outcomes with frailty. Although logistically challenging for emergency surgery, elective surgical timelines may allow such targeted preoperative

optimisation. Moreover, in the postoperative period there may be benefit in addressing specific areas of health deficits for individual patients, to reduce overall operative risk.

5.5.4 Strengths and limitations

Strengths of our study are the inclusion of a broad range of both emergency and elective surgical patients across the spectrum of surgical subspecialties, enhancing generalisability. Although other studies have examined the CFS in specific surgical cohorts, including cardiac surgical[117] and general surgical patients [118], the inclusion of a wide range of surgical specialties is previously limited within the literature (with an exception being McIsaac et al's study of 702 non-cardiac surgical patients[46]). A further strength is the similarity between included and non-included patients, our study cohort thus likely being representative of surgical patients seen in our institution, as well as the completeness of study data.

A study limitation was the use of both the Edmonton and Reported Edmonton scales, with total scores possible varying by one point. Although possibly influencing the comparability of scores obtained, we considered this preferable to having missing physical performance scores for half of the cohort (107 of 218 patients), which would have made assessment of this frailty domain impossible. A further limitation was the fact our study was conducted in a single hospital, which may reduce generalisability, and also that investigators assigned both frailty scores without blinding nor randomisation of assessment order, potentially biasing measurement. However, the risk of bias we consider low since assignment of CFS and Edmonton scores were based on objective criteria and strict definitions regarding function, independence, and medical disease status, and total Edmonton scores were aggregated subsequent to assignment of the CFS score. Moreover, the methodology in this study (data collectors non-blinded to the comparator scale) is common to other studies comparing frailty scales, including in critically ill and other patient populations.[10,35] Future research could improve on ours and others' study designs by utilising blinded assessment in frailty measurement, and by having individual patient frailty measured by more than one investigator, to assess inter-rater reliability and to explore potential differences in assessments according to healthcare provider background. For example, a recent study in

an ICU population revealed similar CFS scores when assigned by raters from medical, research coordinator or occupational therapy backgrounds.[119] This remains unexplored in the perioperative setting. An extension of the study design to compare the CFS with a comprehensive geriatric assessment in surgical patients would also be of value, although we note the significant challenges in administering such a comprehensive tool in the perioperative setting. Forty-two (19%) of our patients were also included in our previous study examining the Edmonton and Clinical Frailty Scales in ICU patients. Sensitivity analyses, however, demonstrated little impact of inclusion of these patients on overall findings. In particular, the screening performance of the CFS with respect to the Edmonton scale was maintained, association with frailty and baseline demographics preserved, and the finding of worse health status across frailty domains persisted regardless of inclusion or omission of these patients. Our conclusions about frailty in the perioperative context, then, remain valid.

5.6 Conclusion

In conclusion, the Clinical Frailty Scale is an accurate, sensitive screening tool, with good face and content validity to measure frailty in the perioperative setting. Frailty in surgical patients affects the spectrum of health-related domains, which are important to include in candidate frailty measurement instruments. Screening for frailty in higher risk patients should occur prior to anesthesia with a cut-point of a CFS ≥ 4 selecting those for more comprehensive measurement. This may help identify particular health domains amenable to interventions to reduce the impact of perioperative frailty.

Authors' contributions:

JND: Study design, patient recruitment, analysis of data, manuscript drafting

JL: Study design, patient recruitment, manuscript review

TB: Study design, patient recruitment, manuscript review

SB: Analysis of data, manuscript review

ADS: Analysis of data, manuscript review

DAS: Study design, manuscript review

WKL: Study design, manuscript review

Table 5.1. Baseline demographics according to Edmonton Frail and Clinical Frailty Scales.

Variable	**Edmonton Frail Scale (N = 218)**			**Clinical Frailty Scale (N = 218)**		
	Frail N = 52	Not Frail N = 166	*P* value	Frail N = 61	Not Frail N = 157	*P* value
Age [years]	77 [68 – 83]	73 [69 – 79]	0.106	80 [74 – 85]	72 [68 – 77]	< 0.001
BMI (kg/m^2)	26.9 (5.6)	28.4 (6.1)	0.116	26.4 (6.0)	28.7 (5.9)	0.013
Female	21 (40.4%)	78 (47.0%)	0.404	31 (50.8%)	68 (43.3%)	0.318
Admission Source						
Home	41 (78.8%)	154 (92.8%)	< 0.001	48 (78.7%)	147 (93.6%)	0.002
Acute hospital	3 (5.8%)	9 (5.4%)		5 (8.2%)	7 (4.5%)	
Residential care	8 (15.4%)	3 (1.8%)		8 (13.1%)	3 (1.9%)	
Surgical type						
Elective	22 (42.3%)	96 (57.8%)	0.050	25 (41.0%)	93 (59.2%)	0.015
Emergency	30 (57.7%)	70 (42.2%)		36 (59.0%)	64 (40.8%)	
Charlson Comorbidity Score	3 [2 – 4]	2 [1 – 4]	0.013	3 [1 – 4]	2 [1 – 4]	0.041
ADL Function (Katz)						
Dependent (0 – 2)	7 (13.5%)	1 (0.6%)	< 0.001	8 (13.1%)	0 (0.0%)	< 0.001
Partially Dependent (3 – 4)	13 (25.0%)	10 (6.0%)		17 (27.9%)	6 (3.8%)	
Independent (5 – 6)	32 (61.5%)	155 (93.4%)		36 (59.0%)	151 (96.2%)	
P-POSSUM mortality risk [%]	7.0 [3.9 – 15.9]	4.2 [2.6 – 9.2]	0.003	6.9 [3.8 – 16.8]	4.1 [2.7 – 9.0]	0.005

Values are expressed as the mean (SD), median [interquartile range], or n (%).

ADL = activities of daily living. BMI = body mass index

Table 5.2. Secondary outcomes according to frailty, Edmonton Frail and Clinical Frailty Scales.

Variable	Edmonton Frail Scale		Clinical Frailty Scale		Univariate regression model Estimate (95% CI)		Multivariate regression model Estimate (95% CI)	
	Frail N = 52	Not Frail N = 166	Frail N = 61	Not Frail N = 157	Edmonton Frail Scale	Clinical Frailty Scale	Edmonton Frail Scale	Clinical Frailty Scale
Mortality within 30 days	5 (9.6%)	3 (1.8%)	5 (8.2%)	3 (1.9%)	5.41 (1.36 to 21.47)	4.30 (1.09 to 16.98)	5.26 (1.28 to 21.62)	4.01 (0.91 to 17.73)
Mortality at six-month follow up	16 (30.8%)	17 (10.5%)	17 (27.9%)	16 (10.5%)	3.76 (1.75 to 8.07	3.28 (1.54 to 6.96)	2.86 (1.25 to 6.51)	2.16 (0.94to 4.97)
Any complication*	29 (55.8%)	39 (23.5%)	28 (45.9%)	40 (25.5%)	4.05 (2.18 to 7.75)	2.47 (1.34 to 4.56)	3.67 (1.84 to 7.30)	2.33 (1.18 to 4.61)
Acute myocardial infarction	2 (3.8%)	2 (1.2%)	2 (3.3%)	2 (1.3%)	3.26 (0.55 to 19.34)	2.61 (0.44 to 15.47)	1.95 (0.27 to 14.10)	0.94 (0.13 to 6.54)
Re-intubation	5 (9.6%)	1 (0.6%)	4 (6.6%)	2 (1.3%)	12.78 (2.04 to 79.96)	4.87 (1.01 to 23.52)	8.25 (1.22 to 55.53)	3.54 (0.62 to 20.32)
Acute pulmonary oedema	9 (17.3%)	8 (4.8%)	7 (11.5%)	10 (6.4%)	4.07 (1.52 to 10.90)	1.93 (0.72 to 5.19)	4.44 (1.55 to 12.68)	1.90 (0.63 to 5.69)
Pulmonary embolus	0 (0.0%)	2 (1.2%)	0 (0.0%)	2 (1.3%)	0.63 (0.03 to 13.26)	0.51 (0.02 to 10.69)	0.36 (0.01 to 20.18)	0.22 (0.00 to 13.81)
Stroke/Transient ischaemic attack	0 (0.0%)	4 (2.4%)	0 (0.0%)	4 (2.5%)	0.34 (0.02 to 6.49)	0.28 (0.01 to 5.23)	0.31 (0.02 to 5.11)	0.28 (0.02 to 4.98)
Wound infection	10 (19.2%)	8 (4.8%)	10 (16.4%)	8 (5.1%)	4.61 (1.75 to 12.10)	3.59 (1.38 to 9.35)	1.52 (0.52 to 2.52)	1.41 (0.38 to 2.45)
Acute kidney injury	8 (15.4%)	20 (12.0%)	10 (16.4%)	18 (11.5%)	1.37 (0.57 to 3.25)	1.54 (0.68 to 3.50)	1.26 (0.50 to 3.14)	1.59 (0.64 to 3.93)
Unplanned re-operation	11 (21.2%)	7 (4.2%)	10 (16.4%)	8 (5.1%)	5.89 (2.21 to 15.72)	3.59 (1.38 to 9.35)	6.20 (2.09 to 18.38)	4.37 (1.47 to 13.02)
Unplanned admission to ICU	13 (25.0%)	12 (7.2%)	13 (21.3%)	12 (7.6%)	4.22 (1.81 to 9.83)	3.24 (1.41 to 7.47)	4.54 (1.83 to 11.26)	3.70 (1.46 to 9.41)
Hospital length of stay (days)	9.0 (5.0 – 14.6)	3.0 (1.0 – 9.0)	8.0 (5.0 – 14.0)	3.0 (1.0 – 9.0)	6.00 (3.15 to 8.85)	5.00 (2.88 to 7.12)	2.97 (-0.35 to 6.29)	2.52 (-0.66 to 5.69)
Other major complications	13 (25.0%)	21 (12.7%)	13 (21.3%)	21 (13.4%)	2.31 (1.08 to 4.98)	1.77 (0.83 to 3.76)	1.95 (0.86 to 4.43)	1.69 (0.73 to 3.93)
Discharge location								
Home	25 (48.1%)	122 (73.5%)	29 (47.5%)	118 (75.2%)	Ref.	Ref.	Ref.	Ref.
Assisted living facility/Rehabilitation	17 (32.7%)	29 (17.5%)	23 (37.7%)	23 (14.7%)	2.86 (1.37 to 5.98)	4.07 (2.01 to 8.25)	1.92 (0.81 to 4.55)	2.66 (1.15 to 6.13)
Other acute hospital	6 (11.5%)	12 (7.2%)	5 (8.2%)	13 (8.3%)	2.44 (0.84 to 7.12)	1.56 (0.52 to 4.74)	2.20 (0.68 to 7.15)	1.10 (0.31 to 3.91)
Died in hospital	4 (7.7%)	3 (1.8%)	4 (6.6%)	3 (1.9%)	6.51 (1.37 to 30.89)	5.43 (1.15 to 25.59)	6.49 (1.25 to 33.79)	5.02 (0.92 to 27.51)

* Defined as at least one of the following: acute myocardial infarction, cardiac arrest, tracheal reintubation, acute pulmonary oedema, deep venous thrombosis, pulmonary embolus, stroke, wound infection, acute kidney injury, unplanned need for re-operation, unplanned admission to ICU.

Values are expressed as median (interquartile range), n (%). Estimates are odds ratio (95% confidence interval), with the exception of the estimates for hospital length of stay (median difference [95% confidence interval]) and the estimates for discharge location (relative risk ratio [95% confidence interval]).

Table 5.3. Analysis of individual frailty domains according to Edmonton and Clinical Frailty Scales

Variable	**Edmonton Frail scale (N = 218)**			**Clinical Frailty Scale (N = 218)**		
	Frail n = 52	Not Frail n = 166	p-value	Frail n = 61	Not Frail n = 157	*P* value
General Health (Number of hospital admissions in past year)			< 0.001			< 0.001
0 admissions	8 (15.4%)	94 (56.6%)		16 (26.2%)	86 (54.8%)	
1-2 admissions	24 (46.2%)	51 (30.7%)		25 (41.0%)	50 (31.8%)	
>2 admissions	20 (38.5%)	21 (12.7%)		20 (32.8%)	21 (13.4%)	
General Health (In general, describe your health)			< 0.001			< 0.001
Good – excellent	10 (19.2%)	96 (57.8%)		16 (26.2%)	90 (57.3%)	
Fair	21 (40.4%)	65 (39.2%)		27 (44.3%)	59 (37.6%)	
Poor	21 (40.4%)	5 (3.0%)		18 (29.5%)	8 (5.1%)	
Functional Independence (Number of activities requiring help*)			< 0.001			< 0.001
0-1	9 (17.3%)	124 (74.7%)		7 (11.5%)	126 (80.3%)	
2-4	21 (40.4%)	35 (21.1%)		28 (45.9%)	28 (17.8%)	
5-8	22 (42.3%)	7 (4.2%)		26 (42.6%)	3 (1.9%)	
Cognition (Clock drawing test†)						< 0.001
No errors	14 (35.9%)	95 (62.9%)	< 0.001	15 (34.9%)	94 (63.9%)	
Minor spacing	11 (28.2%)	38 (25.2%)		11 (25.6%)	38 (25.9%)	
Other errors	14 (35.9%)	18 (11.9%)		17 (39.5%)	15 (10.2%)	
Social support (Can you count on someone to meet your needs?)			<0.001			0.52
Always	33 (63.5%)	127 (76.5%)		44 (72.1%)	116 (73.9%)	
Sometimes	10 (19.2%)	36 (21.7%)		12 (19.7%)	34 (21.7%)	
Never	9 (17.3%)	3 (1.8%)		5 (8.2%)	7 (4.5%)	
Medication use (Five or more different prescription medications)			< 0.001			< 0.001
No	4 (7.7%)	92 (55.4%)		9 (14.8%)	87 (55.4%)	
Yes	48 (92.3%)	74 (44.6%)		52 (85.2%)	70 (44.6%)	
Medication use (Do you forget to take prescription medications?)			0.258			0.38
No	34 (65.4%)	122 (73.5%)		41 (67.2%)	115 (73.2%)	
Yes	18 (34.6%)	44 (26.5%)		20 (32.8%)	42 (26.8%)	
Nutrition (Have you recently lost weight, with clothing looser?)			< 0.001			0.02
No	27 (51.9%)	134 (80.7%)		38 (62.3%)	123 (78.3%)	
Yes	25 (48.1%)	32 (19.3%)		23 (37.7%)	34 (21.7%)	

Mood (“Do you often feel sad or depressed?”)			< 0.001			< 0.001
No	25 (48.1%)	139 (83.7%)		35 (57.4%)	129 (82.2%)	
Yes	27 (51.9%)	27 (16.3%)		26 (42.6%)	28 (17.8%)	
Continence (Do you have a problem with losing control of urine?)			0.007			0.007
No	29 (55.8%)	125 (75.3%)		35 (57.4%)	119 (75.8%)	
Yes	23 (44.2%)	41 (24.7%)		26 (42.6%)	38 (24.2%)	
Physical performance‡ (Timed up-and-go test)			< 0.001			0.004
0 – 10 seconds	2 (11.8%)	44 (46.8%)		4 (20.0%)	42 (46.2%)	
11 – 20 seconds	7 (41.2%)	43 (45.7%)		9 (45.0%)	41 (45.1%)	
> 20 seconds, or requires assistance	8 (47.1%)	7 (7.4%)		7 (35.0%)	8 (8.8%)	
Reported physical performance§ (Number of activities)			< 0.001			< 0.001
All activities able to be performed	2 (5.7%)	35 (48.6%)		1 (2.4%)	36 (54.5%)	
Two activities able to be performed	7 (20.0%)	18 (25.0%)		10 (24.4%)	15 (22.7%)	
One activity able to be performed	10 (28.6%)	9 (12.5%)		10 (24.4%)	9 (13.6%)	
No activities able to be performed	16 (45.7%)	10 (13.9%)		20 (48.8%)	6 (9.1%)	
Edmonton/Clinical Frailty Scale total score, median [IQR]	9 [8 – 11]	4 [2 – 6]	< 0.001	5 [5 – 6]	3 [3 – 4]	< 0.001

Values are expressed as n (%).

* Activities of daily living assessed: meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications.

† 13 frail and 15 non-frail patients (per Edmonton scale) were unable to perform the clock drawing test.

‡ 35 frail and 72 non-frail patients (per Edmonton scale) were unable to perform the timed-up-and-go test; reported physical performance instead used.

§ Reported physical performance domains (for those unable to perform the timed-up-and-go test): "Two weeks ago, were you able to: 1. Do heavy work around the house like washing windows, walls, or floors without help? 2. Walk up and down stairs to the second floor without help? 3. Walk 1 km without help?"

Figure 5.1: Study flow diagram

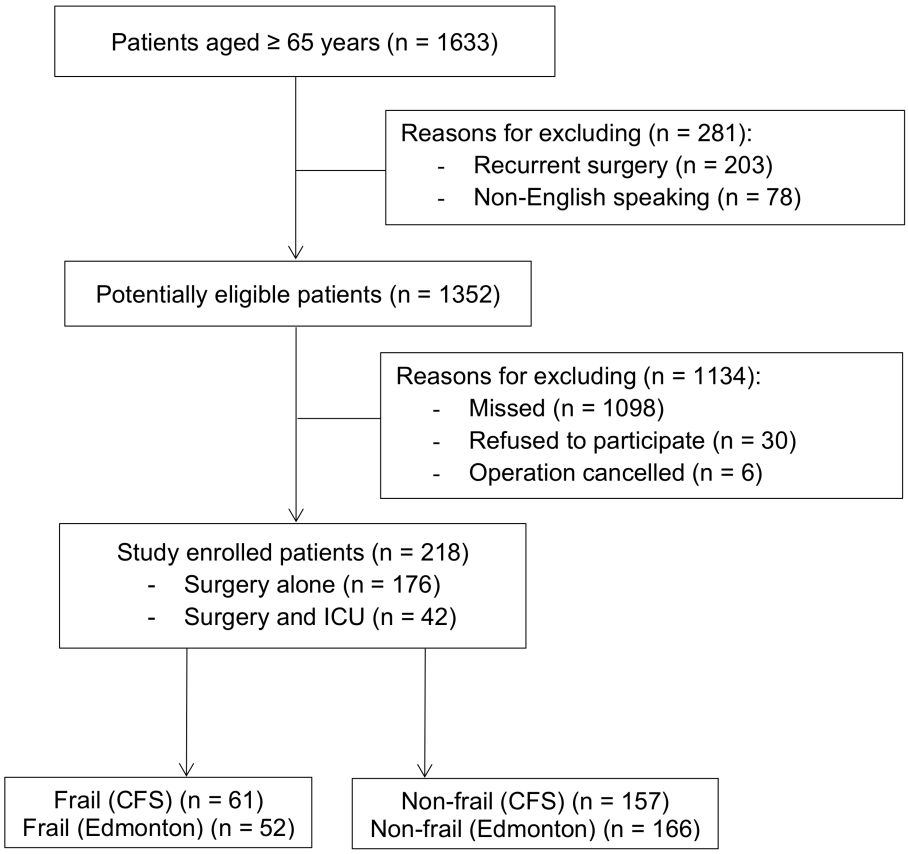
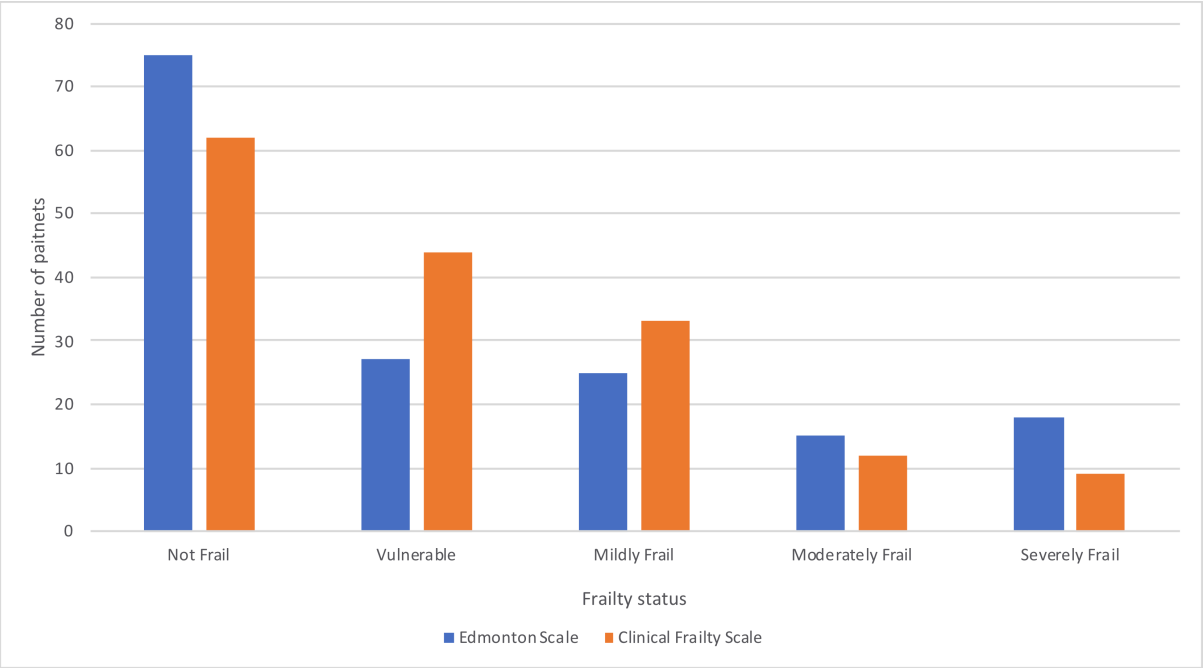


Figure 5.2: Frailty status of study participants at baseline



Supplementary Material

Supplementary Table 5.1. Baseline demographics, with and without patients admitted to the ICU

Variable	Full dataset N = 218	ICU patients omitted N = 176	Combined surgical/ICU patients N = 42	*P* value
Age [years]	74 [69 – 80]	74.5 [69 – 81]	73 [68 – 78]	0.31
BMI (kg/m^2)	28.0 (6.0)	27.6 (6.0)	30.0 (5.7)	0.02
Female	99 (45.4%)	80 (45.5%)	19 (45.2%)	0.98
Admission Source				
Home	195 (89.4%)	155 (88.1%)	40 (95.2%)	0.58
Acute hospital	12 (5.5%)	11 (6.2%)	1 (2.4%)	
Assisted living	11 (5.0%)	10 (5.7%)	1 (2.4%)	
Surgery type				
Elective	118 (54.1%)	101 (57.4%)	17 (40.5%)	0.048
Emergency	100 (45.9%)	75 (42.6%)	25 (59.5%)	
Charlson Comorbidity Score	2 [1-4]	2 [1-4]	2 [1-3]	0.43
ADL Function (Katz)				
Dependent (0 – 2)	8 (3.7%)	7 (4.0%)	1 (2.4%)	0.45
Partially Dependent (3 – 4)	23 (10.6%)	21 (11.9%)	2 (4.8%)	
Independent (5 – 6)	187 (85.8%)	148 (84.1%)	39 (92.9%)	
P-POSSUM mortality risk (%)	4.8 [2.8 – 10.4]	3.9 [2.5-8.1]	9.4 [6.2-20.1]	<0.001

Values are expressed as the mean (SD), median [interquartile range], or n (%).

ADL = activities of daily living. BMI = body mass index.

Supplementary Table 5.2. Supplementary analysis of demographics according to Edmonton Frail Scale, with and without patients admitted to the intensive care unit.

Variable	Full dataset (N = 218)			ICU patients omitted (N = 176)			Combined surgical/ICU patients (N = 42)		
	Frail N = 52	Not Frail N = 166	p-value	Frail N = 35	Not Frail N = 141	p-value	Frail N = 17	Not Frail N = 25	p-value
Age [years]	77 [68 – 83]	73 [69 – 79]	0.11	80 [67 – 86]	73 [69 – 79]	0.02	73 [68 – 77]	73 [68 – 80]	0.88
BMI (kg/m^2)	26.9 (5.6)	28.4 (6.1)	0.12	25.6 (5.5)	28.1 (6.1)	0.03	29.5 (4.9)	30.3 (6.3)	0.65
Female	21 (40.4%)	78 (47.0%)	0.40	13 (37.1%)	67 (47.5%)	0.27	8 (47.1%)	11 (44.0%)	0.85
Admission Source									
Home	41 (78.8%)	154 (92.8%)	< 0.001	26 (74.3%)	129 (91.5%)	< 0.001	15 (88.2%)	25 (100%)	0.16
Acute hospital	3 (5.8%)	9 (5.4%)		2 (5.7%)	9 (6.4%)		1 (5.9%)	0 (0.0%)	
Residential care	8 (15.4%)	3 (1.8%)		7 (20.0%)	3 (2.1%)		1 (5.9%)	0 (0.0%)	
Surgical type									
Elective	22 (42.3%)	96 (57.8%)	0.05	14 (40.0%)	87 (61.7%)	0.02	8 (47.1%)	9 (36.0%)	0.47
Emergency	30 (57.7%)	70 (42.2%)		21 (60.0%)	54 (38.3%)		9 (52.9%)	16 (64.0%)	
Charlson Comorbidity Score	3 [2 – 4]	2 [1 – 4]	0.01	3 [1 – 5]	2 [1 – 4]	0.12	3 [2 – 4]	1 [1 – 2]	0.001
ADL Function (Katz)									
Dependent (0 – 2)	7 (13.5%)	1 (0.6%)	< 0.001	6 (17.1%)	1 (0.7%)	< 0.001	1 (5.9%)	0 (0.0%)	0.50
Partially Dependent (3 – 4)	13 (25.0%)	10 (6.0%)		12 (34.3%)	9 (6.4%)		1 (5.9%)	1 (4.0%)	
Independent (5 – 6)	32 (61.5%)	155 (93.4%)		17 (48.6%)	131 (92.9%)		15 (88.2%)	24 (96.0%)	
P-POSSUM mortality risk [%]	7.0 [3.9 – 15.9]	4.2 [2.6 – 9.2]	0.003	5.4 [3.2-16.8]	3.7 [2.5-7.4]	0.01	8.9 [6.4-14.9]	10.3 [5.8-22.4]	0.43

Values are expressed as the mean (SD), median [interquartile range], or n (%).

ADL = activities of daily living. BMI = body mass index.

Supplementary Table 5.3. Supplementary analysis of demographics according to Clinical Frailty Scale, with and without patients admitted to the ICU

Variable	Full dataset (N = 218)			ICU patients omitted (N = 176)			Combined surgical/ICU patients (N = 42)		
	Frail N = 61	Not Frail N = 157	*P* value	Frail N = 47	Not Frail N = 129	p-value	Frail N = 14	Not Frail N = 28	p-value
Age [years]	80 [74 – 85]	72 [68 – 77]	< 0.001	82 [76 – 86]	72 [68 – 77]	< 0.001	74 [68 – 77]	72 [68 – 79]	0.68
BMI (kg/m^2)	26.4 (6.0)	28.7 (5.9)	0.013	25.4 (5.9)	28.4 (5.9)	0.003	30.0 (5.2)	30.0 (6.0)	0.98
Female	31 (50.8%)	68 (43.3%)	0.318	25 (53.2%)	55 (42.6%)	0.213	6 (42.9%)	13 (46.4%)	0.83
Admission Source									
Home	48 (78.7%)	147 (93.6%)	0.002	36 (76.6%)	119 (92.2%)	0.005	12 (85.7%)	28 (100%)	0.11
Acute hospital	5 (8.2%)	7 (4.5%)		4 (8.5%)	7 (5.4%)		1 (7.1%)	0 (0.0%)	
Residential care	8 (13.1%)	3 (1.9%)		7 (14.9%)	3 (2.3%)		1 (7.1%)	0 (0.0%)	
Surgical type									
Elective	25 (41.0%)	93 (59.2%)	0.015	21 (44.7%)	80 (62.0%)	0.040	4 (28.6%)	13 (46.4%)	0.27
Emergency	36 (59.0%)	64 (40.8%)		26 (55.3%)	49 (38.0%)		10 (71.4%)	15 (53.6%)	
Charlson Comorbidity Score	3 [1-4]	2 [1 – 4]	0.041	3 [1 - 5]	2 [1 – 4]	0.123	3 [2 - 4]	2 [1 - 3]	0.048
ADL Function (Katz)									
Dependent (0 – 2)	8 (13.1%)	0 (0.0%)	< 0.001	7 (14.9%)	0 (0.0%)	< 0.001	1 (7.1%)	0 (0.0%)	0.25
Partially Dependent (3 – 4)	17 (27.9%)	6 (3.8%)		16 (34.0%)	5 (3.9%)		1 (7.1%)	1 (3.6%)	
Independent (5 – 6)	36 (59.0%)	151 (96.2%)		24 (51.1%)	124 (96.1%)		12 (85.7%)	27 (96.4%)	
P-POSSUM mortality risk (%)	6.9 [3.8 – 16.8]	4.1 [2.7 – 9.0]	0.005	5.9 [3.0-14.6]	3.6 [2.5-6.6]	0.005	8.6 [6.4-18.7]	9.9 [5.8-21.4]	0.75

Values are expressed as the mean (SD), median [interquartile range], or n (%).

ADL = activities of daily living. BMI = body mass index.

Supplementary Table 5.4. Analysis of individual frailty domains according to Edmonton Frail Scale, with and without patients admitted to the ICU

Variable	Full dataset (N = 218)			ICU patients omitted (N = 176)			Combined surgical/ICU patients (N = 42)		
	Frail n = 52	Not Frail n = 166	p-value	Frail N = 35	Not Frail N = 141	p-value	Frail N = 17	Not Frail N = 25	p-value
General Health (Number of hospital admissions in past year)									
0 admissions	8 (15.4%)	94 (56.6%)	< 0.001	4 (11.4%)	78 (55.3%)	< 0.001	4 (23.5%)	16 (64.0%)	0.01
1-2 admissions	24 (46.2%)	51 (30.7%)		18 (51.4%)	44 (31.2%)		6 (35.3%)	7 (28.0%)	
>2 admissions	20 (38.5%)	21 (12.7%)		13 (37.1%)	19 (13.5%)		7 (41.2%)	2 (8.0%)	
General Health (In general, describe your health)									
Good – excellent	10 (19.2%)	96 (57.8%)	< 0.001	6 (17.1%)	80 (56.7%)	< 0.001	4 (23.5%)	16 (64.0%)	< 0.001
Fair	21 (40.4%)	65 (39.2%)		17 (48.6%)	57 (40.4%)		4 (23.5%)	8 (32.0%)	
Poor	21 (40.4%)	5 (3.0%)		12 (34.3%)	4 (2.8%)		9 (52.9%)	1 (4.0%)	
Functional Independence (Number of activities requiring help*)									
0-1	9 (17.3%)	124 (74.7%)	< 0.001	4 (11.4%)	102 (72.3%)	< 0.001	5 (29.4%)	22 (88.0%)	< 0.001
2-4	21 (40.4%)	35 (21.1%)		16 (45.7%)	32 (22.7%)		5 (29.4%)	3 (12.0%)	
5-8	22 (42.3%)	7 (4.2%)		15 (42.9%)	7 (5.0%)		7 (41.2%)	0 (0.0%)	
Cognition (Clock drawing test†)									
No errors	14 (35.9%)	95 (62.9%)	< 0.001	9 (36.0%)	86 (65.6%)	0.003	5 (35.7%)	9 (45.0%)	0.75
Minor spacing	11 (28.2%)	38 (25.2%)		8 (32.0%)	33 (25.2%)		3 (21.4%)	5 (25.0%)	
Other errors	14 (35.9%)	18 (11.9%)		8 (32.0%)	12 (9.2%)		6 (42.9%)	6 (30.0%)	
Social support (Can you count on someone to meet your needs?)									
Always	33 (63.5%)	127 (76.5%)	<0.001	22 (62.9%)	105 (74.5%)	0.005	11 (64.7%)	22 (88.0%)	0.10
Sometimes	10 (19.2%)	36 (21.7%)		7 (20.0%)	33 (23.4%)		3 (17.6%)	3 (12.0%)	
Never	9 (17.3%)	3 (1.8%)		6 (17.1%)	3 (2.1%)		3 (17.6%)	0 (0.0%)	
Medication use (Five or more different prescription medications)									
No	4 (7.7%)	92 (55.4%)	< 0.001	2 (5.7%)	81 (57.4%)	< 0.001	2 (11.8%)	11 (44.0%)	0.03

Yes	48 (92.3%)	74 (44.6%)		33 (94.3%)	60 (42.6%)		15 (88.2%)	14 (56.0%)	
Medication use (Do you forget to take prescription medications?)									
No	34 (65.4%)	122 (73.5%)	0.258	23 (65.7%)	104 (73.8%)	0.342	11 (64.7%)	18 (72.0%)	0.62
Yes	18 (34.6%)	44 (26.5%)		12 (34.3%)	37 (26.2%)		6 (35.3%)	7 (28.0%)	
Nutrition (Have you recently lost weight, with clothing looser?)									
No	27 (51.9%)	134 (80.7%)	< 0.001	17 (48.6%)	114 (80.9%)	< 0.001	10 (58.8%)	20 (80.0%)	0.17
Yes	25 (48.1%)	32 (19.3%)		18 (51.4%)	27 (19.1%)		7 (41.2%)	5 (20.0%)	
Mood ("Do you often feel sad or depressed?")									
No	25 (48.1%)	139 (83.7%)	< 0.001	21 (60.0%)	116 (82.3%)	0.005	4 (23.5%)	23 (92.0%)	< 0.001
Yes	27 (51.9%)	27 (16.3%)		14 (40.0%)	25 (17.7%)		13 (76.5%)	2 (8.0%)	
Continence (Do you have a problem with losing control of urine?)									
No	29 (55.8%)	125 (75.3%)	0.007	18 (51.4%)	107 (75.9%)	0.004	11 (64.7%)	18 (72.0%)	0.62
Yes	23 (44.2%)	41 (24.7%)		17 (48.6%)	34 (24.1%)		6 (35.3%)	7 (28.0%)	
Physical performance‡ (Timed up-and-go test)									
0 – 10 seconds	2 (11.8%)	44 (46.8%)	< 0.001	2 (14.3%)	41 (46.6%)	< 0.001	0 (0.0%)	3 (50.0%)	0.46
11 – 20 seconds	7 (41.2%)	43 (45.7%)		4 (28.6%)	40 (45.5%)		3 (100%)	3 (50.0%)	
> 20 seconds/requires assistance	8 (47.1%)	7 (7.4%)		8 (57.1%)	7 (8.0%)		0 (0.0%)	0 (0.0%)	
Reported physical performance§ (Number of activities)									
All activities able to be performed	2 (5.7%)	35 (48.6%)	< 0.001	0 (0.0%)	28 (52.8%)	< 0.001	2 (14.3%)	7 (36.8%)	0.25
Two activities able to be performed	7 (20.0%)	18 (25.0%)		5 (23.8%)	13 (24.5%)		2 (14.3%)	5 (26.3%)	
One activity able to be performed	10 (28.6%)	9 (12.5%)		7 (33.3%)	6 (11.3%)		3 (21.4%)	3 (15.8%)	
No activities able to be performed	16 (45.7%)	10 (13.9%)		9 (42.9%)	6 (11.3%)		7 (50.0%)	4 (21.1%)	
Edmonton Frailty Scale total score	9 (8 – 11)	4 (2 – 6)	< 0.001	9 (8 – 11)	4 (2 – 6)	< 0.001	10 (9 - 11)	4 (3 - 6)	< 0.001

Values are expressed as n (%).

* Activities of daily living assessed: meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications.

† Not all patients were able to perform the clock drawing test.

‡ Not all patients were able to perform the timed-up-and-go test; reported physical performance instead used.

§ Reported physical performance domains (for those unable to perform the timed-up-and-go test): "Two weeks ago, were you able to: 1. Do heavy work around the house like washing windows, walls, or floors without help? 2. Walk up and down stairs to the second floor without help? 3. Walk 1 km without help?"

Supplementary Table 5.5. Analysis of individual frailty domains according to Clinical Frailty Scale, with and without patients admitted to the ICU

Variable	Full dataset (N = 218)			ICU patients omitted (N = 176)			Combined surgical/ICU patients (N = 42)		
	Frail n = 61	Not Frail n = 157	p-value	Frail N = 47	Not Frail N = 129	p-value	Frail N = 14	Not Frail N = 28	p-value
General Health (Number of hospital admissions in past year)									
0 admissions	16 (26.2%)	86 (54.8%)	< 0.001	11 (23.4%)	71 (55.0%)	< 0.001	5 (35.7%)	15 (53.6%)	0.08
1-2 admissions	25 (41.0%)	50 (31.8%)		22 (46.8%)	40 (31.0%)		3 (21.4%)	10 (35.7%)	
>2 admissions	20 (32.8%)	21 (13.4%)		14 (29.8%)	18 (14.0%)		6 (42.9%)	3 (10.7%)	
General Health (In general, describe your health)									
Good – excellent	16 (26.2%)	90 (57.3%)	< 0.001	12 (25.5%)	74 (57.4%)	< 0.001	4 (28.6%)	16 (57.1%)	0.03
Fair	27 (44.3%)	59 (37.6%)		24 (51.1%)11	50 (38.8%)		3 (21.4%)	9 (32.1%)	
Poor	18 (29.5%)	8 (5.1%)		(23.4%)	5 (3.9%)		7 (50.0%)	3 (10.7%)	
Functional Independence (Number of activities requiring help*)									
0-1	7 (11.5%)	126 (80.3%)	< 0.001	5 (10.6%)	101 (78.3%)	< 0.001	2 (14.3%)	25 (89.3%)	< 0.001
2-4	28 (45.9%)	28 (17.8%)		23 (48.9%)	25 (19.4%)		5 (35.7%)	3 (10.7%)	
5-8	26 (42.6%)	3 (1.9%)		19 (40.4%)	3 (2.3%)		7 (50.0%)	0 (0.0%)	
Cognition (Clock drawing test†)									
No errors	15 (34.9%)	94 (63.9%)	< 0.001	12 (37.5%)	83 (66.9%)	<0.001	3 (27.3%)	11 (47.8%)	0.58
Minor spacing	11 (25.6%)	38 (25.9%)		8 (25.0%)	33 (26.6%)		3 (27.3%)	5 (21.7%)	
Other errors	17 (39.5%)	15 (10.2%)		12 (37.5%)	8 (6.5%)		5 (45.5%)	7 (30.4%)	
Social support (Can you count on someone to meet your needs?)									
Always	44 (72.1%)	116 (73.9%)	0.520	34 (72.3%)	93 (72.1%)	0.864	10 (71.4%)	23 (82.1%)	0.51
Sometimes	12 (19.7%)	34 (21.7%)		10 (21.3%)	30 (23.3%)		2 (14.3%)	4 (14.3%)	
Never	5 (8.2%)	7 (4.5%)		3 (6.4%)	6 (4.7%)		2 (14.3%)	1 (3.6%)	
Medication use (Five or more different prescription medications)									
No	9 (14.8%)	87 (55.4%)	< 0.001	7 (14.9%)	76 (58.9%)	< 0.001	2 (14.3%)	11 (39.3%)	0.10

Yes	52 (85.2%)	70 (44.6%)		40 (85.1%)	53 (41.1%)		12 (85.7%)	17 (60.7%)	
Medication use (Do you forget to take prescription medications?)									
No	41 (67.2%)	115 (73.2%)	0.375	32 (68.1%)	95 (73.6%)	0.47	9 (64.3%)	20 (71.4%)	0.73
Yes	20 (32.8%)	42 (26.8%)		15 (31.9%)	34 (26.4%)		5 (35.7%)	8 (28.6%)	
Nutrition (Have you recently lost weight, with clothing looser?)									
No	38 (62.3%)	123 (78.3%)	0.015	29 (61.7%)	102 (79.1%)	0.02	9 (64.3%)	21 (75.0%)	0.49
Yes	23 (37.7%)	34 (21.7%)		18 (38.3%)	27 (20.9%)		5 (35.7%)	7 (25.0%)	
Mood ("Do you often feel sad or depressed?")									
No	35 (57.4%)	129 (82.2%)	< 0.001	32 (68.1%)	105 (81.4%)	0.06	3 (21.4%)	24 (85.7%)	< 0.001
Yes	26 (42.6%)	28 (17.8%)		15 (31.9%)	24 (18.6%)		11 (78.6%)	4 (14.3%)	
Continence (Do you have a problem with losing control of urine?)									
No	35 (57.4%)	119 (75.8%)	0.007	26 (55.3%)	99 (76.7%)	0.006	9 (64.3%)	20 (71.4%)	0.73
Yes	26 (42.6%)	38 (24.2%)		21 (44.7%)	30 (23.3%)		5 (35.7%)	8 (28.6%)	
Physical performance‡ (Timed up-and-go test)									
0 – 10 seconds	4 (20.0%)	42 (46.2%)	0.004	4 (21.1%)	39 (47.0%)	0.008	0 (0.0%)	3 (37.5%)	>0.99
11 – 20 seconds	9 (45.0%)	41 (45.1%)		8 (42.1%)	36 (43.4%)		1 (100%)	5 (62.5%)	
> 20 seconds/requires assistance	7 (35.0%)	8 (8.8%)		7 (36.8%)	8 (9.6%)		0 (0.0%)	0 (0.0%)	
Reported physical performance§ (Number of activities)									
All activities able to be performed	1 (2.4%)	36 (54.5%)	< 0.001	0 (0.0%)	28 (60.9%)	< 0.001	1 (7.7%)	8 (40.0%)	0.03
Two activities able to be performed	10 (24.4%)	15 (22.7%)		8 (28.6%)	10 (21.7%)		2 (15.4%)	5 (25.0%)	
One activity able to be performed	10 (24.4%)	9 (13.6%)		8 (28.6%)	5 (10.9%)		2 (15.4%)	4 (20.0%)	
No activities able to be performed	20 (48.8%)	6 (9.1%)		12 (42.9%)	3 (6.5%)		8 (61.5%)	3 (15.0%)	
Clinical Frailty Scale total score	5 (5 – 6)	3 (3 – 4)	< 0.001	5 (5 – 6)	3 (2 – 4)	< 0.001	5 (5 – 6)	4 (3 – 4)	< 0.001

Values are expressed as n (%).

* Activities of daily living assessed: meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications.

† Not all patients were able to perform the clock drawing test.

‡ Not all patients were able to perform the timed-up-and-go test; reported physical performance instead used.

§ Reported physical performance domains (for those unable to perform the timed-up-and-go test): "Two weeks ago, were you able to: 1. Do heavy work around the house like washing windows, walls, or floors without help? 2. Walk up and down stairs to the second floor without help? 3. Walk 1 km without help?

Supplementary Table 5.6. Comparisons between Edmonton Frail and Clinical Frail Scales, with inclusion and omission of patients admitted to the intensive care unit.

Variable	Full dataset (n = 218)	ICU patients omitted (n = 176)	Combined surgical/ICU patients (N = 42)
Frailty prevalence (Edmonton), n (%)	52 (23.9%), 95% CI (18.4% to 30.1%)	35 (19.9%), 95% CI (14.3% to 26.6%)	17 (40.5%), 95% CI (25.6% to 56.7%)
Frailty prevalence (CFS), n (%)	61 (28.0%), 95% CI (22.1% to 34.4%)	47 (26.7%), 95% CI (20.3% to 33.9%)	14 (33.3%), 95% CI (19.6% to 49.5%)
Spearman correlation coefficient (95% CI)	0.81 (0.77 to 0.86)	0.80 (0.75 to 0.86)	0.85 (0.76 to 0.93)
Kappa coefficient (frail vs. non-frail) (95% CI)	0.65 (0.54 to 0.77)	0.62 (0.49 to 0.76)	0.75 (0.54 to 0.95)
Kappa coefficient (ordinal) (95% CI)	0.76 (0.70 to 0.81)	0.75 (0.67 to 0.81)	0.78 (0.67 to 0.88)
AUCROC (95% CI)	0.91 (0.86 to 0.94)	0.91 (0.85 to 0.94)	0.93 (0.81 to 0.99)
Sensitivity (CFS ≥ 4) (95% CI)	98.1% (89.7% to 100%)	97.1% (85.1% to 99.9%)	100% (80.5% to 100%)
Specificity (CFS ≥ 4) (95% CI)	54.8% (46.9% to 62.5%)	54.6% (46.0% to 63.0%)	56.0% (34.9% to 75.6%)

AUCROC = area under receiver operating curve

Supplementary Table 5.7 Definitions for postoperative complications

Acute myocardial infarction	Increase in cardiac troponin with ECG changes (ST-T segment changes, new bundle-branch block, Q waves)
Acute pulmonary oedema	Increase in oxygen requirements with chest xray changes consistent with radiological acute pulmonary oedema (upper lobe pulmonary venous diversion, peri-bronchial cuffing, septal lines, air space opacification, pleural effusions).
Deep venous thrombosis, pulmonary embolus	Radiological confirmation (lower limb ultrasound/computed tomography pulmonary artery scan)
Stroke	Computed tomography or magnetic resonance imaging evidence of acute ischaemic/haemorrhagic stroke
Wound infection	Defined according to the Centers for Disease Control and Prevention National Healthcare Safety Network (*Berríos-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017;152(8):784–791.):* Superficial incisional infection: Infection occurs within 30 days after an operative procedure *and* involves only skin and subcutaneous tissue of the incision *and* patient has at least one of the following:

	a) Purulent drainage from the superficial incision. b) Organisms isolated from an aseptically-obtained culture of fluid or tissue from the superficial incision. c) Superficial incision that is deliberately opened by a surgeon and is culture-positive or not cultured and patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; redness; or heat. A culture negative finding does not meet this criterion. d) Diagnosis of a superficial incisional SSI by the surgeon or attending physician.
Acute kidney injury	Defined according to the AKIN criteria (*Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury, Crit Care , 2007, vol. 11 pg. R31*): Increase in serum creatinine of ≥ 26.5 µmol/L (≥ 0.3 mg/dL) or a percentage increase in serum creatinine ≥50% (1.5× baseline value).

Chapter 6: Retrospective frailty determination in critical illness from review of the ICU clinical record

This chapter is the study published in *Anaesthesia and Intensive Care*. 2019 Jul;47(4):343-348 (Appendix 2.) (Lightly edited for headings and formatting consistency)

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Keywords: frailty; intensive care unit; mortality; outcomes

6.1 Abstract

Frailty is one of the major challenges for intensive care, affecting one-third of ICU patients and associated with a range of poor health outcomes. Determination of frailty in critical illness using the Clinical Frailty Scale (CFS) has recently been adopted by the Australian and New Zealand Intensive Care Society, but it is not known whether this is able to be measured from the clinical record without interview of patients or their relatives. The aim of this retrospective cohort study was to test whether a CFS score could be assigned in an ICU population from the clinical record, and to assess the inter-rater reliability of frailty measured in this manner. 144 patients were enrolled, 137 (95%) were able to have a CFS score assigned, 22 (15%) were scored frail (CFS ≥ 5). Cohen's kappa coefficient for inter-rater reliability between assessors was 0.67, confirming substantial agreement. Consistent with other critically ill cohorts, frailty was associated on multivariate analysis with age, Charlson comorbidity score, dependence with activities of daily living, and limitation of medical treatment, indicating validity of this approach to frailty measurement. Our results imply that frailty measurement is possible and feasible from the ICU clinical record, of importance as routine measurement and reporting of frailty in ICUs in our region increases. Future work should seek to validate an assigned CFS score with that obtained directly from patients, or their next-of-kin.

6.2 Introduction

As critically ill populations around the world age, patient frailty has become one of the major challenges in intensive care. Over the next decade in Australia, greater than one-quarter of all patients admitted to ICU will be aged > 80 years[31]; based on similar European cohorts, more than 40% of this population will be have coexisting frailty[100]. Frailty is associated with an increased risk of death, functional dependence, hospital readmission, and new discharge to residential care [10 35,120]. Measuring frailty in ICU is challenging, but one validated tool, the Clinical Frailty Scale (CFS), is increasingly used due to its ability to be measured at the bedside, with no requirement for functional testing which is challenging in the ICU environment[6]. Frailty measured according to this scale, a nine-item categorical measure, has been correlated with increased mortality, adverse events and functional

dependence in ICU survivors[10,100]. Given these associations, the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS CORE) has recently added frailty case-finding using the CFS to the data collected at admission for ICU patients in our region.

Despite the importance of frailty to the risk stratification and outcomes of critically ill patients, gathering this data presents a particular challenge in ICU. Unlike other data points for the ANZICS Adult Patient Database, which are for the most part based on objective criteria able to be gathered from the clinical record, frailty measurement via the CFS requires a degree of subjectivity in assessment. Interviewing the patient or the next-of-kin is also often necessary, to determine aspects of functional performance and physical dependency that allow granularity of frailty measurement. Prior frailty studies have employed dedicated research personnel for this purpose, trained in the collection and interpretation of the CFS[10 57], however more recent attempts have been made to routinely collect this data using clinical staff. A single centre Australian study illustrated the challenges posed with this approach, wherein only 59% of eligible patients had a CFS score assigned, and of these, three-quarters were assigned by the nurse-in-charge without next-of-kin involvement[52]. This approach thus raises concerns regarding data completeness and accuracy.

CFS collection in Australasian ICUs, therefore, will likely fall to existing ICU data-collectors, posing significant challenges to workload. In particular, contemporaneous bedside frailty measurement will be problematic for data-collectors, who currently rarely (if ever) are required to interview patients or next of kin, and also often enter data retrospectively using the convenience of medical chart review. It is not known whether this is possible for frailty in critical illness. No prior literature exists to inform whether frailty measurement and scoring is possible from the routine medical admission records of ICU patients. Accordingly, we therefore conducted a retrospective cohort study to test the primary hypothesis that a Clinical Frailty Scale score could be assigned in an ICU population from interrogation of the clinical record. We secondarily hypothesised that the inter-rater reliability of this score between two separate clinician assessors as scored by Cohen's kappa coefficient would be

at least 0.6, implying substantial agreement, and that associations with other patient characteristics and frailty found in other ICU populations would remain when data was collected using this methodology.

6.3 Materials and methods

This study was a secondary analysis of the previously published retrospective case-control study examining contributory factors leading to persisting critical illness.[121] Approval was obtained from the local Human Research Ethics Committee as a quality assurance project (QA2016110). In this previous single-centre study, 72 adult patients between 1st January 2013 and 31st December 2014 with an ICU length of stay (LOS) > 10 days were matched to 72 patients with an ICU LOS < 10 days admitted within the same time frame. Matching hierarchy was as follows: Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD) diagnostic code, sex, age within 10%, and Acute Physiology and Chronic Health Evaluation (APACHE) III risk of death within 10%. Patients admitted to ICU for purposes of organ donation were excluded. In the case of patients readmitted to ICU, only the first ICU episode was eligible for inclusion. Four study members (JD, TB, JN or DM) interrogated the paper medical record after discharge and collected data including age, gender, Charlson comorbidity score, ICU admission source and diagnosis, presence of treatment limitation on admission, dependence with any activities of daily living as determined by the Katz scale (bathing, dressing, toileting, feeding, continence, transferring),[108] daily ICU supports and requirement for ICU care, and outcomes including mortality, discharge destination (home, other acute hospital, chronic care/rehabilitation) and cause of death. In addition, a CFS score was assigned for all patients by the lead intensive care specialist investigator (JD), with a randomly selected subset of 100 patients also independently assigned a CFS score by one of the other three other intensive care resident medical officer investigators (TB, JN, DM) to assess inter-rater reliability. Accepted cut-offs for frailty were used, with frailty defined as CFS ≥ 5, non-frail as CFS < 4, and vulnerable as CFS = 4[6]. Prior to study commencement all data collectors were trained in the role of the CFS and its measurement, with calibration on a sample of five patients. CFS scores were assigned after interrogation of the entire clinical record, with particular

emphasis on the allied health review documentation (IP49 hospital form) in conjunction with the "social history" aspect of the admission note. Data collectors were blind to each other's CFS scores.

6.3.1 Statistical analysis

All data were initially assessed for normality. Data were reported as numbers (%), means (standard deviation) or median (interquartile range) as appropriate. Univariable and multivariable linear regression models were fitted to investigate the association of other variables with frailty, and with in-hospital mortality. Inter-rater agreement between CFS scores was examined via Cohen's kappa coefficients, using quadratic weighting due to the increased magnitude of clinical difference with ascending CFS categories. Cohen's kappa were categorized using the scale of Landis & Koch[110].

6.4 Results

During the study period 72 patients with an ICU length of stay (LOS) > 10 days were matched to 72 control patients with complete medical records and with LOS < 10 days, from a total of 3874 patients admitted to the ICU.[121] Baseline data of the cohort are presented in Table 6.1. CFS scores could be assigned for 137 of the 144 total patients (95.1%); seven patients were unable to have a CFS score assigned due to absent social details in the admission note and no allied health review. Twenty-two (15.3%) of patients were scored frail (CFS ≥ 5), 37 (27.0%) patients scored vulnerable (CFS = 4) and 78 (54.2%) patients non-frail (CFS ≤ 3) (Figure 6.1). As previously reported there were no differences between persistingly critically ill cases and control patients in frailty prevalence.[121]

6.4.1 Frailty score agreement

For the 100 patients with dual CFS assessment, Cohen's kappa coefficient for inter-rater reliability between investigators was 0.67, indicating substantial agreement. Forty-five (45%) of 100 scores agreed perfectly, with a further 41 (41%) differing by only one point and

13 (13%) differing by two points. Only one pair of scores differed by more than two points, a patient scored CFS = 7 by one investigator and CFS = 4 by another.

6.4.2 Outcomes

Frailty (CFS ≥ 5) was associated on univariate analysis with age, Charlson comorbidity score, dependence with activities of daily living, limitation of medical treatment on admission, mortality, and discharge to chronic care/rehabilitation (Table 6.2). On multivariate analysis, age, Charlson comorbidity score, dependence with activities of daily living, and limitation of medical treatment on admission remained significantly associated with frailty (Table 6.2). Although frailty was associated with univariate mortality, there were no statistically significant associations when considered in the multivariable model.

6.5 Discussion

6.5.1 Main findings

In this retrospective cohort study, we found that assignment of frailty status with a Clinical Frailty Scale score from the clinical record of critically ill patients was feasible, able to be completed in 95% of patients, and had substantial inter-rater reliability. As seen in overseas cohorts, frailty was associated with increasing age, medical comorbidity, and functional dependence and limitation of medical treatment on admission, providing evidence of the concurrent validity of this approach to measuring the CFS.

6.5.2 Relationship to prior literature

One prior (non-ICU) study has examined the feasibility of retrospectively assigning a CFS score from the clinical record of 41 geriatric outpatients who had both undergone and had documented a comprehensive geriatric assessment, with similarly substantial inter-rater reliability (Cohen's kappa coefficient = 0.64)[122]. Unlike our investigation, however, this study used the gold-standard comprehensive geriatric assessment, with multiple data points able

to be assessed in arriving at a frailty score. In contrast, our current study has demonstrated that CFS assignment is possible from the usual clinical record of an ICU admission, without specific geriatric assessment. The inter-rater reliability of prospective CFS assignment in the ICU from interviews with patients' surrogates has also been demonstrated in a recent study of 101 critically ill patients in Wales and Scotland, with a linear weighted Kappa between assessors of 0.74, and a similar level of score agreement seen in our study (53% vs. 45% of scores in perfect agreement; 40% vs. 41% of scores differing by one point)[11]. Taken together, our study and these would suggest that the CFS has acceptable inter-rater reliability, including in the ICU environment.

Similar to recent literature using the CFS to measure frailty in critically illness, we also observed poor health status and ICU outcomes in frail patients. A recent study of 421 critically ill Canadian patients demonstrated similarly increased comorbid disease and functional dependence with frailty, as well as a higher rate of limitation of medical treatment (34% frail patients vs. 12% non-frail; $p < 0.001$, very similar to the rate in our study: 34% frail vs. 7.0% non-frail, $p < 0.001$).[10] Although prevalence of frailty in our cohort (15%) was significantly lower than in this Canadian study (33%), this is likely related to significant differences in populations studied. Our cohort was younger, with mean (SD) age 60 (16) years vs. 69 (10) years and 66 (10) years in frail and non-frail patients in the Canadian study, respectively. Our population likely also had less comorbid disease; although this was measured differently between studies (Charlson score in our cohort vs. Elixhauser score,[123] which includes some comorbidities such as hypertension not present in the Charlson scoring system. Almost one-quarter of our population were also admitted following trauma, thus may have been less "medically complex" than in other cohorts studied. The association of frailty with mortality on univariate, but not multivariate, analysis is likely related to the small number of patients studied (22 frail), as well as high overall mortality

6.5.3 Strengths and limitations

Strengths of our study include the assessment of a mixed medical-surgical-trauma ICU population using a paper charting system, thus implying our findings are likely applicable to other similar ICUs in our region. A further strength is that our study investigators were non-geriatric specialists, thus enhancing external validity to data collection by similar non-frailty experts in other ICUs.

Our study had several limitations. It was conducted in a single-centre, with the possibility that differences in data recorded and documented may exist between different hospitals. Given that much documentation is likely common to many Australasian ICUs, however, including mention of patients' relevant social circumstances and the integral role (and hence related documentation) of allied health in ICU, we consider that the standard of our medical records could be reasonably expected to reflect that of units around our region. A further limitation is that we did not compare the CFS assigned through clinical record interrogation to that measured contemporaneously through interviews with patients or their next-of-kin directly, thus we cannot compare the two techniques. Future research should seek to validate this, and assess the accuracy of the methodology we have chosen in this study. We note, however, that one such study exists which demonstrated substantial agreement between prospective and retrospective CFS scores, when derived from a documented comprehensive geriatric assessment[122]. Whether this same level of agreement exists when compared to documentation typical of an ICU admission requires further research. Our methodology is also not translatable to determination of frailty at ICU admission. We assigned a CFS score after access to the entire chronology of the clinical record, in particular (and most usefully) after allied health documentation some days into the admission, which frequently revealed details related to functional capacity and physical dependency allowing granular frailty assessment. Although a limitation for the early measurement of frailty in critical illness, this still has relevance to our hypothesis, allowing determination of patient frailty for benchmarking, data reporting, and audit. There is, however, the potential for bias as a result of assignment of a higher CFS score in those that were sicker or who had a limitation of medical treatment order, although this applied to only 13% of the total cohort. A final limitation is we did not stratify patients by pre-ICU residential location; it is possible that the increased association of discharge to chronic care/rehabilitation was influenced by

a lesser proportion of frail patients residing at home prior to onset of critical illness. There is, however, a strong association in past studies with new onset of residential care admission[42].

6.6 Conclusion

In conclusion, we have demonstrated the feasibility of measuring frailty using the Clinical Frailty Scale from the clinical record in a cohort of critically ill patients. This has significant implications for the ability to routinely measure and report frailty in Australian and New Zealand ICUs, which is likely achievable without extra resourcing for specific bedside data collection. As accurate and complete frailty assessment becomes integral to risk stratification and ongoing treatment decisions made in the ICU, this is an important development.

Table 6.1. Baseline characteristics of the cohort

Baseline characteristic	
n	144
Age, mean (SD)	60.3 (15.7)
Male, n (%)	92 (64%)
APACHE 3 score, mean (SD)	81.8 (24.8)
Charlson comorbidity score, mean (SD)	3.7 (2.6)
Any limitation of medical treatment on admission, n (%)	18 (12.5%)
Clinical frailty scale score, median (IQR)	3 (2-4)
Dependence with any ADLs, n (%)	16 (11.6%)
Discharge destination, n (%)	
Died	48 (33.3%)
Home	41 (28.5%)
Chronic care/rehabilitation	39 (27.1%)
Other hospital	16 (11.1%)

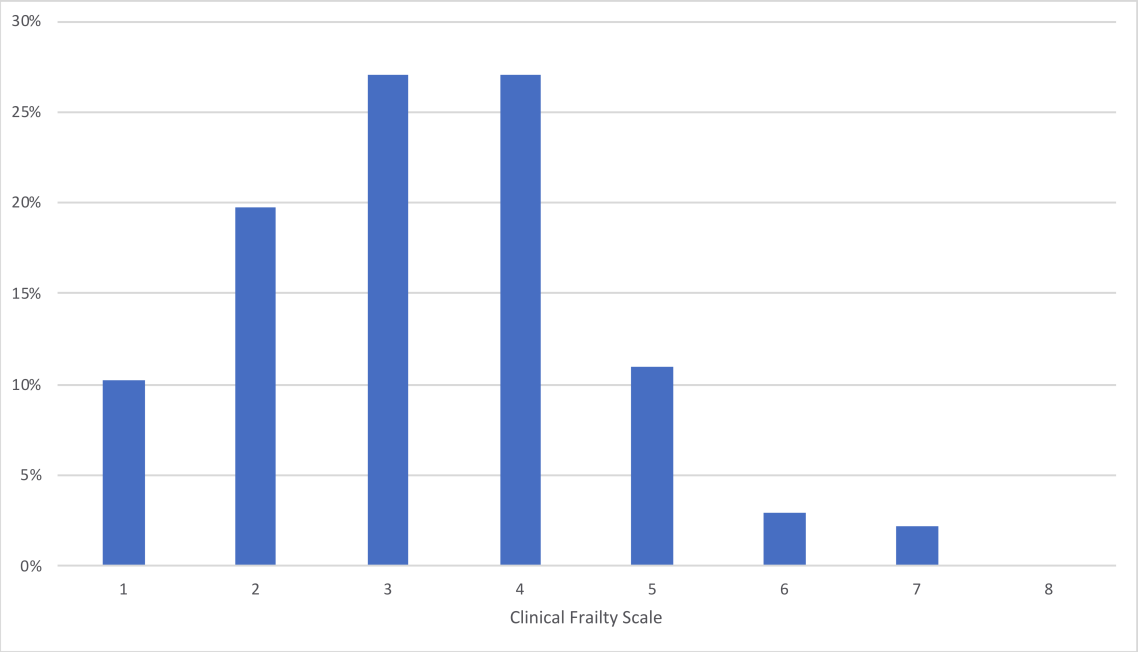
ALDs = dependence with any activities of daily living (bathing, dressing, toileting, feeding, continence, transferring)[108]; APACHE = acute physiology and chronic health evaluation

Table 6.2. Univariate and multivariate association of variables with frailty (CFS ≥ 5)

	Univariate analysis			Multivariate analysis		
Characteristic	**Regression coefficient**	**Standard error**	**P value**	**Regression coefficient**	**Standard error**	**P value**
Age	0.03	0.01	< 0.01	0.02	0.01	0.04
ADLs	1.98	0.33	< 0.01	1.64	0.30	< 0.01
Charlson comorbidity score	0.2	0.4	< 0.01	0.11	0.05	0.03
Limitation of medical treatment	1.33	0.35	< 0.01	0.69	0.31	0.03

ALDs = dependence with any activities of daily living (bathing, dressing, toileting, feeding, continence, transferring)

Figure 6.1: Clinical Frailty Scale scores of study participants



Chapter 7: Frailty in very old critically ill patients in Australia and New Zealand: a population based, cohort study

This chapter is the study published in the *Medical Journal of Australia*. 2019 Oct;211(7):318-323 (Appendix 3.) (Lightly edited for headings and formatting consistency).

7.1 Highlights

- Frailty in older critically ill patients is associated with worse health outcomes in overseas cohorts.
- Over 25% of Australian ICU patients are forecast to be aged ≥ 80 years by 2030.
- Frailty is common in Australian and New Zealand ICUs (39.7% of patients aged ≥ 80 years)
- Frailty is associated with longer length of stay, increased mortality and new discharge to nursing home/chronic care.
- We estimate that each year 9000 frail patients aged ≥ 80 years are admitted to participating ICUs in our region, of whom 1600 die in hospital, and a further 450 survive to be newly discharged to nursing home/chronic care.
- This has major implications for health outcomes and resourcing in this vulnerable population.

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7.2 Abstract

Objective: To explore associations between frailty (Clinical Frailty Scale score of 5 or more) in very old patients in intensive care units (ICUs) and their clinical outcomes (mortality, discharge destination).

Design, setting and participants: Retrospective population cohort analysis of Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database data for all patients aged 80 years or more admitted to participating ICUs between 1 January 2017 and 31 December 2018.

Main outcome measures: Primary outcome: in-hospital mortality; secondary outcomes: length of stay (hospital, ICU), re-admission to ICU during the same hospital admission, discharge destination (including new chronic care or nursing home admission).

Results: Frailty status data were available for 15 613 of 45 773 patients aged 80 years or more admitted to 178 ICUs (34%); 6203 of these patients (39.7%) were deemed frail. A smaller proportion of frail than of non-frail patients were men (47% v 57%), the mean illness severity scores of frail patients were slightly higher than those of non-frail patients, and they were more frequently admitted from the emergency department (28% v 21%) or with sepsis (12% v 7%) or respiratory complications (16% v 12%). In-hospital mortality was higher for frail patients (17.6% v 8.2%; adjusted odds ratio [OR], 1.87 [95% CI, 1.65–2.11]). Median lengths of ICU and hospital stay were slightly longer for frail patients, and they were more frequently discharged to a new nursing home or chronic care facility (4.9% v 2.8%; adjusted OR, 1.61 [95% CI, 1.34–1.95]).

Conclusions: Many very old critically ill patients in Australia and New Zealand are frail, and frailty is associated with considerably poorer health outcomes. Routine screening of older ICU patients for frailty could improve outcome prediction and inform intensive care and community health care planning.

7.3 Introduction

The number of older Australians will increase significantly over the next two decades; by 2036, the number of people aged 85 years or more will have doubled to one million.[55] The demographic features of hospitalised patients, particularly the critically ill, will consequently change. The mean age of patients in intensive care units (ICUs) in our region is climbing rapidly, and it is forecast that by 2030 26% of all people admitted to Australian ICUs will be aged 80 years or more.[31] This demographic change is likely to be accompanied by a shift in ICU practice, from a focus on managing patients with acute, reversible illnesses to caring for people, many near the end of their lives, with exacerbations of chronic disease.

One of the major challenges in caring for critically ill older people is frailty,[10] a multidimensional syndrome characterised by reduced capacity to deal with external stressors. Frailty is common among critically ill older people; more than 40% of ICU patients over 80 are frail.[100] Frailty in people with critical illness is associated with particularly poor outcomes: it doubles the risks of death and functional dependence, significantly increases health care use, and reduces quality of life.[10,57,124] Neither the prevalence of frailty among older ICU patients nor the implications of our ageing populations for ICU resourcing and outcomes for frail older patients have been well explored in our region.

Accordingly, we conducted a multicentre retrospective cohort study of older patients in more than one hundred ICUs in Australia and New Zealand. We describe the demographic features and the admission characteristics and outcomes for frail ICU patients aged 80 years or more. We hypothesised that mortality would be greater among frail than non-frail patients, and that a larger proportion would be discharged to residential care rather than home.

7.4 Methods

We conducted a retrospective population-based cohort study, analysing data from the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database, which includes data on more than 80% of all admissions to ICUs in Australia and New Zealand.[53] Data were gathered by the ANZICS Centre for Outcome and Resource Evaluation, which manages a clinical registry of participating ICUs for benchmarking purposes. Data dictionary use and automated validity checks were obligatory, and ongoing training and quality assurance review was provided for data abstractors.

All patients aged 80 years or more when admitted to an ICU between 1 January 2017 and 31 December 2018 were included in the study. Patients were excluded if they had been admitted to an ICU for organ donation or palliative care only. Only the first ICU admission during a hospital stay was included. Demographic data collected during ICU admission included age, sex, height, weight, admission diagnosis, limitations of medical treatment (because of patient wishes or medical futility; eg, not for intubation or cardiopulmonary resuscitation), Acute Physiology and Chronic Health Evaluation (APACHE) II and III-j illness severity scores[125], and Australian and New Zealand Risk of Death (ANZROD) scores.[126]

Approval for the study was provided by The Alfred Hospital Human Research Ethics Committee, Melbourne, Australia (HREC number 584/18).

7.4.1 Frailty diagnosis

Frailty was measured with a modified version of the Canadian Study of Health and Aging Clinical Frailty Scale, a judgement-based nine-point categorical scale found to be valid and reliable for assessing frailty in a variety of populations, including critically ill patients.[6,10] The eight-point Clinical Frailty Scale (CFS), the most used frailty measure in ICUs,[33], categorises patients as CFS 1 (very fit), CFS 2 (well), CFS 3 (managing well), CFS 4 (vulnerable), CFS 5 (mildly frail), CFS 6 (moderately frail), CFS 7 (severely frail), or CFS 8 (very severely frail).[6] We dichotomised scores according to accepted definitions, defining patients as frail (CFS 5–8) or non-frail (CFS 1–4).[10] Since 2017, frailty has been a non-mandatory variable measured at the time of ICU admission, depending on the patient's level of physical function in the two

months preceding admission. Scores were assigned by data collectors in each participating ICU from the clinical record; no specific education in CFS measurement was provided.

7.4.2 Statistical analysis

Results are reported as counts (with proportions), means (with standard deviations [SDs]), or medians (with interquartile ranges [IQRs]); comparisons of data for frail and non-frail patients employed □2 tests for binary and categorical data, two-sample t tests for normally distributed data, and Wilcoxon rank-sum tests for non-normally distributed continuous data. Sensitivity analyses assessed the association between frailty and mortality, with sites assigned to three groups according to completeness of coding for frailty (< 10%, 10–50%, > 50%).

The primary outcome was in-hospital mortality; secondary outcomes were length of stay (in hospital, in the ICU), re-admission to the ICU during the same hospital admission, and discharge destination (including new chronic care or nursing home admission). Unadjusted and adjusted associations between frailty status and in-hospital mortality were examined by mixed effects logistic regression, and results reported as odds ratios (OR) with 95% confidence intervals (95% CIs); associations between frailty status and discharge to a new nursing home or chronic care facility were assessed for patients who left hospital alive. All multivariable analyses were adjusted for region, sex, hospital type, and severity of illness (estimated with the ANZROD model),[126,127], with patients clustered by site, and site treated as a random effect. ANZROD is a locally derived mortality prediction model that includes age, diagnosis, acute physiological disturbance, chronic comorbid conditions, and treatment limitations as factors, and applies separate regression equations for each major diagnostic group. It accurately predicts mortality of Australian and New Zealand ICU patients, and is well calibrated and highly discriminatory (area under the receiver operating characteristic curve exceeding 0.9 when applied to the entire ICU population).[126] Statistical analyses were performed in Stata 15.1 (StataCorp) and SAS 9.4 (SAS Institute).

Ethics approval

Ethics approval was provided by The Alfred Hospital Human Research Ethics Committee (HREC number 584/18).

7.5 Results

A total of 45 773 eligible patients aged 80 years or more were admitted to 178 ICUs during the study period; frailty scores were available for 15 613 patients from 131 ICUs contributing frailty data (34.1%) (Figure 7.1). The median age of the included patients was 84.6 years (IQR, 82.1–87.8 years); 8247 (52.8%) were men (Table 7.1). The median age and illness severity of the 30 160 patients without recorded frailty scores were similar to those for the patients with frailty scores; median length of ICU stay was also similar, but median length of hospital stay was slightly longer (9.7 days [IQR, 5.6–17 days] *v* 9.2 h [IQR, 5.4–5.9 days]) and mortality higher (7.1% *v* 6.3%) for patients without frailty scores (Supplementary Table 7.1).

In total, 6203 patients (39.7%; 95% CI, 39.0–40.5%) were classified as frail (Figure 7.2); the median frailty score was 4 (IQR, 3–5). The proportion of patients classified as frail increased with age; 2813 of 8389 patients aged 80–84 years (33.5%) were frail, but 203 of 329 patients aged 95 or more years (61.7%) (Figure 7.3). Frail patients aged 80 years or more comprised 6.1% of the 102 102 patients with known frailty status admitted to the 131 ICUs contributing frailty data during the study period.

The median age of frail patients (85.5 years; IQR, 82.8–89.0 years) was higher than that of non-frail patients (84.0 years; IQR, 81.8–87.0 years); a smaller proportion were men (47% *v* 57%), their mean illness severity scores were slightly higher, and a large proportion had treatment limitations on admission to the ICU (33% *v* 11%) (Table 7.1). Frail patients were more frequently admitted to ICU from emergency departments (28% *v* 21%) and less frequently after elective surgery (27% *v* 46%) than non-frail patients (Table 7.1). Larger proportions of frail patients were admitted with sepsis (12% *v* 7%) or respiratory

complications (16% *v* 12%), and a smaller proportion after cardiac surgery (3% *v* 10%) (Table 7.2).

7.5.1 Outcomes

Unadjusted mortality was higher among frail than non-frail patients, both for in-ICU (9.0% *v* 4.5%; *P* < 0.001) and in-hospital deaths (17.6% *v* 8.2%; *P* < 0.001; unadjusted OR, 2.40; 95% CI, 2.17–2.64) (Table 7.2). In our multivariable analysis, frailty was significantly associated with in-hospital mortality after adjusting for sex, baseline severity of illness, and variation between regions and hospital types (adjusted OR, 1.87; 95% CI, 1.65–2.11) (Table 7.3). Frailty was also associated with higher mortality in sensitivity analyses in which sites were grouped by completeness of frailty coding (Supplementary Table 7.5).

Rates of ICU re-admission were similar for frail and non-frail patients (4.4% *v* 4.1%); mean lengths of ICU and hospital stay were slightly longer for frail than non-frail patients, and frail patients were more frequently discharged to a new nursing home or chronic care facility (4.9% *v* 2.8%) (Table 7.2). After adjusting for sex, baseline severity of illness, and variation between regions and hospital types, frailty in patients discharged alive from hospital was associated with an increased risk of discharge to a new nursing home or chronic care (adjusted OR, 1.61; 95% CI, 1.34–1.95) (Table 7.3).

7.6 Discussion

7.6.1 Main findings

We found that 39.7% of ICU patients in Australia and New Zealand aged 80 years or more are frail, or 6.1% of all adults admitted to ICUs. More than half these frail patients were women (53%); larger proportions of frail than non-frail patients were admitted to the ICU from emergency departments, or with sepsis or respiratory failure. Mortality among frail patients, after adjusting for sex, severity of illness, and regional and hospital variation, was almost twice as high as for non-frail patients, and frail patients were more frequently discharged to a new nursing home or chronic care admission than non-frail patients.

7.6.2 Relationship to prior literature

The prevalence of frailty among our patients (39.7%) is comparable with that reported by a European study of 5000 ICU patients aged 80 years or more (43.1%);[100] the authors of the largest systematic review of frailty in critically ill adults (3030 patients aged 18 years or more) reported a lower pooled frailty prevalence (30%).[42] We found that frailty was more frequent among women than men (44.6% *v* 35.4%), as previously reported for various populations, including ICU patients;[10,128] various lifestyle, biological, and inflammatory factors have been invoked to explain this difference.[129]

Our adjusted odds ratio for in-hospital mortality (1.87) is similar to the in-hospital mortality relative risk reported by the large systematic review of frailty in adult ICU patients (1.71; 95% CI, 1.43–2.05).[42] Overall in-hospital mortality in our study (11.9%), however, was considerably lower than reported for other populations of critically ill older patients. In a 2014 study of 28 000 Victorian ICU patients aged 80 years or more, mortality was 24.1%;[130] in a 2009 study of 15 000 Australian and New Zealand ICU patients aged 80 years or more, it was 25%.[131] Mortality was 22.1% in a recent study of very old European ICU patients,[100] and in a Canadian study, even higher (35%).[132] The reason for the lower number of deaths in our study is unclear, but may be related to population differences (eg, the prevalence of sepsis was lower in our study than in other reports), the inclusion of patients with less severe illness (mean APACHE III score: our study, 61.3 *v* 2009 study, 67.5[131]), and recent improvements in ICU outcomes. We found that the proportion of patients with limitations of medical treatment on admission was larger for frail than non-frail ICU patients, consistent with other studies, [10,100,133] suggesting that clinicians more frequently apply restricted goals of care to older critically ill patients who are frail.

Our finding that a greater proportion of frail than non-frail survivors of critical illness were discharged to residential care (7.6% *v* 3.1%) is consistent with the findings of the systematic review mentioned above (relative risk of home discharge [416 frail, 912 non-frail patients],

0.59; 95% CI, 0.49–0.71).[42] Our finding that the incidence of new residential care admission was higher for frail patients (4.9% v 2.8%), however, is novel.

The frailty measure we applied, the CFS, is the most employed frailty instrument in ICUs, and has been validated in a variety of hospital and community health care settings.[6,134] We have recently reported that the CFS can be used to measure frailty in critical ill patients across the spectrum of health domains, and its performance in ICU patients is comparable with that of comprehensive multidimensional frailty assessment tools.[106] Interest in using hospital coding data to generate automated frailty indexes is growing; for example, the Modified Frailty Index (mFI) was recently employed in a Brazilian study including more than 130 000 ICU patients.[36] Nine of 11 variables in the mFI, however, are comorbid conditions, and it does not include information on important domains of frailty, such as mobility impairment, malnutrition, and cognitive deficits. Before such screening tools can be adopted in ICUs, it is important that they are validated against accepted frailty scales.

7.6.3 Implications of our findings

We found that frailty is prevalent among critically ill patients aged 80 years or more in Australia and New Zealand, and that it is associated with higher rates of in-hospital mortality and discharge to residential care. That the risk of new residential care admission is 1.6 times as high for frail as for non-frail very old patients suggests that post-recovery impairment is greater for frail patients, a finding with major implications for health care and community resource planning for frail survivors of critical illness. We estimate that 9000 frail patients aged 80 years or more are admitted to participating ICUs in Australia and New Zealand each year, of whom 1600 die in hospital and 450 are discharged to new nursing home or chronic care.

7.6.4 Strengths and limitations

Our study is the largest to have applied the Clinical Frailty Scale to very old critically ill patients, and the first large scale study of frailty in ICUs in Australia and New Zealand. The binational database upon which the study is based is large, and its data are regularly audited and validated, ensuring their high quality. However, we reviewed medical records to assign frailty scores, whereas previous CFS-based studies have interviewed patients or their relatives.[10,33] Inaccurate CFS scoring was therefore possible, although substantial inter-rater reliability in CFS scores assigned on the basis of ICU medical records has been reported.[135] Further, CFS scores based on chart review are comparable with scores based on direct ICU patient interview;[119] the accuracy of retrospective CFS scores obtained in this manner, when compared with scores assigned after comprehensive geriatric medical assessments, has also been reported.[122]

A further limitation was that frailty status was not available for most ICU patients, as CFS reporting, a relatively recent addition to the ANZICS dataset, was not mandatory in the participating ICUs. However, differences in baseline characteristics and outcomes between patients with and without known frailty status were small and not clinically relevant. For example, overall in-hospital mortality (11.9% v 12.9%), median APACHE III scores (58 v 59), and Australian and New Zealand Risk of Death score (4.9 v 5.0) were all similar for patients with and without frailty scores, and the distributions of diagnostic categories were also comparable (Supporting Table 7.1). Further, frailty was associated with higher in-hospital mortality both overall and when assessed in groups of ICUs classed by the degree of completeness of frailty score recording (except for ICUs with completion rates below 10%; however, the small proportions of patients with frailty data in these ICUs renders comparison difficult) (Supporting Table 7.5).

7.7 Conclusion

A large proportion of very old critically ill patients in Australia and New Zealand are frail, and frailty is associated with considerably poorer health outcomes, including increased risk of in-hospital death and of new admission to residential care for survivors. These findings have important public health implications. Routine screening of older ICU patients for frailty

could improve outcome prediction and inform intensive care and community health care planning on discharge.

Figure 7.1. Selection of intensive care unit (ICU) patients for inclusion in our analysis

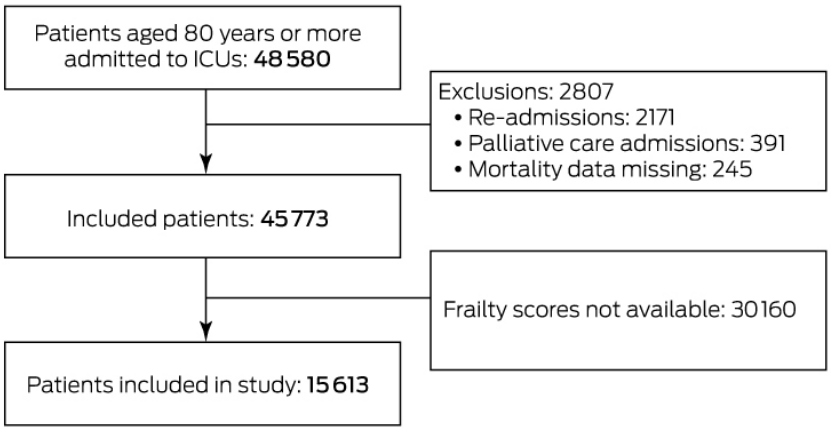


Table 7.1. Baseline demographic characteristics of intensive care unit (ICU) patients included in study, by frailty status

Characteristic	All patients	Frail patients	Non-frail patients
Number	15 613	6203	9410
Age (years), median (IQR)	84.6 (82.1–87.8)	85.5 (82.8–89.0)	84.0 (81.8–87.0)
Sex (men)	8247 (52.8%)	2917 (47.0%)	5330 (56.6%)
APACHE II score, median (IQR)	16 (13–20)	17 (14–22)	15 (12–19)
APACHE III-j score, median (IQR)	58 (48–71)	62 (51–75)	56 (46–67)
ANZROD, mean (SD), median (IQR)	13.1% (18.8), 4.8% (1.6–16.2%)	17.9% (20.9), 9.2% (2.9–25.1%)	10.0% (16.5), 3.2% (1.2–10.3%)
Treatment limitations on admission	3013 (19.9%)	2039 (33.0%)	1064 (11.3%)
One or more chronic disease	5404 (34.6%)	2688 (43.3%)	2716 (28.9%)
Two or more chronic disease	1539 (9.9%)	850 (13.7%)	689 (7.3%)
Admission type			
Non-surgical	6878 (44.1%)	3330 (53.7%)	3548 (37.7%)
Elective surgical (planned ICU admission)	5988 (38.4%)	1683 (27.1%)	4305 (45.8%)
Emergency surgical	2747 (17.6%)	1190 (19.2%)	1557 (16.5%)
Hospital admission source			
Home	12 173 (81.4%)	4594 (75.5%)	7579 (85.5%)
Chronic care/palliative care/nursing home	476 (3.2%)	402 (6.6%)	74 (0.8%)
Transfer from other acute hospital	2153 (14.4%)	992 (16.3%)	1161 (13.1%)
Mental health	6 (< 0.1%)	4 (0.1%)	2 (< 0.1%)
Rehabilitation	138 (0.9%)	92 (1.5%)	46 (0.5%)
ICU admission source			
Operating theatre	8563 (55.4%)	2839 (45.8%)	5814 (61.8%)
Emergency department	3649 (23.4%)	1720 (27.7%)	1929 (20.5%)
Hospital ward	2554 (16.4%)	1320 (21.3%)	1234 (13.1%)
Direct transfer from other ICU	156 (1.0%)	54 (0.9%)	102 (1.1%)
Direct admission from other hospital	529 (3.4%)	243 (3.9%)	286 (3.0%)
Direct admission from home	72 (0.5%)	27 (0.4%)	45 (0.5%)

ANZROD = Australian and New Zealand Risk of Death; APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range.

Figure 7.2. Distribution of Clinical Frailty Scale scores for 15 613 patients aged 80 years or more admitted to intensive care units in Australia and New Zealand, 2017–2018

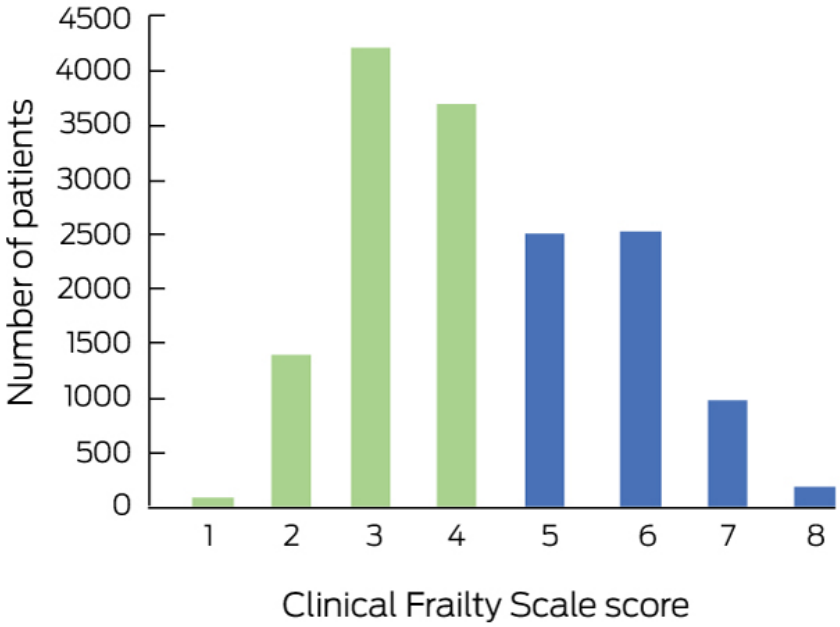
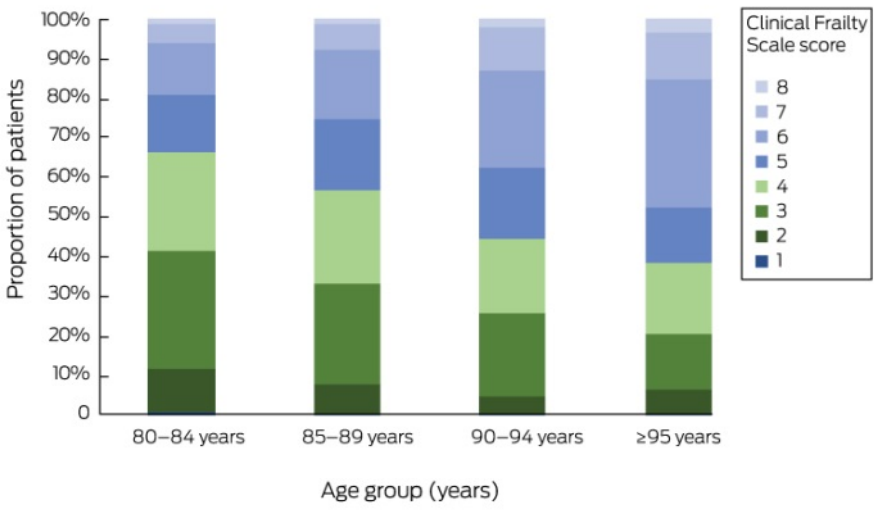


Figure 7.3. Distribution of Clinical Frailty Scale scores, stratified by 5-year age groups



Number of patients: 80–84 years, 8389; 80–84 years, 5132; 80–84 years, 1763; 95 years or more, 329.

Table 7.2. Clinical characteristics and outcomes for 15 613 patients aged 80 years or more admitted to intensive care units (ICUs) in Australia and New Zealand, 2017–2018

Characteristic	Frail patients	Non-frail patients
Number	6203	9410
ICU diagnostic category		
Sepsis	742 (12.0%)	680 (7.2%)
Trauma	274 (4.4%)	357 (3.8%)
Cardiac surgery	196 (3.2%)	969 (10.3%)
Other cardiovascular	1148 (18.5%)	1739 (18.4%)
Respiratory	999 (16.1%)	1126 (12.0%)
Neurological	437 (7.0%)	885 (9.4%)
Gastrointestinal	1231 (19.8%)	1939 (20.6%)
Other	1176 (19.0%)	1715 (18.2%)
Re-admission to ICU	271 (4.4%)	382 (4.1%)
Length of stay (days), median (IQR)		
ICU	1.80 (0.93–3.31)	1.65 (0.90–2.97)
Hospital (including ICU)	10.0 (5.84–17.7)	8.86 (5.19–15.0)
Deaths		
ICU	554 (9.0%)	425 (4.5%)
Hospital (including ICU)	1090 (17.6%)	769 (8.2%)
Discharge destination		
Died	1090 (17.6%)	769 (8.2%)
Home	2831 (45.6%)	5604 (59.6%)
Nursing home/chronic care	472 (7.6%)	295 (3.1%)
New nursing home/chronic care	302 (4.9%)	267 (2.8%)
Rehabilitation	959 (15.5%)	1485 (15.8%)
Other hospital	789 (12.8%)	1177 (12.5%)
Other	62 (1.0%)	80 (1.0%)

IQR = interquartile range.

Table 7.3. Frailty and outcomes: summary of multivariable analyses

Analysis (frail *v* non frail patients)	Odds ratio (95% CI)	*P*	Area under receiver operating characteristic curve
In-hospital mortality (all patients)			
Univariable analysis	2.40 (2.17–2.64)	< 0.001	0.61 (0.60–0.62)
Multivariable analysis*	1.87 (1.65–2.11)	< 0.001	0.88 (0.88–0.89)
Discharge to new nursing home/chronic care (survivors only)			
Univariable analysis	1.96 (1.66–2.33)	< 0.001	0.58 (0.56–0.60)
Multivariable analysis*	1.61 (1.34–1.95)	< 0.001	0.82 (0.80–0.83)

* Mixed effects logistic regression adjusted for sex, region, hospital type, and severity of illness (ANZROD) at admission to the intensive care unit, with site as random effect. Full models are presented in the Supporting Information, tables 2–4.

Supplementary Table 7.1. Baseline demographic characteristics and outcomes for intensive care unit (ICU) patients with recorded frailty scores (included in main analysis) or without recorded frailty scores

Variable	Patients with frailty scores	Patients without frailty scores	*P*
Number	15 613	30 160	
Age (years), median (IQR)	84.6 (82.1–87.8)	84.3 (81.9–87.4)	< 0.001
Sex (male)	8247 (52.8%)	16 388 (54.3%)	0.002
APACHE II score, median (IQR)	16 (13–20)	16 (13–21)	< 0.001
APACHE III-j score, median (IQR)	58 (48–71)	59 (49–73)	< 0.001
ANZROD, median (IQR)	4.9 (1.6–16.2)	5.0 (1.7–15.8)	0.67
Treatment limitations on admission	3103 (19.9%)	4885 (16.4%)	< 0.001
Admission type			< 0.001
Non-surgical	6878 (44.1%)	13 338 (44.2%)	
Elective surgical (planned ICU admission)	5988 (38.4%)	12 046 (40.8%)	
Emergency surgical	2747 (17.6%)	4776 (15.8%)	
ICU diagnostic category			< 0.001
Sepsis	1422 (9.1%)	2539 (8.4%)	
Trauma	631 (4.0%)	1321 (4.4%)	
Cardiac surgery	1165 (7.5%)	2663 (8.8%)	
Other cardiovascular	2887 (18.5%)	5231 (17.3%)	
Respiratory	2125 (13.6%)	4045 (13.4%)	
Neurological	1322 (8.5%)	2713 (9.0%)	
Gastrointestinal	3170 (20.3%)	6297 (20.9%)	
Other	2891 (18.5%)	5351 (17.7%)	
Length of stay (hours), median (IQR)			
ICU	1.7 (0.91–3.0)	1.8 (0.92–3.1)	0.025
Hospital	9.2 (5.4–5.9)	9.7 (5.6–17)	< 0.001
Deaths			
ICU	979 (6.3%)	2141 (7.1%)	0.001
Hospital	1859 (11.9%)	3895 (12.9%)	0.002

IQR = interquartile range; APACHE = Acute physiology and chronic health evaluation; ANZROD = Australian and New Zealand Risk of Death.

Supplementary Table 7.2. Mixed effects logistic regression analysis of hospital mortality adjusted for sex overall predicted risk of death (ANZROD), regional variation, and hospital type (with site as random effect)

Hospital mortality	Odds ratio (95% confidence interval)	*P*
Sex (men)	1.18 (1.05–1.33)	0.005
ANZROD (per percentage point)	1.06 (1.06–1.06)	< 0.001
Jurisdiction		
Australian Capital Territory	1	
New South Wales	1.20 (0.61–2.37)	0.59
Northern Territory	0.96 (0.24–3.80)	0.95
New Zealand	1.13 (0.49–2.63)	0.77
Queensland	1.35 (0.68–2.71)	0.40
South Australia	1.52 (0.73–3.18)	0.27
Tasmania	1.04 (0.21–5.09)	0.97
Victoria	1.42 (0.71–2.81)	0.32
Western Australia	1.64 (0.77–3.48)	0.20
Hospital type		
Rural/regional	1	
Metropolitan	1.23 (0.92–1.63)	0.16
Tertiary	1.85 (1.41–2.44)	< 0.001
Private	1.10 (0.85–1.43)	0.46
Frailty	1.87 (1.65–2.11)	< 0.001

ANZROD = Australian and New Zealand Risk Of Death.

Total number of patients, 15 606; area under receiver operating characteristic, 0.87 (95% CI, 0.86–0.88).

Supplementary Table 7.3. Mixed effects logistic regression analysis of hospital mortality, adjusted for all individual components of ANZROD (age, ventilation status, elective surgical status, chronic comorbid conditions, acute physiological disturbance, diagnosis, source of admission to intensive care unit (ICU)and to hospital, time in hospital prior to ICU admission, treatment limitation), sex, regional variation, and hospital type (with site as random effect)

Hospital mortality	Odds ratio (95% confidence interval)	*P*
Sex (men)	1.18 (1.04–1.35)	0.011
Age	1.03 (1.01–1.05)	< 0.001
Ventilated	1.59 (1.31–1.92)	< 0.001
Elective surgery	0.51 (0.38–0.68)	< 0.001
Chronic respiratory disease	1.26 (1.04–1.53)	0.017
Chronic cardiovascular disease	1.19 (1.01–1.40)	0.043
Chronic liver disease	1.30 (0.63–2.67)	0.48
Chronic renal disease	0.94 (0.73–1.20)	0.61
Immune disease	0.85 (0.52–1.39)	0.52
Immunosuppression	1.07 (0.78–1.47)	0.65
Lymphoma	1.40 (0.81–2.43)	0.23
Metastatic cancer	1.43 (1.04–1.95)	0.027
Leukaemia	1.76 (1.12–2.75)	0.014
Albumins core	1.07 (1.05–1.09)	< 0.001
Bilirubin score	1.05 (1.01–1.08)	0.006
Creatinine score	1.06 (1.03–1.08)	< 0.001
Glucose score	1.02 (0.98–1.05)	0.42
Hematocrit score	0.84 (0.79–0.90)	< 0.001
Heart rate score	1.04 (1.02–1.05)	< 0.001
Mean arterial pressure score	1.02 (1.01–1.04)	< 0.001
Sodium score	1.05 (0.98–1.13)	0.15
Neurological score	1.04 (1.03–1.04)	< 0.001
Oxygenation score	1.05 (1.03–1.06)	< 0.001
pH score	1.09 (1.06–1.11)	< 0.001
Respiratory rate score	1.02 (1.00–1.04)	0.015
Temperature score	1.03 (1.01–1.05)	< 0.001
Urea score	1.04 (1.01–1.06)	< 0.001
Urine output score	1.09 (1.07–1.10)	< 0.001
White cell count score	1.02 (0.99–1.06)	0.15
APACHE III diagnostic code		
100	1	
101	9.46 (2.23–40.1)	< 0.001
102	4.43 (1.06–18.6)	0.042
103	5.49 (0.95–31.5)	0.06
104	2.97 (0.72–12.3)	0.13
105	3.91 (0.42–36.4)	0.23
106	0.99 (0.23–4.36)	0.99
107	3.50 (0.80–15.3)	0.10
108	1.82 (0.22–14.7)	0.58
109	1.70 (0.39–7.33)	0.48
110	15.7 (1.54–160)	0.02
111	4.13 (0.31–54.6)	0.28

Hospital mortality	Odds ratio (95% confidence interval)	*P*
201	4.18 (0.98–17.9)	0.05
202	9.36 (1.41–61.9)	0.020
203	1.87 (0.30–11.8)	0.50
204	3.83 (0.84–17.4)	0.08
206	3.84 (0.93–15.9)	0.06
207	3.47 (0.74–16.4)	0.12
208	1.08 (0.14–8.17)	0.94
209	1.35 (0.11–15.8)	0.81
210	47.6 (2.51–903)	0.010
211	5.07 (1.22–21.0)	0.03
212	4.36 (1.07–17.8)	0.04
213	4.24 (0.97–18.6)	0.06
301	10.1 (1.63–62.5)	0.013
303	1.71 (0.10–28.3)	0.71
305	2.06 (0.47–9.11)	0.34
306	1.11 (0.21–5.78)	0.90
307	3.25 (0.67–15.9)	0.15
308	2.36 (0.42–13.3)	0.33
309	3.92 (0.84–18.2)	0.08
310	4.96 (0.71–34.6)	0.11
311	3.01 (0.60–15.1)	0.18
312	6.24 (0.51–75.7)	0.15
313	0.35 (0.04–2.83)	0.32
401	11.3 (2.46–52.3)	< 0.001
402	6.83 (1.23–38.0)	0.028
403	4.38 (1.02–18.9)	0.05
404	8.02 (1.03–62.6)	0.05
405	40.3 (3.56–455)	< 0.001
406	7.18 (0.98–52.57	0.05
407	1.44 (0.30–7.00)	0.65
408	1.63 (0.26–10.4)	0.61
409	8.09 (0.98–67.0)	0.05
410	1.95 (0.40–9.43)	0.41
501	2.44 (0.60–9.99)	0.21
502	1.51 (0.35–6.55)	0.59
503	2.81 (0.69–11.5)	0.15
504	1.00 (0.23–4.42)	1.00
601	5.86 (1.27–27.0)	0.023
602	3.54 (0.83–15.2)	0.09
603	1.71 (0.13–23.3)	0.69
604	1.46 (0.12–17.1)	0.77
605	6.37 (0.43–95.2)	0.18

Hospital mortality	Odds ratio (95% confidence interval)	*P*
701	0.73 (0.06–8.88)	0.80
702	1.36 (0.24–7.77)	0.73
703	1.39 (0.28–6.84)	0.69
704	1.22 (0.27–5.43)	0.79
801	2.87 (0.41–20.1)	0.29
802	1.80 (0.24–13.2)	0.57
901	1.34 (0.31–5.78)	0.70
1101	1.46 (0.21–9.98)	0.70
1102	1.18 (0.14–10.3)	0.88
1202	2.50 (0.47–13.5)	0.29
1203	1.00 (0.14–7.18)	1.00
1204	2.01 (0.35–11.6)	0.44
1205	0.58 (0.07–4.59)	0.60
1206	0.71 (0.13–3.69)	0.68
1207	0.76 (0.15–3.91)	0.74
1208	1.30 (0.27–6.29)	0.75
1209	5.96 (0.90–39.4)	0.06
1210	2.04 (0.31–13.4)	0.46
1212	0.90 (0.16–4.99)	0.90
1213	1.05 (0.15–7.25)	0.96
1301	2.57 (0.30–22.4)	0.39
1302	2.27 (0.43–12.1)	0.34
1304	1.75 (0.33–9.22)	0.51
1401	2.79 (0.59–13.3)	0.20
1403	1.94 (0.39–9.57)	0.42
1404	1.81 (0.39–8.38)	0.45
1405	1.63 (0.34–7.72)	0.54
1406	0.26 (0.04–1.62)	0.15
1408	1.01 (0.20–5.04)	0.99
1409	0.39 (0.03–5.86)	0.49
1410	4.31 (0.83–22.4)	0.08
1411	0.97 (0.04–25.5)	0.98
1412	2.00 (0.32–12.5)	0.46
1413	0.32 (0.02–4.85)	0.41
1501	10.02 (1.41–71.2)	0.021
1502	4.96 (0.94–26.2)	0.06
1503	4.71 (0.40–55.1)	0.22
1504	1.13 (0.20–6.33)	0.89
1505	2.02 (0.29–14.1)	0.48
1506	2.19 (0.38–12.4)	0.38
1601	16.00 (2.44–105)	0.004
1602	1.78 (0.37–8.60)	0.47

Hospital mortality	Odds ratio (95% confidence interval)	*P*
1604	5.75 (0.39–84.7)	0.20
1605	53.7 (2.97–972)	0.007
1701	1.46 (0.23–9.16)	0.69
1703	2.19 (0.40–11.9)	0.37
1705	1.02 (0.16–6.44)	0.99
1801	1.68 (0.14–20.8)	0.69
1803	1.37 (0.10–18.4)	0.81
1902	0.99 (0.21–4.61)	0.99
1903	0.51 (0.04–6.22)	0.60
1904	3.26 (0.58–18.4)	0.18
2201	1.09 (0.09–13.3)	0.95
Source of admission to ICU		
Operating theatre	1	
Emergency department	1.04 (0.44–2.49)	0.93
Ward	1.00 (0.42–2.38)	1.00
ICU within the same hospital	0.41 (0.06–2.57)	0.34
Another hospital	1.13 (0.47–2.67)	0.79
ICU within another hospital	1.25 (0.40–3.90)	0.70
Unknown	0.55 (0.14–2.11)	0.38
Source of admission to ICU		
Home	Reference	
Other acute hospital (not ICU/ED)	0.78 (0.59–1.02)	0.07
Nursing home / chronic or palliative care	0.82 (0.60–1.12)	0.22
Other hospital ICU	1.04 (0.49–2.17)	0.92
Rehabilitation	1.11 (0.64–1.92)	0.71
Other hospital ED	0.86 (0.67–1.09)	0.21
Hours in hospital prior to ICU admission		
< 12	1	
12–23.9	1.09 (0.88–1.35)	0.43
24–47.9	1.11 (0.88–1.40)	
48–71.9	1.25 (0.93–1.69)	0.15
≥ 72	1.74 (1.41–2.14)	< 0.001
Missing data	1.00	
Hospital type		
Rural/regional	1	
Metropolitan	1.16 (0.89–1.50)	0.27
Tertiary	1.64 (1.26–2.14)	< 0.001
Private	1.65 (1.27–2.13)	< 0.001
Jurisdiction		
Australian Capital Territory	1	
New South Wales	1.11 (0.57–2.16)	0.76

Hospital mortality	Odds ratio (95% confidence interval)	*P*
Northern Territory	1.25 (0.32–4.93)	0.75
New Zealand	1.14 (0.50–2.61)	0.76
Queensland	1.16 (0.59–2.29)	0.67
South Australia	1.26 (0.62–2.58)	0.52
Tasmania	0.76 (0.16–3.63)	0.73
Victoria	1.23 (0.63–2.41)	0.55
Western Australia	1.35 (0.65–2.82)	0.43
Treatment limitation present at ICU admission	2.44 (2.10–2.82)	< 0.001
Frailty	1.74 (1.52–2.00)	< 0.001

ANZROD = Australian and New Zealand Risk Of Death; ED = emergency department.

Total number of patients entered, 14 642; area under receiver operating characteristic, 0.88 (95% CI, 0.88–0.89).

Supplementary Table 7.4. Mixed effects logistic regression analysis of new discharge to chronic care/nursing home, adjusted for sex, overall predicted risk of death (ANZROD), regional variation and hospital type (with site as random effect); survivors only

New discharge to chronic care/nursing home	Odds ratio (95% confidence interval)	*P*
Sex (men)	0.72 (0.60–0.86)	< 0.001
ANZROD (per percentage point)	1.02 (1.01–1.02)	< 0.001
Jurisdiction		
New South Wales	2.64 (0.55–12.7)	0.23
Northern Territory	1	
New Zealand	2.25 (0.33–15.3)	0.41
Queensland	3.53 (0.71–17.4)	0.12
South Australia	5.49 (1.00–30.0)	0.05
Victoria	2.95 (0.60–14.5)	0.18
Western Australia	1.21 (0.20–7.28)	0.84
Hospital type		
Rural/regional	1	
Metropolitan	1.00 (0.54–1.86)	1.00
Tertiary	0.61 (0.32–1.16)	0.13
Private	0.47 (0.27–0.83)	0.01
Frailty	1.61 (1.34–1.95)	< 0.001

ANZROD = Australian and New Zealand Risk Of Death.

Total number of patients entered, 13 697; area under receiver operating characteristic, 0.82 (95% CI, 0.80–0.83).

Supplementary Table 7.5. Sensitivity analysis of mortality, by site completeness of frailty coding

Completeness of frailty coding	Frailty status Unknown	Frail	Not frail	Unadjusted odds ratio	Adjusted odds ratio*
Low levels (< 10%) (*N* = 64)					
Number of patients	14 913	122	151		
Mortality	13.0%	13.9%	4.6%	3.33 (1.33–8.32)	2.61 (0.92–7.42)
Medium levels (10–50%) (*N* = 55)					
Number of patients	10 473	2381	3317		
Mortality	13.5%	18.6%	9.2%	2.27 (1.94–2.66)	1.94 (1.59–2.36)
High levels (> 50%) (*N* = 59)					
Number of patients	4774	3700	5942		
Mortality	11.3%	17.0%	7.7%	2.45 (2.16–2.79)	1.75 (1.50–2.05)

* Mixed effects logistic regression adjusted for sex, region, hospital type, and severity of illness (ANZROD) on admission to the intensive care unit, with site as random effect.

Chapter 8. Exploratory development of a frailty index from routine hospital data in perioperative and critical care: a prospective cohort study

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Keywords: frailty, perioperative care, risk assessment

Funding: This work was supported by an emerging researcher scholarship from the Australian and New Zealand College of Anaesthetists

Declaration of interest: The authors declare no conflicts of interest.

8.1 Abstract

Background: Frailty is common in surgical and intensive care unit (ICU) populations, yet is not routinely measured. Frailty indices are able to quantify this across a range of health deficits. We aimed to develop a frailty index (FI) from routinely collected hospital data in a surgical and ICU population.

Design: Prospective, observational single centre cohort study

Setting: A tertiary referral metropolitan Australian hospital.

Participants: 336 patients aged ≥ 65 years undergoing surgery or aged ≥ 50 years admitted to ICU.

Measurement: Routine admission health data were used to derive an FI, comprising 36 health deficits. We examined the FI correlation with existing frailty tools (Clinical Frailty Scale and Edmonton Frail Scale) and assessed its predictive ability for negative outcomes including 30-day mortality.

Results: Median (inter-quartile range, IQR) FI was 0.17 (0.10 – 0.24) for ICU patients, and 0.17 (0.11 – 0.25) for surgical patients; maximum FI was 0.58, and 25% (95% CI [10.4 – 29.6]) of patients overall were diagnosed with frailty (FI score of ≥0.25). Correlation was strong between the FI and the Edmonton Frail scale (Spearman coefficient [95% CI] = 0.76, [0.70 – 0.83] for ICU patients; 0.71 [0.64 – 0.78] for surgical patients), and the Clinical Frailty Scale (0.77 [0.70 – 0.84] for ICU patients; 0.72 [0.65 – 0.79] for surgical patients). The FI had good discriminative ability for prediction of 30-day mortality in ICU patients (multivariate OR [95% CI] for each increase in FI of 0.1 = 2.04 [1.19 – 3.48]; comparable with the performance of the Acute Physiology and Chronic Health Evaluation (APACHE) III score (ICU patients), and

the Portsmouth-Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (P-POSSUM) score (surgical patients).

Conclusion: It is feasible to construct a FI from hospital admission data in a cohort of critically ill and surgical patients.

8.2 Introduction

Frailty is a state of vulnerability resulting from deficit accumulation in many domains of health.[6] In a range of acutely hospitalised populations, frailty predisposes to poor outcomes, in particular surgical and intensive care unit (ICU) patients. In surgical cohorts, frailty affects up to 40-50% of patients,[105] and is associated with increased mortality, length of stay, discharge to institutional care and post-operative complications.[43] Similar associations are seen in ICU cohorts, in which 30% of critically ill patients aged ≥ 65 years are considered frail.[42] In light of its importance to risk stratification and outcome prediction in these groups, measurement of frailty is a major priority. Unfortunately, considerable challenges exist in frailty determination in ICU and surgical patients. This includes barriers to interview (eg. coma, sedation, mechanical ventilation), difficulties in performing functional testing, and confounding of the patient's baseline state of function by acute illness.[92] Prospective collection of data to measure patient frailty also requires considerable resources and time from trained personnel. This ranges from as little as one minute for the Clinical Frailty Scale[46] (although this tool merely "case finds" for frailty without providing considerable granularity) up to two hours for a proper comprehensive geriatric assessment upon which the 70-item original frailty index (FI) is based.[7]

In recent years, promising developments have been made in using the large amount of data collected during acute hospitalization to derive a "frailty index" (FI), or automatic measure of patient frailty. Such indices are one of the most comprehensive ways of measuring patient frailty, and are calculated by summing the number of positive health deficits divided by the total number of possible health deficits.[9] Surgery and intensive care, in particular, are

especially “data-rich” areas of acute healthcare in which much information relevant to frailty index construction is collected regarding the health status of patients.[136] A plethora of scales derived from hospital coding data purporting to measure frailty have hence emerged, unfortunately with questionable degrees of utility. The modified frailty index (mFI) derived from the National Surgical Quality Improvement Program, for example, only measures 11 variables (of which nine are comorbidities)[20], and the Johns Hopkins Adjusted Clinical Groups Indicator, perhaps the most widely available population health analysis tool, provides only a dichotomous frailty measure without the granularity required to adequately conceptualize risk to an individual patient.[137] Expert guidelines exists in constructing an FI- at least 30 deficits should be included, which increase in prevalence with age (but do not saturate too early in life), are associated with health status, and cover a range of health systems.[9] If appropriately constructed, small variations in specific health deficit variables collected for a particular FI are not important, and the index value will demonstrate reproducibility and comparability across different populations. There is, however, limited work to date in comparing properly constructed FIs against other frailty assessment tools.

Our aim, therefore, was to develop an FI of accumulated health deficits, based on hospital data that is routinely collected in our institution for surgical and ICU patients. We aimed to examine how this index compares to existing frailty and risk measurement scales and to assess the predictive ability of the FI for patient-centred outcomes, including in-hospital mortality and institutional discharge.

8.3 Methods

We conducted a prospective, observational cohort study in the Departments of Intensive Care and Anaesthesia and Pain Management of the Royal Melbourne Hospital; the protocol for this program of frailty research has been published previously.[107] The methodology of data collection has also been previously reported.[106] The Human Research and Ethics Committee of Melbourne Health approved this program of research (20/01/2017, HREC/16/MH/321). Between February and June, 2017, patients aged ≥ 50 years (when admitted to ICU), or aged ≥ 65 years (admitted for surgery), were enrolled following patient or surrogate written informed consent (the latter if there was patient incapacity). Based on study investigator availability, a convenience sample of non-consecutively admitted patients were enrolled. Patients were able to be enrolled both pre- and post-operatively, or at any stage during their ICU stay, thus the time of ICU admission or operation did not influence eligibility for inclusion in the study. Routine data recorded on admission to our health service were used in the derivation of an FI, comprising 36 health deficits (Supplementary Table 8.1). These health deficits were compiled from the malnutrition risk assessment and management plan, daily nursing care plan, falls risk assessment and management plan, pressure injury prevention plan, and nursing admission and assessment form. An FI for each patient was then calculated by summing all positive deficit scores divided by the total number of non-missing possible deficit scores, thus deriving a score ranging from 0 (no deficits) to 1 (all deficits).[97] Patients with an FI score of ≥0.25 were considered frail, consistent with accepted definitions.[62] The Clinical Frailty Scale (CFS) and Edmonton Frail Scale were also measured by one of the study investigators, based on the period of time two weeks prior to the onset of acute illness or hospitalisation.[62] A Reported Edmonton Frail Scale was measured for those patients who were not able to undergo a timed-up-and-go

test.[16] Patients' next-of-kin were used for history taking in the event of sedation, mechanical ventilation, or delirium. Frailty scores were not shared with the clinical team.

Our primary aim was to develop an FI from routinely collected data within an Australian health service by comparing against existing frailty tools for both screening (the CFS) and measurement (the Edmonton Frail Scale). Secondary aims were to investigate the predictive ability of the FI for adverse outcomes, including mortality within 30 days which was compared to reference mortality risk-prediction tools: the Acute Physiology and Chronic Health Evaluation (APACHE) III score (ICU patients), and the Portsmouth-Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (P-POSSUM) score (surgical patients).[93] Secondary outcomes were discharge to a non-home location, peri-operative complications (cardiac arrest, acute myocardial infarction, tracheal reintubation, acute pulmonary oedema, pulmonary embolus, deep venous thrombosis, stroke, acute kidney injury, wound infection, unplanned admission to the ICU, unplanned need for re-operation) and ICU complications (acute kidney injury, cardiac arrest, sepsis, new treatment limitation); (definitions in Supplementary Table 8.2).

8.3.1 Statistical analysis

Data were summarized using mean (standard deviation [SD]), median [25^{th} – 75^{th} percentile (IQR)] for continuous data, and frequencies (percentages) for categorical data. Patients were considered frail if FI ≥ 0.25, CFS ≥ 5, or Edmonton Frail Scale ≥ 8.[15,62] Comparisons between frail and non-frail groups were conducted with two-sample t-tests, Fisher's exact or Chi-square tests, and Wilcoxon rank-sum tests as indicated. FI values were further

categorized by age deciles, from ≥ 50 years (ICU) and ≥ 65 years (surgery). Univariable and multivariable regression models were fitted to listed outcomes, the latter adjusting for age, sex, Charlson comorbidity index and admission source for ICU patients, and additionally adjusted for emergency or elective surgery for surgical patients. Binary outcomes with ≥ patient were analysed using Firth logistic regression to obtain the estimated odds ratio (OR) and 95% confidence interval (CI).[109] Correlation was measured using Spearman correlation coefficient between the continuous FI, Edmonton and CFS scales. Firth logistic regression models were used to compare the FI as a mortality predictor with the APACHE 3 score (ICU) and P-POSSUM score (surgery), obtaining the area under the receiver operating characteristic curve (AUCROC, 95% CI), which was categorized using standard guidelines (Hosmer, Lemeshow, and Sturdivant).[111] Hospital length of stay (days) between patients with and without frailty was analysed via estimated median difference (95% CI) using bootstrapped quantile regression with 5000 replications. Discharge location was analysed via estimated relative risk ratios (95% CI) using multinomial logistic regression. All enrolled patients were included in analyses, without adjustment for multiple testing. STATA 15.0 (College Station, TX, USA) was used for statistical analyses.

8.3.2 Sample size

We planned a convenience sample of 200 surgical and 150 ICU patients, based on a predicted combined frailty prevalence of 24% and mortality rate of 10%. These predictions were in turn based on the largest systematic review and meta-analysis of over 8000 surgical patients demonstrating a frailty prevalence of 20%, and pooled mortality rate of 5%[98]; and a multicentre study of frailty in critical care showing a frailty prevalence of 30%, and mortality rate of 21%.[10] We calculated that the 95% CI would be ±4.4% around a prevalence of frailty

of 24%, with a sample size of 350. Additionally, we predicted a surgical mortality of 5% (based on the above meta-analysis pooled mortality rate) and 21% in ICU patients; combined approximately 10%. Based on combined ORs in two prior systematic reviews[45,98], we assumed the odds of in-hospital mortality for patients with frailty would be 3.5 times greater, and overall in-hospital mortality would be 6.8% in patients without frailty. With a sample size of 350 patients, the power to detect this effect was 87% (two-sided 5% alpha). A sample size of 200 surgical patients and 150 ICU patients was also calculated to provide a power of at least 80% (two-sided alpha of 5%) for the Spearman coefficient between the FI with existing frailty tools (CFS and EFS) to be at least 0.70, assuming a correlation of 0.80 (strong).

8.4 Results

Three-hundred and thirty six patients were enrolled during the study period, 218 surgical patients, 160 patients admitted to ICU, with 42 patients undergoing both surgery and an ICU admission (Flowchart). An FI was measured for all patients; median (IQR) FI was 0.17 (0.10 – 0.24) for ICU patients, and 0.17 (0.11 – 0.25) for surgical patients, with maximum FI = 0.58 in both cohorts (Figure 1). Baseline demographics by frailty status are presented in Table 8.1 (combined cohort demographics in Supplementary Tables 8.3 and 8.4). Eighty-four patients (25%, 95% CI [20.4 – 29.6]) in total were diagnosed with frailty via the FI, 40 of 160 (25.0%, [18.3 – 31.7]) ICU-admitted patients and 55 of 218 (25.2%, [19.5 – 31.0]) surgical patients, with an increase in frailty seen with advancing age (4% of patients aged 50 – 59 years diagnosed with frailty compared with 34% of those aged > 80 years) (Supplementary Table 8.5). The prevalence of individual FI health deficits are presented in Table 8.2, which were

broadly comparable across ICU and surgical populations. The most common health deficits were falls (44% and 48% of ICU and surgical patients respectively), polypharmacy (73% and 64%), visual impairment (43% and 51%) and hearing impairment (36% and 38% of patients). Compared to patients without frailty, those with frailty were older, less likely to be admitted from home, less independent with activities of daily living, had higher Charlson comorbidity, APACHE 3 and P-POSSUM scores (Table 8.1).

8.4.1 Comparison between frailty index and other scales

Correlation was strong between the FI and the Edmonton Frail scale for ICU patients (Spearman coefficient [95% CI] = 0.76 , [0.70 – 0.83]) and between the FI and the CFS (0.77 [0.70 – 0.84]). Similar results were seen in the surgical cohort (Spearman correlation coefficient between the FI and Edmonton scale = 0.71 [0.64 – 0.78]; between the FI and CFS = 0.72 [0.65 – 0.79]).

8.4.2 Outcomes

Mortality at 30 days was greater for ICU patients with frailty (11/40 [28%] vs. 12/120 [10%] without frailty, adjusted p = 0.009), compared to surgical patients (3/55 [5%] with frailty vs. 5/163 [3%] without frailty, adjusted p = 0.056). Patients with frailty were more likely to be discharged to an assisted living facility or rehabilitation vs. home discharge, although on multivariable analysis this association was less evident for ICU patients (Tables 8.3 and 8.4). On multivariable analysis, the FI had good discriminative ability for prediction of hospital mortality in ICU patients (AUC-ROC [95% CI] = 0.75 [0.64 – 0.85], OR [95% CI] for each increase in FI of 0.1 = 2.04 [1.19 – 3.48]), comparable with the performance of the APACHE-III illness severity score (AUC-ROC = 0.80 [0.72 – 0.88]). For surgical patients, the

discriminative ability of the FI for prediction of hospital mortality was comparable with the P-POSSUM score (AUC-ROC = 0.76 [0.61 – 0.91] vs. 0.81 [0.71 – 0.92], OR [95% CI] for each increase in FI of 0.1 = 1.90 [0.98 – 3.66]).

Among ICU complications, only new institution of treatment limitations was significantly associated with the frailty index (20/40 [50%] patients with frailty vs. 29/120 [24.2%] patients without frailty); this association persisted on multivariable analysis (OR [95% CI] = 1.82 [1.14 – 2.88], adjusted p = 0.011). For surgical patients, both unplanned return to the operating theatre (7/55 [12.7%] patients with frailty vs. 11/163 [6.7%] patients without frailty, OR = 1.76 [1.08 – 2.86], p = 0.024) and unplanned admission to the ICU (8/55 [14.5%] patients with frailty vs. 17/163 [10.4%] patients without frailty, OR = 1.56 [1.00 – 2.43], adjusted p = 0.051) were more common in patients with frailty (Tables 8.3 and 8.4).

8.5 Discussion

8.5.1 Main findings

In a prospective cohort study, we found that a frailty index was able to be derived from routine hospital admission data in a cohort of ICU and surgical patients, which correlated strongly with existing frailty screening and measurement tools. Although not designed for this purpose, the FI also had good discriminative ability for the prediction of mortality, comparable with existing risk stratification tools used in surgical and critically ill cohorts. Patients with frailty had worse outcomes both post-operatively and with critical illness, including increased mortality and discharge to institutional care.

8.5.2 Relationship to prior literature

Other settings, including primary care, have seen important progress in the development of automated FI derivation. The "Electronic Frailty Index" (or "eFI") has been developed for application in the general practice setting in the UK National Health Service, to identify patients aged ≥ 65 years living in the community with frailty. Encompassing 36 deficits, this index comprises 20 disease states, seven "disabilities" (eg. visual/hearing impairment, social vulnerability, activity limitation), eight "symptoms and signs" (eg. polypharmacy, falls, weight loss) and one laboratory variable (anaemia). As such, it forms a comprehensive multi-dimensional assessment. This tool has demonstrated good predictive validity for mortality, hospitalization and nursing home admission.[23] Further work in 353 community-dwelling adults has also demonstrated the validity of this primary-health setting tool when compared with existing tools, the research-standard FI (Spearman correlation coefficient [ρ] = 0.68, 95% CI 0.62 – 0.74), the Edmonton Frail Scale (ρ = 0.63, 95% CI 0.57 – 0.69), and the CFS (ρ = 0.59, 95% CI 0.49 – 0.65).[24] A recent Australian study also managed to derive an eFI from routinely collected Australian primary care data.[25] Our study extends the findings of these primary-care setting measures to acutely hospitalized patients, with our correlation coefficients comparing the FI, CFS and Edmonton Frail Scale all exceeding > 0.70, thus indicating even stronger correlation than that observed in the general practice setting.

More recently, McIsaac et al have developed a Canadian surgical-specific FI based on administrative health data, derived in over 400,000 patients and validated in a further 95,000.[112] This "perioperative frailty index", or pFI, encompasses 30-items, and was shown to be associated with post-operative mortality and institutional discharge. Consistent with

modelling of “ceiling” frailty indices, a maximum FI of 0.66 was observed (similar to the 0.58 maximum demonstrated in our cohort). This study demonstrates the potential of automated data collection in the calculation of frailty indices in a surgical cohort, and extends our findings to a major dataset based on administrative records. Other investigators have also developed institution-specific FIs, including Shahrokni et al in New York (15 variables, hospital coding data) and Orouji Jokar et al in Arizona (15 variables, collected by trained researchers).[138,139] These also demonstrate the feasibility of FI application in surgery, although with fewer variables potentially risking over-simplification of the construct of frailty, and being too weighted (eg. towards comorbid disease). A different (non-surgical specific) approach to FI contruction is the “claims-based” FI of Kim et al.[140] Using administrative Medicare data, this approach considers both the variable prevalence and correlation with age. Their FI was found to be predictive of mortality, disability and health care utilization. Our study is novel in that the scope and granularity of data collected is part of the routine admission process, thus implementation is not reliant on additional researcher time in collection, nor subject to problems with administrative data, such as variable removal from datasets over time, as has challenged the mFI. A recent study of 18000 surgical patients demonstrated data for 5 of 11 variables were missing in 55% of patients in 2011, increasing to 100% missing in 2013 coinciding with removal of mandatory NSQIP variable reporting in 2012.[141] Our study applying an FI to the measurement of frailty in ICU patients is, we believe, novel.

Limited prior work has compared frailty scales. A 2018 Canadian study comparing the Fried phenotype and Clinical Frailty Scale in 702 surgical patients demonstrated only moderate

agreement (kappa = 0.51) between these scales.[46] A 2017 epidemiological study examined agreement between 35 different frailty scales, based on mapping variables collected in the English Longitudinal Study of Ageing (ELSA) registry to existing frailty scales.[102] This study cautioned that agreement between scales varied widely, with misclassification common, however multi-dimensional deficit model scales had the best agreement. Although such agreement is separate from any conclusions about the validity of frailty measures examined, it likely explains the high levels of agreement found in our study, with all scales based on the multi-dimensional, deficit accumulation paradigm of frailty. Although various constructs of frailty exist, and it is important that the choice of frailty instrument measures the underlying construct it represents,[142] our findings thus lend weight to the concept that frailty indices, the CFS and the EFS belong to the similar deficit-model construct of frailty. Taken together, these results suggest that multi-dimensional frailty scales are promising and comparable measures when used both in patient care and in advancing the research agenda.

A major finding of our study was of comparable mortality prediction with the FI in both ICU and surgical cohorts when compared to reference scales, APACHE III and P-POSSUM. This was surprising, particularly when considering that unlike these latter tools, which include a considerable number of variables relating to acute illness, patient age, surgical magnitude and physiological derangement, the FI contains solely information relating to chronic health deficits. The FI is also not conceptualized nor designed as a mortality risk-scoring system. This is hypothesis generating, and suggests that detrimental outcomes in these cohorts may be more a function of chronic underlying health status than of severity of acute pathology. A similar epidemiological phenomenon has been observed in long-staying critically ill

populations, with the recognition of a state of "persisting critical illness" developing after 10 days in ICU, with the ultimate determination of death in this cohort more a function of pre-ICU characteristics than illness severity after this time point.[143] We have previously examined reasons for this, finding in-ICU complications in this cohort develop more commonly, including delirium, new sepsis and ICU acquired weakness.[121] Similarly, it is likely that frailty imparts a vulnerability to critical illness and surgical stress than may outweigh the impact of acute illness in outcome determination. Future research should seek to further understand the complex interplay between acute illness severity, chronic health status, and ultimate outcome in patients with frailty, and integrate frailty in these risk prediction models. It is likely that the addition of frailty to the risk-scores used in this study would lead to even better predictive ability for mortality.

8.5.3 Strengths and Limitations

Strengths of our study include the wide range of patients enrolled, with both critically ill cohorts and emergency and elective surgical patients included from a major metropolitan referral health service. Our results are likely generalisable to other similar healthcare settings. The construction of our FI, furthermore, conformed to accepted guidelines for inclusion of candidate health deficits, which numbered over 30.[9] Limitations included the single centre design, as well as overlap of 42 patients between cohorts, although overall findings were similar between groups. We did not quantify the time taken to collect data from our currently paper-based medical records (although this will be reduced in hospitals utilizing electronic medical records), nor did we quantify missing data rates as any missing variables were completed by the study investigators directly. Although this improved overall FI quality, further work will be required to quantify feasibility in the presence of missing

data. Patient data collected on admission also vary between health services; it is thus likely that an exact replica FI is not able to be reproduced in alternative hospital settings. The attraction of properly constructed frailty indices, however, is that results are generalisable between populations without exact deficits needing to be reproduced.[9] The variables chosen were also deliberately simple and selected to be relevant to most surgical and ICU admissions in other health services in developed-world settings, thus more likely to be collected routinely as part of nursing, allied health or other admission processes. As the nature of these health deficits measured on admission to hospital are likely very similar (including data relating to comorbidities, malnutrition, pressure injuries, falls risk, and cognitive status, among others), comparable FIs should be able to be constructed across health services in our region. Further work is required to assess the external validity of such FI application from routine health data in other hospitals, ideally validating this approach in a multi-centre study using electronic health records to include much larger datasets. We also enrolled a convenience sample; although patients were eligible to be enrolled at any point during their ICU stay or either before or after surgery, it is however possible that our study cohort was less representative of the overall population. Given that primary analyses compared the FI with CFS and Edmonton scale in the same patients, however, this is unlikely to have materially affected our results.

8.6 Conclusion

In conclusion, it is feasible to construct a FI in a cohort of critically ill and surgical patients based on admission data in a metropolitan Australian hospital. The FI correlates well with accepted screening and measurement tools, and is predictive for negative outcomes including mortality and institutional discharge. This study provides the necessary background work prior to widespread development and implementation of frailty indices in routine peri-operative and ICU care.

Figure 8.1: Study flow diagram

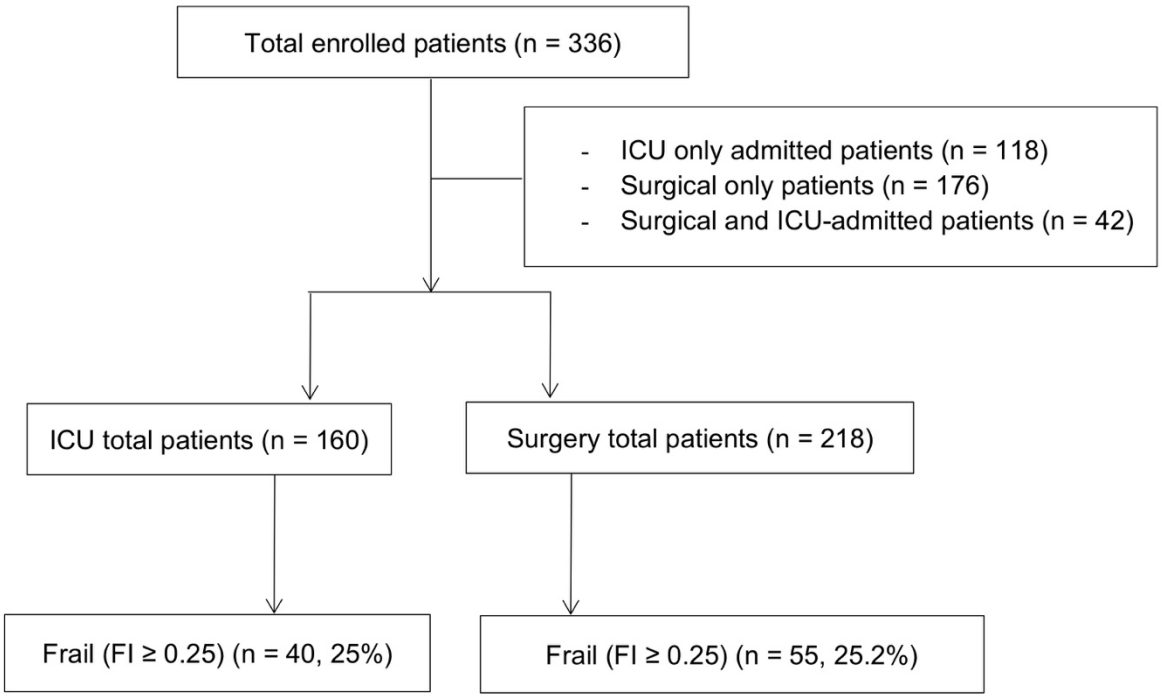

Figure 8.2: Frailty index distribution

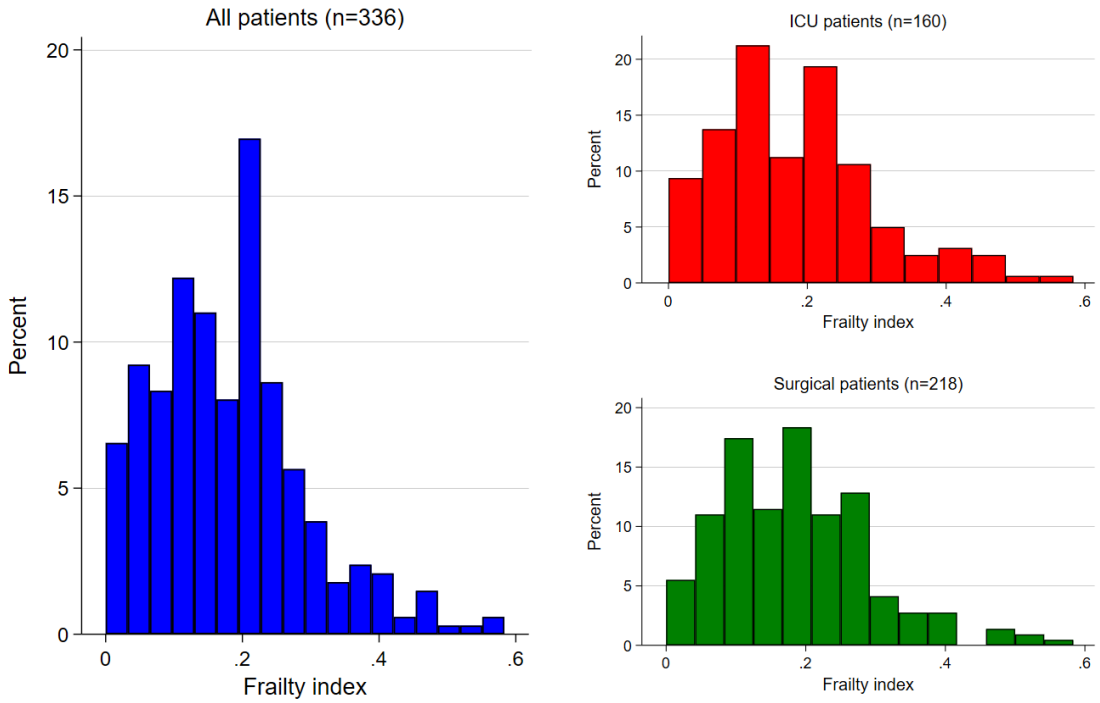

Table 8.1. Baseline demographics according to Frailty Index frailty status.

Variable	ICU patients (N = 160)			Surgical patients (N = 218)		
	Frail N = 40	Not Frail N = 120	*P* value	Frail N = 55	Not Frail N = 163	*P* value
Frailty index	0.31 (0.26 – 0.39)	0.14 (0.08 – 0.19)	< 0.001	0.28 (0.25 – 0.36)	0.14 (0.08 – 0.19)	< 0.001
Age (years)	75 (69 – 80)	69 (61 – 77)	0.004	77 (69 – 83)	73 (68 – 79)	0.036
BMI (kg/m^2)	28 (24 – 32)	30 (26 – 33)	0.10	26 (24 – 31)	28 (24 – 32)	0.15
Female	22 (55.0%)	48 (40.0%)	0.10	24 (43.6%)	75 (46.0%)	0.76
Admission Source						
Home	31 (77.5%)	114 (95.0%)	0.003	43 (78.2%)	152 (93.3%)	< 0.001
Acute hospital	6 (15.0%)	5 (4.2%)		2 (3.6%)	10 (6.1%)	
Residential care	3 (7.5%)	1 (0.8%)		10 (18.2%)	1 (0.6%)	
Admission type						
Medical	29 (72.5%)	71 (59.2%)	0.13			
Surgical	11 (27.5%)	49 (40.8%)				
Surgical type						
Elective				28 (50.9%)	90 (55.2%)	0.58
Emergency				27 (49.1%)	73 (44.8%)	
Charlson Comorbidity Score	4 (2 – 5)	2 (0 – 3)	< 0.001	4 (2 – 6)	2 (1 – 3)	<0.001
ADL Function (Katz)						
Dependent	8 (20.0%)	0 (0.0%)	< 0.001	7 (12.7%)	1 (0.6%)	<0.001
Partially	7 (17.5%)	2 (1.7%)		13 (23.6%)	10 (6.1%)	
Dependent	25 (62.5%)	118 (98.3%)		35 (63.6%)	152 (93.3%)	
Independent						
APACHE 3 score	80 (70 - 90)	62 (49 - 82)	<0.001			
P-POSSUM mortality risk (%)				7% (3% – 17%)	4% (3% – 9%)	0.015

Values are expressed as the mean (SD), median (interquartile range), or n (%).

ADL = activities of daily living (Katz number: Dependent = 0 – 2, Partially Dependent = 3 – 4, Independent = 5 – 6). BMI = body mass index. APACHE = Acute Physiology and Chronic Health Evaluation. P-POSSUM = Portsmouth-Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity=

Table 8.2: Frailty index individual variable prevalence.

	ICU patients	Surgical patients	All patients
	(N=160)	**(N=218)**	**(N=336)**
Falls in last 12 months, n (%)	71 (44.4%)	105 (48.2%)	154 (45.8%)
Dementia diagnosis, n (%)	7 (4.4%)	6 (2.8%)	12 (3.6%)
Altered cognition, n (%)	25 (15.6%)	25 (11.5%)	45 (13.4%)
On ≥ 4 medications, ≥ 1 affecting CNS/CVS, n (%)	116 (72.5%)	140 (64.2%)	224 (66.7%)
Vision impairment, n (%)	68 (42.5%)	111 (50.9%)	161 (47.9%)
Hear impairment, n (%)	57 (35.6%)	82 (37.6%)	125 (37.2%)
Assistance with transferring, n (%)	11 (6.9%)	19 (8.7%)	28 (8.3%)
Assistance with mobilising, n (%)	53 (33.1%)	69 (31.7%)	105 (31.3%)
Assistance with toileting, n (%)	8 (5.0%)	20 (9.2%)	27 (8.0%)
Assistance with bathing, n (%)	15 (9.4%)	32 (14.7%)	45 (13.4%)
Assistance with dressing, n (%)	18 (11.3%)	23 (10.6%)	36 (10.7%)
Postural hypotension/dizziness, n (%)	46 (28.7%)	89 (40.8%)	118 (35.1%)
Bowel incontinence, n (%)	17 (10.6%)	21 (9.6%)	35 (10.4%)
Urinary incontinence, n (%)	39 (24.4%)	58 (26.6%)	85 (25.3%)
Eating poorly, n (%)	55 (34.4%)	52 (23.9%)	94 (28.0%)
Lost weight without trying*, n(%)	54 (33.8%)	57 (26.1%)	99 (29.5%)
Pressure injury - current or past, n (%)	5 (3.1%)	9 (4.1%)	13 (3.9%)
Neuropathic foot disease, n (%)	31 (19.4%)	20 (9.2%)	43 (12.8%)
Problems managing at home prior to admission, n (%)	34 (21.3%)	47 (21.6%)	69 (20.5%)
Often feels sad or depressed, n (%)	57 (35.6%)	40 (18.3%)	82 (24.4%)
Needs assistance with eating, n (%)	7 (4.4%)	8 (3.7%)	14 (4.2%)
Myocardial infarction, n (%)	34 (21.3%)	39 (17.9%)	62 (18.5%)
Congestive heart failure, n (%)	26 (16.3%)	25 (11.5%)	43 (12.8%)
Peripheral vascular disease, n (%)	19 (11.9%)	31 (14.2%)	45 (13.4%)
Cerebrovascular disease, n (%)	27 (16.9%)	38 (17.4%)	58 (17.3%)
Hemiplegia, n (%)	1 (0.6%)	3 (1.4%)	3 (0.9%)
Chronic lung disease, n (%)	29 (18.1%)	40 (18.3%)	63 (18.8%)
Connective tissue disease, n (%)	12 (7.5%)	15 (6.9%)	23 (6.8%)
Peptic ulcer disease, n (%)	9 (5.6%)	29 (13.3%)	35 (10.4%)
Chronic liver disease, n (%)	2 (1.3%)	3 (1.4%)	5 (1.5%)
Diabetes, n (%)	43 (26.9%)	52 (23.9%)	84 (25.0%)
Leukaemia/lymphoma, n (%)	12 (7.5%)	5 (2.3%)	17 (5.1%)
Malignant tumour, n (%)	19 (11.9%)	63 (28.9%)	73 (21.7%)
Metastatic cancer, n (%)	9 (5.6%)	17 (7.8%)	25 (7.4%)
Moderate/severe kidney disease, n (%)	16 (10.0%)	24 (11.0%)	35 (10.4%)
Moderate/ severe liver disease, n (%)	2 (1.3%)	2 (0.9%)	4 (1.2%)
Total score, median (IQR)	0.2 (0.1-0.2)	0.2 (0.1-0.3)	0.2 (0.1-0.2)
Frail, n (%)	**40 (25.0%)**	**55 (25.2%)**	**84 (25.0%)**

Table 8.3. Main outcomes according to frailty status

Variable	ICU patients (N = 160)		Surgical patients (N = 218)		All patients (N = 336)	
	Frail N = 40	Not Frail N = 120	Frail N = 55	Not Frail N = 163	Frail N = 84	Not Frail N = 252
Mortality within 30 days	11 (27.5%)	12 (10.0%)	3 (5.5%)	5 (3.1%)	14 (56.0%)	17 (35.4%)
Mortality (six-month follow up)	13 (34.2%)	26 (22.0%)	12 (22.2%)	22 (13.8%)	25 (30.9%)	47 (19.0%)
Hospital length of stay (days)	14.0 (8.8-19.2)	11.8 (7.8-22.9)	8.0 (1.0-14.0)	4.0 (1.0-9.8)	8.8 (3.0-15.9)	7.0 (2.0-14.1)
Discharge location						
Home	13 (32.5%)	64 (53.3%)	25 (45.5%)	122 (74.8%)	34 (40.5%)	169 (67.1%)
Assisted living facility/rehabilitation	14 (35%)	27 (22.5%)	22 (40%)	24 (14.7%)	30 (35.7%)	42 (16.7%)
Other acute hospital	2 (5.0%)	17 (14.2%)	5 (9.1%)	13 (8.0%)	6 (7.1%)	25 (9.9%)
Died in hospital	11 (27.5%)	12 (10.0%)	3 (5.5%)	4 (2.5%)	14 (16.7%)	16 (6.3%)
Acute myocardial infarction			1 (1.8%)	3 (1.8%)		
Re-intubation			3 (5.5%)	3 (1.8%)		
Acute pulmonary oedema			5 (9.1%)	12 (7.4%)		
Wound infection			7 (12.7%)	11 (6.7%)		
Acute kidney injury	3 (7.5%)	9 (7.5%)	8 (14.5%)	20 (12.3%)	11 (61.1%)	25 (56.8%)
Unplanned return to operating theatre			7 (12.7%)	11 (6.7%)		
Unplanned admission to ICU			8 (14.5%)	17 (10.4%)		
New sepsis	10 (25.0%)	47 (39.2%)				
Critical illness weakness	1 (2.5%)	5 (4.2%)				
New limitation of medical treatment	20 (50.0%)	29 (24.2%)				

Table 8.4. Logistic regression models for outcomes and complications with frailty..

Variable	Univariate regression model		Multivariate regression model	
ICU patients (N = 160)	**Estimate (95% CI)**	**P value**	**Estimate (95% CI)**	**P value**
Mortality within 30 days	1.64 (1.15 - 2.35)	0.006	2.04 (1.19 - 3.48)	0.009
Mortality at six-month follow up	1.44 (1.06 - 1.96)	0.021	1.57 (0.99 - 2.48)	0.054
New sepsis	0.82 (0.61 - 1.11)	0.198	1.00 (0.66 - 1.51)	0.987
Acute kidney injury	1.20 (0.74 - 1.92)	0.459	1.14 (0.57 - 2.28)	0.702
Critical illness weakness	1.23 (0.65 - 2.33)	0.529	1.27 (0.50 - 3.24)	0.614
New limitation of medical treatment	1.88 (1.36 - 2.60)	<0.001	1.82 (1.14 - 2.88)	0.011
Hospital length of stay (days)	2.31 (-2.84 - 7.46)	0.377	2.00 (-3.52 - 7.53)	0.474
Discharge location				
Home	Ref.	0.007	Ref.	0.151
Assisted living facility/rehabilitation	2.55 (1.06 - 6.15)		1.43 (0.49 - 4.24)	
Other acute hospital	0.58 (0.12 - 2.82)		0.67 (0.12 - 3.93)	
Died in hospital	4.51 (1.64 - 12.42)		3.58 (1.06 - 12.08)	
Surgical patients (N = 218)	**Estimate (95% CI)**	**P value**	**Estimate (95% CI)**	**P value**
Mortality within 30 days	1.57 (0.91 - 2.71)	0.102	1.90 (0.98 - 3.66)	0.056
Mortality at six-month follow up	1.58 (1.14 - 2.19)	0.006	1.32 (0.88 - 1.99)	0.176
Acute myocardial infarction	1.15 (0.48 - 2.75)	0.749	0.73 (0.18 - 2.95)	0.663
Re-intubation	2.00 (1.12 - 3.57)	0.018	2.10 (0.96 - 4.61)	0.064
Acute pulmonary oedema	0.92 (0.57 - 1.49)	0.727	0.88 (0.48 - 1.60)	0.665
Wound infection	1.42 (0.95 - 2.12)	0.089	1.43 (0.89 - 2.32)	0.143
Acute kidney injury	1.11 (0.77 - 1.59)	0.583	1.19 (0.77 - 1.84)	0.433
Unplanned return to operating theatre	1.57 (1.06 - 2.33)	0.025	1.76 (1.08 - 2.86)	0.024
Unplanned admission to ICU	1.31 (0.91 - 1.88)	0.142	1.56 (1.00 - 2.43)	0.051
Hospital length of stay (days)	4.00 (1.49 - 6.51)	0.002	2.33 (-0.07 - 4.73)	0.057
Discharge location				
Home	Ref.	0.0005	Ref.	0.005
Assisted living facility/rehabilitation	4.47 (2.18 - 9.20)		4.97 (1.99 - 12.43)	
Other acute hospital	1.88 (0.61 - 5.74)		2.44 (0.69 - 8.68)	
Died in hospital	3.66 (0.77 - 17.37)		5.22 (0.93 - 29.30)	

Multivariable regression models are adjusted for age, sex, admission source and Charlson comorbidity score for ICU patients and additionally adjusted for emergency/elective surgery for surgical patients.

Estimates are odds ratios (95% confidence intervals), with the exception of the estimates for hospital length of stay (median difference (95% confidence interval) and the estimates for discharge location (relative risk ratios (95% confidence intervals)).

Estimates and 95% confidence intervals correspond to a 0.1 unit change in Frailty Index.

The outcomes cardiac arrest, deep venous thrombosis, pulmonary embolus, stroke and cardiac arrest were not analysed due to numbers of patients < 5.

Supplementary Table 8.1. List of individual health deficits comprising the Frailty Index

1	Falls in last 12 months
2	Dementia diagnosis
3	Altered cognition
4	On four or more medications, at least one affecting CNS/CVS
5	Vision impairment
6	Hearing impairment
7	Assistance with transferring
8	Assistance with mobilising
9	Assistance with toileting
10	Assistance with bathing
11	Assistance with dressing
12	Postural hypotension/dizziness
13	Bowel incontinence
14	Urinary incontinence
15	Eating poorly?
16	Lost weight without trying?
17	Pressure injury- current or past
18	Neuropathic foot disease
19	Problems managing at home prior to admission
20	Often feels sad or depressed?
21	Requires assistance with eating?
22	Ischaemic heart disease
23	Congestive heart failure
24	Peripheral vascular disease
25	Cerebrovascular disease
26	Hemiplegia
27	Chronic lung disease
28	Connective tissue disease
29	Peptic ulcer disease
30	Chronic liver disease
31	Diabetes
32	Leukaemia/lymphoma
33	Malignant tumour
34	Metastatic cancer
35	Moderate/severe kidney disease
36	Moderate/severe liver disease

Supplementary Table 8.2. Definitions for complications

Acute myocardial infarction	Increase in cardiac troponin with ECG changes (ST-T segment changes, new bundle-branch block, Q waves)
Acute pulmonary oedema	Increase in oxygen requirements with chest xray changes consistent with radiological acute pulmonary oedema (upper lobe pulmonary venous diversion, peri-bronchial cuffing, septal lines, air space opacification, pleural effusions).
Deep venous thrombosis, pulmonary embolus	Radiological confirmation (lower limb ultrasound/computed tomography pulmonary artery scan)
Stroke	Computed tomography or magnetic resonance imaging evidence of acute ischaemic/haemorrhagic stroke
Wound infection	Defined according to the Centers for Disease Control and Prevention National Healthcare Safety Network (*Berríos-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surg. 2017;152(8):784–791.):* Superficial incisional infection: Infection occurs within 30 days after an operative procedure *and* involves only skin and subcutaneous tissue of the incision *and* patient has at least one of the following: a) Purulent drainage from the superficial incision. b) Organisms isolated from an aseptically-obtained culture of fluid or tissue from the superficial incision. c) Superficial incision that is deliberately opened by a surgeon and is culture-positive or not cultured and patient has at least one of

	the following signs or symptoms: pain or tenderness; localized swelling; redness; or heat. A culture negative finding does not meet this criterion. d) Diagnosis of a superficial incisional SSI by the surgeon or attending physician.
Acute kidney injury	Defined according to the AKIN criteria (*Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury, Crit Care , 2007, vol. 11 pg. R31*): Increase in serum creatinine of ≥ 26.5 µmol/L (≥ 0.3 mg/dL) or a percentage increase in serum creatinine ≥50% (1.5× baseline value).
Sepsis	Defined according to the ACCP/SCCM Consensus Conference Committee (*Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101: 1644-55.*) Suspected infection and at least two of: 1. Core temperature > 38°C or < 36°C. 2. Heart rate > 90 beats per minute. 3. Respiratory rate > 20 breaths per minute or PaCO2 < 32 mmHg or mechanical ventilation for an acute process. 4. White blood cell count > 12 x 10^9/L or < 4 x 10^9/L or > 10% immature neutrophils.

Supplementary Table 8.3: Baseline demographics of all study participants

Variable	ICU patients N = 160	Surgical patients N = 218	All patients N = 336
Age (years)	71 (63 – 79)	74 (69 – 80)	73 (67 – 80)
BMI (kg/m^2)	29 (25 – 32)	27 (24 – 32)	28 (24 – 32)
Female	70 (43.8%)	99 (45.4%)	150 (44.6%)
Admission Source			
Home	145 (90.6%)	195 (89.4%)	300 (89.3%)
Acute hospital	11 (6.9%)	12 (5.5%)	22 (6.5%)
Assisted living	4 (2.5%)	11 (5.0%)	14 (4.2%)
Admission type			
Medical	100 (62.5%)		
Surgical	60 (37.5%)		
Surgical type			
Elective		118 (54.1%)	
Emergency		100 (45.9%)	
Charlson Comorbidity Score	2 (1 – 4)	2 (1 – 4)	2.0 (1.0-4.0)
ADL Function (Katz)			
Dependent (0 – 2)	8 (5.0%)	8 (3.7%)	15 (4.5%)
Partially Dependent (3 – 4)	9 (5.6%)	23 (10.6%)	30 (8.9%)
Independent (5 – 6)	143 (89.4%)	187 (85.8%)	291 (86.6%)
APACHE 3 score	69 (53 - 85)		
P-POSSUM mortality %		4.8% (2.8% – 10.4%)	

Values are expressed as the mean (SD), median (interquartile range), or n (%).

SD = standard deviation; IQR = interquartile range; ADL = activities of daily living; APACHE = Acute Physiology and Chronic Health Evaluation

Forty-two patients are included in both cohorts.

Supplementary Table 8.4. Baseline demographics according to Frailty Index frailty status.

Variable	ICU patients (N = 160)			Surgical patients (N = 218)			All patients (N = 336)		
	Frail N = 40	Not Frail N = 120	*P* value	Frail N = 55	Not Frail N = 163	*P* value	Frail N = 84	Not Frail N = 252	*P* value
Frailty index	0.31 (0.26 – 0.39)	0.14 (0.08 – 0.19)	< 0.001	0.28 (0.25 – 0.36)	0.14 (0.08 – 0.19)	< 0.001	0.31 (0.26 - 0.37)	0.14 (0.08 - 0.19)	<0.001
Age (years)	75 (69 – 80)	69 (61 – 77)	0.004	77 (69 – 83)	73 (68 – 79)	0.036	76 (69 - 83)	72 (67 - 79)	0.003
BMI (kg/m^2)	28 (24 – 32)	30 (26 – 33)	0.10	26 (24 – 31)	28 (24 – 32)	0.15	26 (24 - 31)	28 (24 - 32)	0.025
Female	22 (55.0%)	48 (40.0%)	0.10	24 (43.6%)	75 (46.0%)	0.76	39 (46.4%)	111 (44.0%)	0.70
Admission Source									
Home	31 (77.5%)	114 (95.0%)	0.003	43 (78.2%)	152 (93.3%)	< 0.001	65 (77.4%)	235 (93.3%)	<0.001
Acute hospital	6 (15.0%)	5 (4.2%)		2 (3.6%)	10 (6.1%)		7 (8.3%)	15 (6.0%)	
Residential care	3 (7.5%)	1 (0.8%)		10 (18.2%)	1 (0.6%)		12 (14.3%)	2 (0.8%)	
Admission type									
Medical	29 (72.5%)	71 (59.2%)	0.13						
Surgical	11 (27.5%)	49 (40.8%)							
Surgical type									
Elective				28 (50.9%)	90 (55.2%)	0.58			
Emergency				27 (49.1%)	73 (44.8%)				
Charlson Comorbidity Score	4 (2 – 5)	2 (0 – 3)	< 0.001	4 (2 – 6)	2 (1 – 3)	<0.001	4 (2 – 5)	2 (0 – 3)	<0.001
ADL Function (Katz)									
Dependent (0 – 2)	8 (20.0%)	0 (0.0%)	< 0.001	7 (12.7%)	1 (0.6%)	<0.001	14 (16.7%)	1 (0.4%)	<0.001
Partially Dependent (3 – 4)	7 (17.5%)	2 (1.7%)		13 (23.6%)	10 (6.1%)		20 (23.8%)	10 (4.0%)	
Independent (5 – 6)	25 (62.5%)	118 (98.3%)		35 (63.6%)	152 (93.3%)		50 (59.5%)	241 (95.6%)	
APACHE 3 score	80 (70 - 90)	62 (49 - 82)	<0.001						
P-POSSUM mortality risk (%)				7% (3% – 17%)	4% (3% – 9%)	0.015			

Values are expressed as the mean (SD), median (interquartile range), or n (%).
ADL = activities of daily living. BMI = body mass index. APACHE = Acute Physiology and Chronic Health Evaluation. P-POSSUM = Portsmouth-Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity.

Supplementary Table 8.5. Frailty Index by age deciles

Variable	ICU patients (N = 160)				Surgical patients (N = 218)		
	50-59 years	60-69 years	70-79 years	≥ 80 years	65-74 years	75-84 years	≥ 85 years
	(N=26)	(N=48)	(N=53)	(N=33)	(N=113)	(N=74)	(N=31)
Frail, n (%)	1 (3.8%)	11 (22.9%)	17 (32.1%)	11 (33.3%)	21 (18.6%)	23 (31.1%)	11 (35.5%)
Frailty index (median, IQR)	0.13 (0.06 – 0.17)	0.14 (0.08 – 0.22)	0.19 (0.11 – 0.28)	0.19 (0.14 – 0.25)	0.14 (0.08 – 0.21)	0.19 (0.11 – 0.26)	0.21 (0.14 – 0.26)

Chapter 9. Discussion and Conclusions

9.1 Summary of findings

This thesis presents a number of studies in support of the primary hypotheses of this PhD: that frailty in surgical and intensive care patients affects the full spectrum of health domains, that the Clinical Frailty Scale is an appropriate screening tool for frailty in these populations, and that frailty indices derived from routinely collected hospital data are valid and feasible to measure frailty.

9.2 Frailty indices in surgery and intensive care

The results from the systematic review of frailty indices in surgical and critical care (Chapter 2) demonstrate that application of comprehensive frailty indices is possible in these populations.[136] Frailty diagnosed in this manner correlates with a range of negative outcomes, including longer duration of hospital stay, increased complications, higher mortality and increased discharge to institutional care. An additional major finding was that no studies had yet used automated data collected for comprehensive frailty index generation in surgery or critical care, although very recently, new research has come to light that shows promising results.

9.2.1 Frailty vs. comorbidity in generating automated frailty indices

A very recent study has further supported the notion of comprehensive frailty indices being constructed from large-scale administrative health data. This 2019 Canadian study by McIsaac and colleagues derived a 30-variable "perioperative frailty index", or pFI, in 400,000 patients, which was then validated in a further 95,000 patients.[112] This study demonstrated a 2.2-fold increase in odds of mortality, and 1.7-fold increase in odds of institutional discharge, in surgical patients diagnosed with frailty via this frailty index. Perhaps most importantly, this study demonstrated that frailty indices are able to be constructed from hospital administrative data without being overly "weighted" towards medical comorbidity

(only half the total 30 variables in this scale were comorbid conditions, with an otherwise reasonable representation of other health domains).[112] This study illustrates the possibilities of combining properly constructed frailty indices with large datasets.

9.2.2 Surgical and ICU frailty index from routine data

The frailty index derivation studies presented in this thesis (Chapter 8) extend the findings of the studies presented above, and demonstrate that it is possible to construct a multidimensional, comprehensive frailty measurement index from health data that is collected routinely in surgical and intensive care patients within a major Australian health service. The health deficits used in deriving this frailty index were purposely chosen to be common and simple variables that are likely present in the data capture of similar hospitals. The next step in progressing this line of research would be in automating the generation of similar frailty indices within health services utilising electronic medical records. This approach has been demonstrated successfully in 1400 geriatric patients admitted to 11 hospitals in Queensland, Australia, based on the "inter-RAI" data collection system for acute care admissions.[64] This study demonstrated an association with increased mortality and a range of inpatient complications, and length of stay.[120] Demonstrating feasibility in surgical and critically ill cohorts should be the focus of future work.

9.3 Health domains affected by frailty

The combined results of the studies into the domains of health affected by frailty in both ICU and surgical patients (Chapters 4 and 5) demonstrate that frailty is not a simple concept in these populations.[106,144] Far from being confined to one particular area of health, frailty manifests as deficits throughout the gamut of health domains. Strengthening this conclusion is the fact that the increased proportion of health deficits in patients with frailty was observed across different cohorts of ICU and surgical patients, suggesting that this finding may be consistent regardless of the population studied. This requires confirmation in future studies in different settings, including other acutely hospitalised populations, as well as community dwelling adults.

Limited research to date has examined this with a similar degree of granularity. A 2020 study of 9803 older community-dwelling adults in the UK demonstrated participants with frailty were more likely to have poor mobility outdoors, lower physical activity levels, more problems with self-care, greater restriction in usual activities, less energy, more loss of appetite and unexplained weight loss, greater weakness and loss of balance, more cognitive impairment, and more falls.[145] An additional 2019 study of 408 older South Indian rural community-dwelling adults revealed similar differences, in the areas of body mass index, sex, physical activity and alcohol intake.[146] Taken together, it is likely a safe assumption that frailty is a condition of wide-ranging health deficits, which holds true throughout distinct populations.

9.3.1 Inaccuracy of non-multidimensional frailty tools

This concept, that frailty requires comprehensive measurement across many domains, has important implications for both research and clinical communities active in this area. The dominant "frailty index", certainly in the surgical literature, is the modified frailty index (mFI).[20] The limitations of this 11-point scale have been addressed throughout this thesis, and increasingly in the peer reviewed literature[37], but it is likely that despite these concerns its prominence will only increase. Indeed, demonstrating that simplicity and ease of use outweigh concerns over accuracy and content validity, an even-more reductive five-point (mFI-5) index has been developed, which incorporates only one non-comorbid condition.[147] Given the findings of this thesis, the ability of a five-item comorbidity scale to measure the complex condition of frailty is questionable.

The dramatic increase in studies using the mFI is matched only by the surprising lack of validation work. To date, no published studies have compared the mFI with reference frailty indices in the same population, in contrast to the comparison between scales contained in this thesis. The few comparison studies with other frailty scales that do exist are not reassuring. A very recent study, for example, compared the performance of the mFI and the phenotypic Hopkins frailty scale in 1042 non-cardiac surgical patients.[148] This study

demonstrated weak correlation between scales (Spearman coefficient = 0.28), with a stark difference in numbers of comorbidities as measured by Charlson comorbidity scores between patient diagnosed as frail with each measure. The median (IQR) number of comorbidities was 6 (4 – 8) in patients with frailty diagnosed via the mFI, vs. 3 (2 – 6) in patients with frailty via the phenotype scale. This lends further weight to the notion that the mFI is predominantly a comorbidity index, with higher scores a result of increased comorbid conditions, rather than frailty.

9.3.2 Future validation work required

Given the uptake of the mFI and related simplistic tools, there is hence a significant need to undertake high quality, well designed trials to validate these measures- ideally against a reference frailty index. Without this validation work, there is a real risk that conclusions around frailty prevalence, and its impact in particular cohorts, may be derailed by reliance on inaccurate tools. A 2017 study encompassing over 5000 community-dwelling UK adults illustrated these challenges, in comparing the performance of 35 different frailty measures.[102] This study demonstrated significant variability in associations with outcomes including mortality depending on which scale was employed, with the highest accuracy between multidimensional tools. Improving the utilisation of such comprehensive frailty measures, and increasing the scrutiny of research employing more simplistic, inaccurate scales, will require a concerted and coordinated effort from the frailty research community.

9.3.3 Implications of frailty being a multi-dimensional condition

Taken together, these findings (of wide-ranging health deficits with frailty) provide the necessary epidemiological setting both for understanding the complex effects of frailty on patients, and also in developing interventions to mitigate against these effects. In surgical patients, for example, mechanisms of “pre-habilitation” that solely focus on nutritional supplementation or physical activity training have not demonstrated benefit in frail patients.[113] This is in contrast to more unselected populations, in which pre-habilitation has been found to reduce postoperative complications after major abdominal surgery,[149,150] cardiac surgery[151] and some early promising evidence also in cancer surgery.[152] That frailty

in these populations affects more than just one or two more easily modifiable areas of health is an important finding of this thesis, as is the implication that individualising frailty assessment is important, as the severity of impairment in health domains may vary between patients. It is hoped that these findings may prompt a more comprehensive and nuanced approach to future interventions that seek to improve outcomes in frail surgical and ICU patients. It is likely that a multi-pronged approach to the modification of frailty in these populations will be required, particularly in the critical ill. Nutritional supplementation, combined with delirium management, attention to the ill-effects of polypharmacy, potential exercise training post-critical illness, careful discharge-planning to improve the chances of return to the home environment, and optimisation of comorbid disease, are all likely intervention targets as part of a comprehensive approach to improving the care of these at-risk patients with frailty.

9.4 Frailty screening

There is an increasing recognition that frailty screening in higher-risk hospitalised populations, including critically ill and surgical cohorts, should occur routinely.[60 153] The increased incidence of detrimental outcomes among patients with frailty makes such screening a high-yield proposition. The benefits of case-finding frailty in these cohorts are numerous: to identify patients for whom in-depth geriatrician assessment may provide opportunities to optimise management, to individualise interventions to particular areas of specific health deficits, and to assist goals-of-care discussions in high-risk patients undergoing complication-prone interventions. The best tool to feasibly and reliably screen for frailty in these populations has, however, been debated. The studies presented in this thesis provide significant support for the Clinical Frailty Scale as the candidate screening tool. Firstly, the CFS is logistically possible to administer in surgical and intensive care cohorts, requiring less than one minute on average, with a high degree of successful completion.[46] Secondly, in the two studies contained in this thesis comparing performance with the multidimensional Edmonton scale (Chapters 4 and 5), the CFS saw high correlation and agreement in both surgical and ICU patients.[106,144] This lends support to the hypothesis that the CFS performs adequately in assessment across the spectrum of health domains

which frailty is known to affect. Thirdly, the study examining the retrospective application of the CFS in ICU patients (Chapter 6) demonstrates the ability of the CFS to be determined from review of the clinical record without contemporaneous access to patients.[135] This has important implications for the way in which data is gathered in health services, and provides reassurance that this is a valid approach. Fourthly, the CFS was predictive of outcomes in both ICU and surgical patients, demonstrating its utility as a stand-alone tool should more in-depth frailty measures not be feasible to administer in a particular healthcare setting.

9.4.1 Frailty screening at a population level

As frailty becomes recognised as a condition with important implications in surgical and ICU cohorts, there is likely to be increased interest in rolling out such screening on a large-scale, population level. The results presented throughout this thesis provide evidence that, where available, using electronic health data to generate frailty indices are the most accurate and comprehensive way of achieving this. Where this capability does not exist, however, and collection of frailty data by clinical staff is required, then the Clinical Frailty Scale is arguably the best option. The results of the large registry ICU study (Chapter 7) demonstrate that at the population level the CFS is able to be determined in critically ill patients. This process also only began in our region in 2017; as time goes on, it is likely that frailty in Australia and New Zealand will become part of the "language" of patient admission to ICU, with clinical staff becoming more literate about the importance and effects of frailty as a result.

In surgical cohorts, this process is harder to achieve. This is in part due to fragmentation of care (with the majority of elective surgery in older patients in Australia occurring in the private hospital sector.[27]) This necessarily involves more disparate clinical personnel, with multiple different surgeons, anaesthetists and hospital staff involved in surgical care in many different locations, compared with the centralised capture of critically ill patients within the walls of an ICU. As a consequence, it is likely that improvements in frailty screening in surgical populations will initially come from within the academic-affiliated, tertiary hospital settings. This will be enhanced by the mature multi-disciplinary groups that exist in many of these healthcare settings. In the elective surgical setting, it is feasible that a

frailty screening tool could be incorporated into the pre-admissions process; indeed, patients could fill out many of the data points required for generation of a frailty index (or calculation of, for example, an Edmonton Frail Scale score) in conjunction with the health screening questionnaire that is used prior to presentation to the pre-admission clinic.

9.5 Conclusion

The hypotheses of this thesis were:

- Frailty in critical illness and peri-operative care affects a wide range of health domains.
- The Clinical Frailty Scale is a valid, feasible screening tool for frailty in these populations.
- Frailty indices are able to be derived from routinely collected hospital data.
- Frailty measurement in the critically ill is possible on a population level.

The multi-dimensional frailty assessment studies presented in Chapters 4 and 5 support the hypothesis that frailty does affect a wide range of health domains in these patients. This work should be extended to investigate whether this hypothesis holds in other populations and health care settings; based on limited data, it is likely that it does.

Various studies presented in this thesis provide evidence in support of the hypothesis regarding the utility of the Clinical Frailty Scale. The ability of this scale to be determined retrospectively (Chapter 6), and correlation with multi-dimensional frailty tools including the Edmonton Scale (Chapters 4 and 5) and frailty index (Chapter 8) demonstrate its versatility and accuracy as a simple frailty screening tool.

The development of a frailty index (Chapter 8) in an ICU and surgical cohort provide support for the hypothesis that this is indeed possible from routine hospital data. The next phase of research will be to extend this in scope and scale with electronic medical records. Initial

studies from other groups both overseas and within Australia have demonstrated that this approach is likely achievable.

Finally, the hypothesis that frailty in the critically ill is able to be measured at a population scale is supported by the registry cohort study (Chapter 7), demonstrating that the CFS is feasible to collect on admission to ICU, and is associated with a range of negative outcomes. This routine and increasing frailty screening may prompt a shift in frailty "literacy" among the intensive care community. Future research should explore the addition of frailty to existing risk stratification tools, and whether outcomes for frail survivors of critical illness can be improved.

Implications for practice

- Frailty is a multidimensional state, which requires consideration in measurement.
- Caution should be exercised in using non-multidimensional scales such as the mFI until validation work is completed.
- Screening for frailty in surgical and intensive care patients with the Clinical Frailty Scale is appropriate.
- The decision of the Australian and New Zealand Intensive Care Society to routinely screen for frailty is warranted.
- Frailty indices are the most comprehensive frailty measurement tools. Further development of these with electronic medical records shows promise.

Frailty is a vitally important and increasing condition in our ageing surgical and ICU populations. Improving identification of frailty will be increasingly important in the coming years, to provide the best possible healthcare for these vulnerable groups of patients.

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Appendix 1: Darvall JN, Braat S, Story DA, Greentree K, Bose T, Loth J, Lim WK. Protocol for a prospective observational study to develop a frailty index for use in perioperative and critical care. *BMJ Open*. 2019 Jan 9; 9(1): e024682.

BMJ Open

Protocol for a prospective observational study to develop a frailty index for use in perioperative and critical care

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To cite: Darvall JN, Braat S, Story DA, *et al*. Protocol for a prospective observational study to develop a frailty index for use in perioperative and critical care. *BMJ Open* 2019;**9**:e024682. doi:10.1136/bmjopen-2018-024682

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-024682).

Received 12 June 2018
Revised 29 November 2018
Accepted 29 November 2018

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ABSTRACT

Introduction Frailty is of increasing importance to perioperative and critical care medicine, as the proportion of older patients increases globally. Evidence continues to emerge of the considerable impact frailty has on adverse outcomes from both surgery and critical care, which has led to a proliferation of different frailty measurement tools in recent years. Despite this, there remains a lack of easily implemented, comprehensive frailty assessment tools specific to these complex populations. Development of a frailty index using routinely collected hospital data, able to leverage the automated aspects of an electronic medical record, would aid risk stratification and benefit clinicians and patients alike.

Methods and analysis This is a prospective observational study. 150 intensive care unit (ICU) patients aged ≥50 years and 200 surgical patients aged ≥65 years will be enrolled. The primary objective is to develop a frailty index. Secondary objectives include assessing its ability to predict in-hospital mortality and/or discharge to a new non-home location; the performance of the frailty index in predicting postoperative and ICU complications, as well as health-related quality of life at 6 months; to compare the performance of the frailty index against existing frailty measurement and risk stratification tools; and to assess its modification by patients' health assets.

Ethics and dissemination This study has been approved by the Melbourne Health Human Research Ethics Committee(20 January 2017, HREC/16/MH/321). Dissemination will be via international and national anaesthetic and critical care conferences, and publication in the peer-reviewed literature.

Strengths and limitations of this study

- This is a prospective, large-scale study in a tertiary metropolitan setting.
- There are limited prospective studies using well-constructed comprehensive frailty indices in the surgical and critical care fields.
- It is not known how frailty indices compare with traditional risk stratification tools in these areas.
- A limitation is that routinely collected hospital data varies slightly between health services, although sensitivity analyses will help to determine the impact of individual variables on results.

INTRODUCTION

Frailty is increasingly recognised as a clinical entity of importance to clinicians, patients and the health system at large. In particular, the relevance of patient frailty to perioperative and critical care is growing, as older adults comprise an increasing proportion of patients presenting for surgery and to intensive care units (ICUs) worldwide. Over the next decade, adults aged >65 years will account for more than one-quarter of all ICU admissions in many countries, and up to half of all surgical patients.[1–5] In the largest ICU study to date,[6] frailty was associated with almost twice the odds of mortality and new functional dependence, and in the largest meta-analysis of postsurgical complications (encompassing over 12 000 surgical patients across 44 studies) frailty was perhaps the most important predictor of adverse outcome, with more than doubled odds of postoperative complications.[7] In the almost-decade since the 2010 UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) examined older adults undergoing surgery, the recommendation that 'An agreed means of assessing frailty in the perioperative period should be developed and included in risk assessment' remains unfulfilled.[8]

Frailty can be described as either a phenotypic construct (criteria such as exhaustion, weakness, low activity or weight loss are present) or as a deficit model (risk accumulates due to impairments in health-related domains such as medical comorbidities, cognition, mood and behaviour, communication, sensorium, continence, nutrition and medications).[9 10] Although various frailty measurement tools have been devised, these can be of limited use in the ICU or surgical setting. Performance-based measures, for example, such as 'timed-up-and-go' tests or grip strength assessment are impossible for

mechanically ventilated or acutely unwell patients to perform.[11] Similarly, assessments including subjective questions requiring patient input may not be possible in this cohort, with potential for error when information is derived from surrogates.[12] Conversely, the perioperative and ICU environments are incredibly data-rich, with much information collected routinely for all admitted patients. Particularly in the era of electronic medical records, this has the potential to allow automated data integration and rapid derivation of relevant risk stratification scores.

In addition to potential automated calculation, a frailty index based on accumulated deficits has other advantages. As described by Searle *et al*, frailty indices demonstrate reproducibility across different populations, despite differences in composition related to which individual health deficits are present in a particular index.[13] As such, as long as certain prerequisites regarding candidate deficits are met (at least 30 deficits should be included, they should be associated with health status, increase in prevalence with age, not saturate too early, cover a range of systems and remain constant if intended for repeated use in the same population), subtle variation in terminology or specific data collected between health services for use in a frailty index do not matter.

The objective of this study, then, is to develop a frailty index, based on accumulated health deficits, that is able to be incorporated into routine hospital management of ICU and surgical patients.

AIMS

The primary aim of this study is to develop a frailty index based on accumulated health deficits, using routinely collected hospital data, enabling rapid and easily scalable assessment of surgical and ICU patients' frailty. Secondary aims are to assess the performance of the frailty index in predicting in-hospital mortality and/or discharge to a new non-home location, postoperative and ICU complications, as well as health-related quality of life at 6 months; to compare the performance of the frailty index against existing frailty measurement and risk stratification tools; and to assess its modification by patients' health assets (protective factors that support health and well-being).

METHODS

Study design

This study is designed as a prospective, single-centre cohort study, with follow-up period 6 months postdischarge.

Study setting

This study will be conducted at the Royal Melbourne Hospital (RMH), Melbourne, Australia, a tertiary metropolitan hospital that admits over 2000 ICU patients and with a surgical volume of over 25 000 operations annually. Enrolment and follow-up are expected between February 2017 and December 2018.

Inclusion and exclusion criteria

Patients are eligible if they are:

- Aged ≥65 years on admission for any surgery (emergency or elective).
- Aged ≥50 years on admission to the ICU for any indication.
- Provide written informed consent (or the person responsible in the event of incapacitation).

Patients are ineligible if they are:

- Non-English speaking (or the person responsible is non-English speaking).
- Admitted to the ICU or operating theatre for reasons of organ retrieval.

Data collection (routine for all patients)

Baseline demographics: preoperatively (surgical patients) or on admission to the ICU (ICU patients): age, gender, height and weight will be collected.

Surgical data: operative type (surgical specialty)/severity (defined according to the P-POSSUM scoring system), blood loss and American Society of Anesthesiology score will be recorded.

ICU data: routine ICU data collected (relating to the entire ICU admission episode) will include mechanical ventilation, renal replacement therapy, cardiac arrest, inotropes/vasoactive infusions, Acute Physiology and Chronic Health Evaluation (APACHE) III illness severity score and presence of any limitations to medical treatment.

Other hospital data: routine data recorded on admission for RMH patients (and common to most health services) will be used to generate a frailty index, consisting of 36 health deficits (table 1). Data will be derived from the falls risk assessment and management plan (RMH form designation: form IP8L), malnutrition risk assessment and management plan (IP63C), pressure injury prevention plan (IP8G), daily nursing care plan (IP8F), and nursing admission and assessment (IP8). Chosen deficits increase in prevalence with age and encompass a range of systems associated with health status.

Data collection (additional, by study investigators)

Additional admission data: the Katz Index of independence in activities of daily living and Charlson comorbidity score will be collected, with information added to the frailty index (table 1) below. Data related to surgical risk stratification will be collected, including the P-POSSUM Score,[14] albumin and lactate (where available), and will be compared with the frailty index for prediction of secondary outcomes listed.

Other frailty measurements: the Clinical Frailty Score[10] and the Edmonton Frailty Score[15] will both be collected. For patients who are unable to perform the 'Timed Up and Go Test' component of the latter scale (eg, emergency surgical or mechanically ventilated ICU patients), a Reported Edmonton score will be derived.[16] Data collected represent the health status of the patient prior to the onset of acute illness.

Table 1 Frailty Index (from routine data collection)

1	Falls in last 12 months	0=no, 1=yes
2	Dementia diagnosis	0=no, 1=yes
3	Altered cognition	0=no, 1=yes
4	On four or more medications, at least one affecting CNS/CVS	0=no, 1=yes
5	Vision impairment	0=no, 1=yes
6	Hearing impairment	0=no, 1=yes
7	Assistance with transferring	0=no, 1=yes
8	Assistance with mobilising	0=no, 1=yes
9	Assistance with toileting	0=no, 1=yes
10	Assistance with bathing	0=no, 1=yes
11	Assistance with dressing	0=no, 1=yes
12	Postural hypotension/dizziness	0=no, 1=yes
13	Bowel incontinence	0=no, 1=yes
14	Urinary incontinence	0=no, 1=yes
15	Eating poorly?	0=no, 1=yes
16	Lost weight without trying?	0=no, 0.5=1–10 kg, 1 =>10 kg
17	Pressure injury- current or past	0=no, 1=yes
18	Neuropathic foot disease	0=no, 1=yes
19	Problems managing at home prior to admission	0=no, 1=yes
20	Often feels sad or depressed? (Edmonton)*	0=no, 1=yes
21	Requires assistance with eating? (Katz)†	0=no, 1=yes
	Charlson Comorbidity Data‡	
22	Ischaemic heart disease	0=no, 1=yes
23	Congestive heart failure	0=no, 1=yes
24	Peripheral vascular disease	0=no, 1=yes
25	Cerebrovascular disease	0=no, 1=yes
26	Hemiplegia	0=no, 1=yes
27	Chronic lung disease	0=no, 1=yes
28	Connective tissue disease	0=no, 1=yes
29	Peptic ulcer disease	0=no, 1=yes
30	Chronic liver disease	0=no, 1=yes
31	Diabetes	0=no, 1=yes
32	Leukaemia/lymphoma	0=no, 1=yes
33	Malignant tumour	0=no, 1=yes
34	Metastatic cancer	0=no, 1=yes
35	Moderate/severe kidney disease	0=no, 1=yes
36	Moderate/severe liver disease	0=no, 1=yes
		Total=

*Derived from the Edmonton Frail Scale.
†Derived from the Katz Index of independence in activities of daily living.
‡Derived from the Charlson Comorbidity Index.
CNS, central nervous system; CVS, cardiovascular system.

Health asset data: the health assets index developed by Gregorevic *et al*[17] will be used, with data collected including educational level, family proximity, financial means, social engagement and psychosocial well-being (representing patients' baseline state prior to hospital admission).

Outcomes: endpoints collected will include in-hospital mortality (primary outcome); length of stay (time in days between either admission to the intensive care unit and discharge from hospital, or surgical operation and discharge from hospital); discharge destination (including new non-home discharge, including assisted living facility, rehabilitation or other acute hospital location); and postoperative/ICU complications (acute myocardial infarction, cardiac arrest, sepsis, acute pulmonary oedema, deep venous thrombosis, pulmonary embolism, stroke/transient ischaemic attack, wound infection, unplanned return to operating theatre, unplanned ICU/HDU admission) (all secondary outcomes). The outcome assessors will have access to frailty information collected.

6-month follow-up: health-related quality of life (EQ-5D scale), place of residence (home, residential care facility and hospital) and Clinical Frailty Scale will be recorded. A scripted telephone text will be used, proven feasible and valid in both geriatric populations and ICU survivors.[18 19] In addition, we believe that this study will be the first to administer the Clinical Frailty Scale by telephone, thus will provide an assessment of its feasibility through this modality.

Statistical analyses

We will calculate a frailty index score for each patient with ≥80% non-missing health deficit scores.[20] A frailty index score will be derived for each patient as the sum of the deficit scores divided by the total number of non-missing deficit scores thus ranging from 0 (no deficits) to 1 (all deficits). Patients with a frailty index score of ≥0.25 will be considered frail.[21] A histogram and descriptive statistics of the frailty index scores will be provided for the entire patient sample and by surgical/ICU patients, gender and age. Mean frailty index scores will be plotted versus age for all patients and by surgical/ICU status. A linear regression analysis of the frailty index on age will be performed and by surgical/ICU status to obtain the rate of accumulation of health deficits over age, in case of positive skewness, the frailty index scores may be log transformed before analysis. A random sampling procedure using 80% of frailty index items without replacement will be used and repeated several times to investigate the impact of an individual item on the rate. This approach has been successfully used in similar studies of frailty indices.[22]

A logistic regression model will be fitted to the outcomes of in-hospital mortality (primary outcome), discharge to a new non-home location, in-hospital mortality or discharge to a new non-home location, postoperative and ICU complications, including in the model the frailty index, surgical/ICU status, gender and age. Receiver operating characteristic (ROC) curves and the area under the ROC curves will be obtained to assess the ability of the model to discriminate between two classes of these outcomes. Health-related quality of life at 6 months, whereby death will be coded as 0, will be analysed with

a linear regression model using the explained variation to evaluate overall model performance. Anticipating about 5% missing quality of life data, we will use multiple imputations to explore the sensitivity of the results to underlying missing data assumptions. We will obtain Spearman's rank correlation between the frailty measurement tools (the frailty index, Edmonton and Clinical Frailty Scales) on admission and between the frailty index and risk stratification tools (APACHE for ICU and P-POSSUM for surgery). Each patient's score will be categorised into frail, vulnerable and non-frail (reference); for the frailty index (frail ≥0.25, vulnerable 0.2–<0.25, non-frail 0–<0.2), Edmonton (frail ≥8, vulnerable 6–7, non-frail 0–5) and Clinical Frailty Scale (frail ≥5, vulnerable 4, non-frail 1–3). We will examine the difference in the strength in an association between each categorised frailty scale and the outcomes using the models described earlier. Furthermore, we will obtain the measures listed above to compare the ability of the models to predict these outcomes between the three categorised frailty tools and to predict in-hospital mortality between the frailty index and risk stratification tools. Modification of the effect in frail versus non-frail patients by health assets for outcomes (death, new non-home discharge location, and postoperative and ICU complications) will be examined for the frailty index using interaction tests.

Sample size

A convenience sample of 200 surgical and 150 ICU patients from a single hospital is planned. Based on comparative literature (including a systematic review and meta-analysis of over 8000 surgical patients, and the largest multicentre study of ICU frailty), we assume that 20% of surgical patients and 30% of ICU patients, combined about 24%, will be frail.[6 23] We will be able to obtain a 95% CI of ±4.4% around the prevalence of frailty of 24% with a sample size of 350. In addition, we anticipate an in-hospital mortality of 5% in surgical patients (based on the pooled mortality rate in the meta-analysis above) and 21% in ICU patients, overall about 10%. Assuming the odds of in-hospital mortality of frail patients is 3.5 times than that of non-frail patients (based on pooled ORs from previous systematic reviews[23 24]) and in-hospital mortality is 6.8% in those who are not frail, the power to detect this effect with a sample size of 350 patients is 87% (two-sided 5% alpha).

Patient and public involvement

The development of the study design was informed by patient-centred endpoints—rather than just assessing mortality, new residential care admission, postoperative and post-ICU complications are outcome measures of importance to patients. Similarly, assessment of the quality of life (and potential decrement in quality of life) is also patient-centred. During the consent process, patients or their person responsible are given verbal and written information that study results are available to be disseminated to them. A written summary of the study findings will be provided in this instance. Specific patients were not however formally involved in the study design.

DISCUSSION

The importance of routine frailty assessment in the perioperative and ICU setting has been emphasised by various organisations, including the American College of Surgeons, the American Geriatrics Society and the Association of Anaesthetists of Great Britain and Ireland.[25 26] Given this pressing need for an easily implementable and valid frailty assessment tool, various scales have been developed. One such frailty measure, the 'modified frailty index' (mFI), has the advantage of using automatically collected variables from the US National Surgical Quality Improvement Program (NSQIP) database. Unfortunately, only 11 items are contained in this index, with the majority (9) representing medical comorbidities, thus it can perhaps be more accurately described as predominantly a 'comorbidity' scale.[27] The Groningen frailty scale, although encompassing a wider range of health deficits, numbers only 15 deficits in total.[28] A third proposed scale, the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses indicator, only comprises 12 items and includes criteria such as 'poverty' and 'barriers to access to care' which may more accurately be described as absent health assets, rather than deficits contributing to frailty per se.[29] More recently, frailty indices in non-surgical/ICU specific populations have been developed using other health databases such as Medicare claims-based data,[30] or the inter-RAI assessment system, which aids the comprehensive geriatric assessment of older hospitalised inpatients.[22]

This study will thus provide a comprehensive and timely assessment measure of frailty, and its importance in an increasingly elderly surgical and critically ill population. Although routinely collected data do vary slightly between health services, potentially limiting generalisability, conducting sensitivity analyses will allow for an individual variable effect to be assessed. As this group poses new challenges for anaesthetists, intensivists, surgeons, perioperative physicians and health services alike, derivation of an automated frailty index using routine hospital data has the potential to revolutionise risk stratification and improve outcomes, as the prevalence of frailty increases dramatically in coming years.

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Funding This work has been partially supported by an Emerging Researcher Scholarship for the first author by the Australian and New Zealand College of Anaesthetists, from a grant from Dr Peter Lowe.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Melbourne Health Human Research Ethics Committee .

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 2: Darvall JN, Boonstra T, Norman J, Murphy D, Bailey M, Iwashyna TJ, Bagshaw SM, Bellomo R. Retrospective frailty determination in critical illness from review of the ICU clinical record. *Anaesth Intensive Care*. 2019 Jul;47(4):343-348

Article

Anaesthesia and Intensive Care

Anaesthesia and Intensive Care
2019, Vol. 47(4) 343–348

DOI: 10.1177/0310057X19856895
journals.sagepub.com/home/aic
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Retrospective frailty determination in critical illness from a review of the intensive care unit clinical record

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Abstract

Frailty is one of the major challenges for intensive care, affecting one-third of intensive care unit patients and being associated with a range of poor health outcomes. Determination of frailty in critical illness using the Clinical Frailty Scale has recently been adopted by the Australian and New Zealand Intensive Care Society, but it is not known whether this is able to be measured from the clinical record without interviewing patients or their relatives. The aims of this retrospective cohort study were to test whether a Clinical Frailty Scale score could be assigned in an intensive care unit population from the clinical record, and to assess the inter-rater reliability of frailty measured in this manner. A total of 144 patients were enrolled. Of these, 137 (95%) were able to have a Clinical Frailty Scale score assigned, and 22 (15%) were scored as frail (Clinical Frailty Scale $\geq$5). Cohen's kappa coefficient for inter-rater reliability between assessors was 0.67, confirming substantial agreement. Consistent with other critically ill cohorts, frailty was associated on multivariate analysis with age, Charlson comorbidity score, dependence with activities of daily living, and limitation of medical treatment, indicating validity of this approach to frailty measurement. Our results imply that frailty measurement is possible and feasible from the intensive care unit clinical record, which is of importance as routine measurement and reporting of frailty in intensive care units in our region increases. Future work should seek to validate an assigned Clinical Frailty Scale score with that obtained directly from patients or their next of kin.

Keywords

Frailty, intensive care, mortality, outcomes

Introduction

As critically ill populations around the world age, patient frailty has become one of the major challenges in intensive care. Over the next decade in Australia, more than a quarter of all patients admitted to the intensive care unit (ICU) will be aged >80 years.[1] Based on similar European cohorts, >40% of this population will have coexisting frailty.[2] Frailty is associated with an increased risk of death, functional dependence, hospital readmission and new discharge to residential care.[3–5] Measuring frailty in the ICU is challenging, but one validated tool—the Clinical Frailty Scale (CFS)—is increasingly being used due to its ability to be measured at the bedside, with no requirement for functional testing, which is challenging in the ICU environment.[6] Frailty measured according to this scale, a nine-item categorical measure, has been correlated with increased

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mortality, adverse events and functional dependence in ICU survivors.[2,3] Given these associations, the Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcome and Resource Evaluation has recently added frailty case finding using the CFS to the data collected at admission for ICU patients in our region.

Despite the importance of frailty to the risk stratification and outcomes of critically ill patients, gathering these data presents a particular challenge in the ICU. Unlike other data points for the ANZICS Adult Patient Database (APD), which are for the most part based on objective criteria able to be gathered from the clinical record, frailty measurement via the CFS requires a degree of subjectivity in assessment. Interviewing the patient or the next of kin is also often necessary in order to determine aspects of functional performance and physical dependency that allow granularity of frailty measurement. Prior frailty studies have employed dedicated research personnel for this purpose, trained in the collection and interpretation of the CFS.[3,7] However, more recent attempts have been made to collect these data routinely using clinical staff. A single-centre Australian study illustrated the challenges posed with this approach, wherein only 59% of eligible patients had a CFS score assigned, and of these, three-quarters were assigned by the nurse in charge without next of kin involvement.[8] This approach thus raises concerns regarding data completeness and accuracy.

CFS collection in Australasian ICUs will therefore likely fall to existing ICU data collectors, posing significant challenges to workload. In particular, contemporaneous bedside frailty measurement will be problematic for data collectors, who currently rarely (if ever) are required to interview patients or next of kin, and also often enter data retrospectively using the convenience of medical chart review. It is not known whether this is possible for frailty in critical illness. No prior literature exists to inform whether frailty measurement and scoring is possible from the routine medical admission records of ICU patients. Accordingly, we therefore conducted a retrospective cohort study to test the primary hypothesis that a CFS score could be assigned in an ICU population from interrogation of the clinical record. Second, we hypothesised that the inter-rater reliability of this score between two separate clinician assessors as scored by Cohen's kappa coefficient would be at least 0.6, implying substantial agreement, and that associations with other patient characteristics and frailty found in other ICU populations would remain when data were collected using this methodology.

Materials and methods

This study was a secondary analysis of the previously published retrospective case-control study examining contributory factors leading to persisting critical illness.[9] Approval was obtained from the local Human Research Ethics Committee as a quality assurance project (QA2016110). In this previous single-centre study, 72 adult patients between 1 January 2013 and 31 December 2014 with an ICU length of stay (LOS) of >10 days were matched to 72 patients with an ICU LOS of <10 days admitted within the same time frame. The matching hierarchy was as follows: ANZICS APD diagnostic code, sex, age within 10% and Acute Physiology and Chronic Health Evaluation III risk of death within 10%. Patients admitted to the ICU for purposes of organ donation were excluded. In the case of patients readmitted to the ICU, only the first ICU episode was eligible for inclusion. Four study members (JD, TB, JN or DM) interrogated the paper medical record after discharge and collected data including age, sex, Charlson comorbidity score, ICU admission source and diagnosis, presence of treatment limitation on admission, dependence with any activities of daily living (ADLs) as determined by the Katz scale (bathing, dressing, toileting, feeding, continence and transferring),[10] daily ICU supports and requirement for ICU care, and outcomes including mortality, discharge destination (home, other acute hospital or chronic care/rehabilitation) and cause of death. In addition, a CFS score was assigned for all patients by the lead intensive care specialist investigator (JD), with a randomly selected subset of 100 patients also independently assigned a CFS score by one of the other three other intensive care resident medical officer investigators (TB, JN or DM) to assess inter-rater reliability. Accepted cut-offs for frailty were used, with frailty defined as a CFS score ≥ 5, non-frail as a CFS score of <4 and vulnerable as a CFS score of 4.[6] Prior to study commencement, all data collectors were trained in the role of the CFS and its measurement, with calibration on a sample of five patients. CFS scores were assigned after interrogation of the entire clinical record, with particular emphasis on the allied health review documentation (IP49 hospital form) in conjunction with the 'social history' aspect of the admission note. Data collectors were blind to each other's CFS scores.

Statistical analysis

All data were initially assessed for normality. Data were reported as numbers (%), means (standard deviation) or median (interquartile range) as appropriate. Univariable and multivariable linear regression models

were fitted to investigate the association of other variables with frailty and with in-hospital mortality. Inter-rater agreement between CFS scores was examined via Cohen's kappa coefficients, using quadratic weighting due to the increased magnitude of clinical difference with ascending CFS categories. Cohen's kappa were categorised using the scale of Landis and Koch.[11]

Results

During the study period, 72 patients with an ICU LOS of >10 days were matched to 72 control patients with complete medical records and with a LOS of <10 days from a total of 3874 patients admitted to the ICU.[9] The baseline data of the cohort are presented in Table 1. CFS scores could be assigned for 137 of the 144 (95.1%) patients; seven patients were unable to have a CFS score assigned due to absent social details in the admission note and no allied health review. Twenty-two (15.3%) patients were scored as frail (CFS score ≥5), 37 (27.0%) patients were scored as vulnerable (a CFS score of 4) and 78 (54.2%) patients were scored as non-frail (a CFS score of ≤3; Figure 1). As previously reported, there were no differences between persistently critically ill cases and control patients in frailty prevalence.[9]

Table 1. Baseline characteristics of the cohort.

Baseline characteristic	
n	144
Age, years, mean (*SD*)	60.3 (15.7)
Male, *n* (%)	92 (64%)
APACHE 3 score, mean (*SD*)	81.8 (24.8)
Charlson comorbidity, mean (*SD*)	3.7 (2.6)
Any limitation of medical treatment on admission, *n* (%)	18 (12.5%)
Clinical Frailty Scale score, median (IQR)	3 (2–4)
Dependence with any ADLs, *n* (%)	16 (11.6%)
Discharge destination, *n* (%)	
Died	48 (33.3%)
Home	41 (28.5%)
Chronic care/rehabilitation	39 (27.1%)
Other hospital	16 (11.1%)

ADLs: activities of daily living (bathing, dressing, toileting, feeding, continence and transferring)[10]; APACHE: Acute Physiology and Chronic Health Evaluation; IQR: interquartile range; *SD*: standard deviation.

For the 100 patients with a dual CFS assessment, Cohen's kappa coefficient for inter-rater reliability between investigators was 0.67, indicating substantial agreement. Forty-five (45%) of 100 scores agreed perfectly, with a further 41 (41%) differing by only one point and 13 (13%) by two points. Only one pair of scores differed by more than two points: a patient with a CFS score of 7 by one investigator and a CFS score of 4 by another.

On univariate analysis, frailty (a CFS score ≥5) was associated with age, Charlson comorbidity score, dependence with ADLs, limitation of medical treatment on admission, mortality, and discharge to chronic care/rehabilitation (Table 2). On multivariate analysis, age, Charlson comorbidity score, dependence with ADLs and limitation of medical treatment on admission remained significantly associated with frailty (Table 2). Although frailty was associated with univariate mortality, there were no statistically

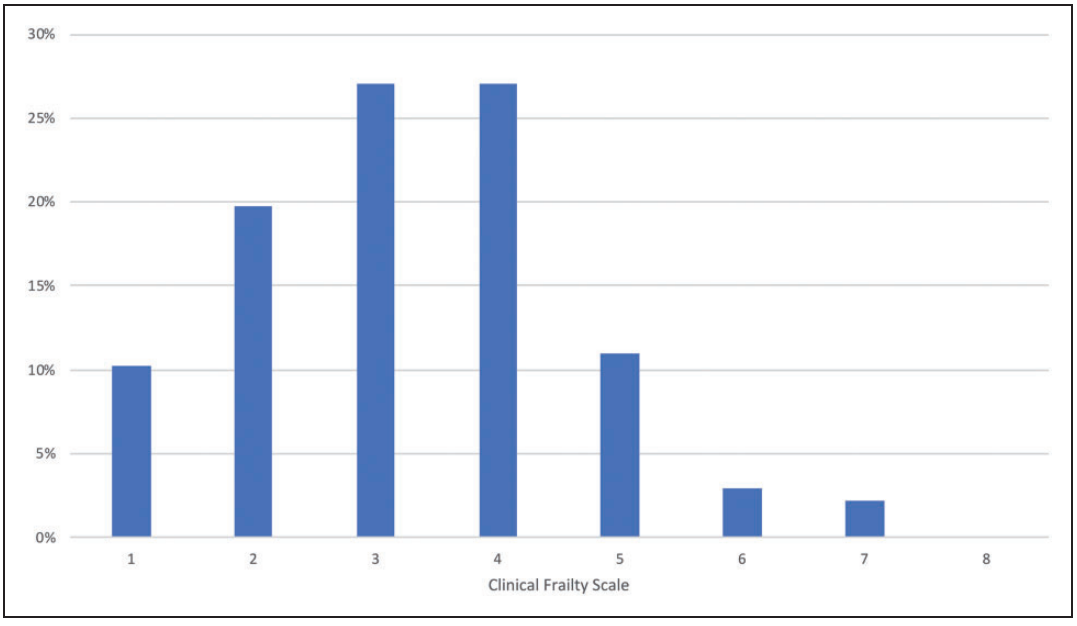

Figure 1. Clinical Frailty Scale scores of study participants.

Table 2. Univariate and multivariate association of variables with frailty (CFS score ≥5).

	Univariate analysis			Multivariate analysis		
Characteristic	Regression coefficient	Standard error	*p*-Value	Regression coefficient	Standard error	*p*-Value
Age	0.03	0.01	<0.01	0.02	0.01	0.04
ADLs	1.98	0.33	<0.01	1.64	0.30	<0.01
Charlson co-morbidity score	0.2	0.4	<0.01	0.11	0.05	0.03
Limitation of medical treatment	1.33	0.35	<0.01	0.69	0.31	0.03

CFS: Clinical Frailty Scale.

significant associations when considered in the multivariable model.

Discussion

In this retrospective cohort study, we found that the assignment of frailty status with a CFS score from the clinical record of critically ill patients was feasible, able to be completed in 95% of patients and had substantial inter-rater reliability. As seen in overseas cohorts, frailty was associated with increasing age, medical comorbidity, functional dependence and limitation of medical treatment on admission, providing evidence of the concurrent validity of this approach to measuring the CFS.

One prior (non-ICU) study examined the feasibility of retrospectively assigning a CFS score from the clinical record of 41 geriatric outpatients who had both undergone and had documented a comprehensive geriatric assessment, with similarly substantial inter-rater reliability (Cohen's $\kappa = 0.64$).[12] Unlike our investigation, however, this study used the gold-standard comprehensive geriatric assessment, with multiple data points able to be assessed in arriving at a frailty score. In contrast, the current study has demonstrated that CFS assignment is possible from the usual clinical record of an ICU admission, without specific geriatric assessment. The inter-rater reliability of prospective CFS assignment in the ICU from interviews with patients' surrogates was also demonstrated in a recent study of 101 critically ill patients in Wales and Scotland, with a linear weighted kappa between assessors of 0.74, and a similar level of score agreement seen in our study (53% versus 45% of scores in perfect agreement; 40% versus 41% of scores differing by one point).[1] Taken together, our study and these prior studies suggest that the CFS has acceptable inter-rater reliability, including in the ICU environment.

Similar to recent literature using the CFS to measure frailty in critical illness, we also observed poor health status and ICU outcomes in frail patients. A recent study of 421 critically ill Canadian patients demonstrated similarly increased comorbid disease and functional dependence with frailty, as well as a higher rate of limitation of medical treatment (34% frail patients versus 12% non-frail, $P < 0.001$, very similar to the rate in our study: 34% frail vs. 7.0% non-frail, $P < 0.001$).[14] Although the prevalence of frailty in our cohort (15%) was significantly lower than in this Canadian study (33%), this is likely related to significant differences in populations studied. Our cohort was younger, with a mean (standard deviation) age of 60 (16) years compared to 69 (10) years and 66 (10) years in frail and non-frail patients in the Canadian study, respectively. Our population likely also had less comorbid disease, although this was measured differently between studies (Charlson score in our cohort versus Elixhauser score,[15] which includes some comorbidities such as hypertension not present in the Charlson scoring system). Almost a quarter of our population were also admitted following trauma and thus may have been less medically complex than in other cohorts studied. The association of frailty with mortality on univariate but not multivariate analysis is likely related to the small number of patients studied (22 frail), as well as high overall mortality.

The strengths of our study include the assessment of a mixed medical/surgical/trauma ICU population using a paper charting system, thus implying our findings are likely applicable to other similar ICUs in our region. A further strength is that our study investigators were non – geriatric specialists, thus enhancing external validity to data collection by similar non-frailty experts in other ICUs. Our study had several limitations. It was conducted in a single centre, with the possibility that differences in data recorded and documented may exist between different hospitals. Given that much documentation is likely common to many Australasian ICUs, however, including mention of patients' relevant social circumstances and the integral role (and hence related documentation) of allied health in ICU, we consider that the standard of our medical records could be reasonably expected to reflect that of units around our

region. A further limitation is that we did not compare the CFS assigned through clinical record interrogation to that measured contemporaneously through interviews with patients or their next of kin directly. Thus, we cannot compare the two techniques. Future research should seek to validate this and to assess the accuracy of the methodology we have chosen in this study. We note, however, that one such study exists which demonstrated substantial agreement between prospective and retrospective CFS scores when derived from a documented comprehensive geriatric assessment.[12] Whether this same level of agreement exists when compared to documentation typical of an ICU admission requires further research. Our methodology is also not translatable to the determination of frailty at ICU admission. We assigned a CFS score after access to the entire chronology of the clinical record, in particular (and most usefully) after allied health documentation some days into the admission, which frequently revealed details related to functional capacity and physical dependency, allowing granular frailty assessment. Although a limitation for the early measurement of frailty in critical illness, this still has relevance to our hypothesis, allowing determination of patient frailty for benchmarking, data reporting and audit. There is, however, the potential for bias as a result of assignment of a higher CFS score in those who were sicker or who had a limitation of medical treatment order, although this applied to only 13% of the total cohort. A final limitation is we did not stratify patients by pre-ICU residential location. It is possible that the increased association of discharge to chronic care/rehabilitation was influenced by a smaller proportion of frail patients residing at home prior to the onset of critical illness. There is, however, a strong association in past studies with new onset of residential care admission.[16]

In conclusion, we have demonstrated the feasibility of measuring frailty using the CFS from the clinical record in a cohort of critically ill patients. This has significant implications for the ability to measure and report frailty routinely in Australian and New Zealand ICUs, which is likely achievable without extra resourcing for specific bedside data collection. As accurate and complete frailty assessment becomes integral to risk stratification and ongoing treatment decisions made in the ICU, this is an important development.

Declaration of conflicting interests

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

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from the Veterans Administration Health Services Research and Development (17-045) to TJI.

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Appendix 3: Darvall JN, Bellomo R, Paul E, Subramaniam A, Santamaria J, Bagshaw S, Rai S, Hubbard RE, Pilcher D. Frailty in very old critically ill patients in Australia and New Zealand: a population based, cohort study*. Medical Journal of Australia*. 2019 Oct;211(7):318-323

Frailty in very old critically ill patients in Australia and New Zealand: a population-based cohort study

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The known: Frailty in older critically ill patients is associated overseas with poorer health outcomes.

The new: Frailty is common in Australian and New Zealand ICUs, affecting 39.7% of patients more than 80 years of age for whom frailty data were available. Frailty in these patients is associated with increased likelihood of death in hospital and of new admission of survivors to nursing home or chronic care facilities.

The implications: Intensive care and community health care planning needs to take into account that by 2030 more than one-quarter of patients in Australian ICUs will be aged 80 years or more.

Abstract

Objective: To explore associations between frailty (Clinical Frailty Scale score of 5 or more) in very old patients in intensive care units (ICUs) and their clinical outcomes (mortality, discharge destination).

Design, setting and participants: Retrospective population cohort analysis of Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database data for all patients aged 80 years or more admitted to participating ICUs between 1 January 2017 and 31 December 2018.

Main outcome measures: Primary outcome: in-hospital mortality; secondary outcomes: length of stay (hospital, ICU), re-admission to ICU during the same hospital admission, discharge destination (including new chronic care or nursing home admission).

Results: Frailty status data were available for 15 613 of 45 773 patients aged 80 years or more admitted to 178 ICUs (34%); 6203 of these patients (39.7%) were deemed frail. A smaller proportion of frail than non-frail patients were men (47% v 57%), the mean illness severity scores of frail patients were slightly higher than those of non-frail patients, and they were more frequently admitted from the emergency department (28% *v* 21%) or with sepsis (12% *v* 7%) or respiratory complications (16% *v* 12%). In-hospital mortality was higher for frail patients (17.6% *v* 8.2%; adjusted odds ratio [OR], 1.87 [95% CI, 1.65–2.11]). Median lengths of ICU and hospital stay were slightly longer for frail patients, and they were more frequently discharged to new nursing home or chronic care (4.9% *v* 2.8%; adjusted OR, 1.61 [95% CI, 1.34–1.95]).

Conclusions: Many very old critically ill patients in Australia and New Zealand are frail, and frailty is associated with considerably poorer health outcomes. Routine screening of older ICU patients for frailty could improve outcome prediction and inform intensive care and community health care planning.

The number of older Australians will increase significantly over the next two decades; by 2036, the number of people aged 85 years or more will have doubled to one million.[1] The demographic character of hospitalised patients, particularly the critically ill, will consequently change. The mean age of patients in intensive care units (ICUs) in our region is climbing rapidly, and it is forecast that by 2030 26% of all people admitted to Australian ICUs will be aged 80 years or more.[2] This demographic change is likely to be accompanied by a shift in ICU practice, from a focus on managing patients with acute, reversible illnesses to caring for people, many near the end of life, with exacerbations of chronic disease.

One of the major challenges in caring for critically ill older people is frailty,[3] a multidimensional syndrome characterised by reduced capacity to deal with external stressors. Frailty is common among critically ill older people; more than 40% of ICU patients over 80 are frail.[4] Frailty in people with critical illness is associated with particularly poor outcomes: it doubles the risks of death and functional dependence, significantly increases health care use, and reduces quality of life.[3,5,6] Neither the prevalence of frailty among older ICU patients nor the implications of our ageing populations for ICU resourcing and outcomes for frail older patients have been comprehensively explored in our region.

Accordingly, we conducted a multicentre retrospective cohort study of older patients in more than one hundred ICUs in Australia and New Zealand. We describe the demographic features and the admission characteristics and outcomes for frail ICU patients aged 80 years or more. We hypothesised that mortality would be greater among frail than non-frail patients, and that a larger proportion would be discharged to residential care rather than home.

Methods

We conducted a retrospective population-based cohort study, analysing data from the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database, which includes data on more than 80% of all admissions to ICUs in Australia and New Zealand.[7] Data was gathered by the ANZICS Centre for Outcome and Resource Evaluation, which manages a clinical registry of participating ICUs for benchmarking purposes. Data dictionary use and automated validity checks were obligatory, and ongoing training and quality assurance review was provided for data abstractors.

All patients aged 80 years or more when admitted to an ICU between 1 January 2017 and 31 December 2018 were included in the study. Patients were excluded if they had been admitted to an ICU for organ donation or palliative care only. Only the first ICU admission during a hospital stay was included. Demographic data collected during ICU admission included age, sex, height, weight, admission diagnosis, limitations of medical treatment (because of patient wishes or medical futility; eg, not for intubation or cardiopulmonary resuscitation), Acute Physiology and Chronic Health Evaluation (APACHE) II and III-j illness

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jai.darvall@mh.org.au • doi: 10.5694/mja2.50329 • See Editorial (Mudge).

severity scores,[8] and Australian and New Zealand Risk of Death (ANZROD) scores.[9]

Frailty assessment

Frailty was measured with a modified version of the Canadian Study of Health and Aging Clinical Frailty Scale, a judgement-based nine-point categorical scale found to be valid and reliable for assessing frailty in a variety of populations, including critically ill patients.[3,10] The eight-point Clinical Frailty Scale (CFS), the most used frailty measure in ICUs,[11] categorises patients as CFS 1 (very fit), CFS 2 (well), CFS 3 (managing well), CFS 4 (vulnerable), CFS 5 (mildly frail), CFS 6 (moderately frail), CFS 7 (severely frail), or CFS 8 (very severely frail).[10] We dichotomised scores according to accepted definitions, defining patients as frail (CFS 5–8) or non-frail (CFS 1–4).[3] Since 2017, frailty has been a non-mandatory variable measured at the time of ICU admission, depending on the patient's level of physical function in the two months preceding admission. Scores were assigned by data collectors in each participating ICU from the clinical record; no specific education in CFS measurement was provided.

Statistical analysis

Results are reported as counts (with proportions), means (with standard deviations [SDs]), or medians (with interquartile ranges [IQRs]); comparisons of data for frail and non-frail patients employed χ^2 tests for binary and categorical data, two-sample t tests for normally distributed data, and Wilcoxon rank-sum tests for non-normally distributed continuous data. Sensitivity analyses assessed the association between frailty and mortality, with sites assigned to three groups according to completeness of coding for frailty (< 10%, 10–50%, > 50%).

The primary outcome was in-hospital mortality; secondary outcomes were length of stay (in hospital, in the ICU), re-admission to the ICU during the same hospital admission, and discharge destination (including new chronic care or nursing home admission). Unadjusted and adjusted associations between frailty status and in-hospital mortality were examined by mixed effects logistic regression, and results reported as odds ratios (OR) with 95% confidence intervals (CIs); associations between frailty status and discharge to a new nursing home or chronic care facility were assessed for patients who left hospital alive. All multivariable analyses were adjusted for region, sex, hospital type, and severity of illness (estimated with the ANZROD model),[9,12] with patients clustered by site, and site treated as a random effect. ANZROD is a locally derived mortality prediction model that includes age, diagnosis, acute physiological disturbance, chronic comorbid conditions, and treatment limitations as factors, and applies separate regression equations for each major diagnostic group. It accurately predicts mortality of Australian and New Zealand ICU patients, and is well calibrated and has good discrimination (area under the receiver operating characteristic curve greater than 0.9 when applied to the entire ICU population).[7] Statistical analyses were performed in Stata 15.1 (StataCorp) and SAS 9.4 (SAS Institute).

Ethics approval

Ethics approval was provided by The Alfred Hospital Human Research Ethics Committee (HREC number 584/18).

Results

A total of 45 773 eligible patients aged 80 years or more were admitted to 178 ICUs during the study period; frailty scores were available for 15 613 patients from 131 ICUs (34.1%) (Box 1). The median age of the included patients was 84.6 years (IQR, 82.1–87.8 years); 8247 (52.8%) were men (Box 2). The median age and illness severity of the 30 160 patients without recorded frailty scores were similar to those for the patients with frailty scores; median length of ICU stay was also similar, but median length of hospital stay was slightly longer (9.7 days [IQR, 5.6–17 days] *v* 9.2 h [IQR, 5.4–5.9 days]) and mortality higher (7.1% *v* 6.3%) for patients without frailty scores (Supporting Information, table 1).

In total, 6203 patients (39.7%; 95% CI, 39.0–40.5%) were classified as frail (Box 3); the median frailty score was 4 (IQR, 3–5). The proportion of patients classified as frail increased with age; 2813 of 8389 patients aged 80–84 years (33.5%) were frail, but 203 of 329 patients aged 95 or more years (61.7%) (Box 4). The 15 613 frail very old patients comprised 6.1% of the 102 102 patients with known frailty status admitted to the 131 ICUs contributing frailty data (after study exclusions, such as. re-admissions and palliative admissions.

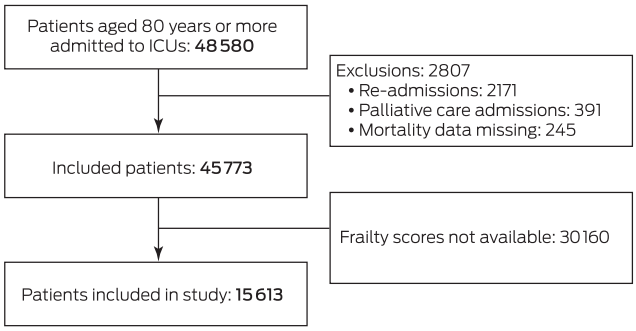
The median age of frail patients (85.5 years; IQR, 82.8–89.0 years) was higher than that of non-frail patients (84.0 years; IQR, 81.8–87.0 years); a smaller proportion were men (47% *v* 57%), their mean illness severity scores were slightly higher, and a larger proportion had treatment limitations on admission to the ICU (33% *v* 11%) (Box 2). Frail patients were more frequently admitted to ICU from emergency departments (28% *v* 21%) and less frequently after elective surgery (27% *v* 46%) than non-frail patients (Box 2). Larger proportions of frail patients were admitted with sepsis (12% *v* 7%) or respiratory complications (16% *v* 12%), and a smaller proportion after cardiac surgery (3% *v* 10%) (Box 5).

Outcomes

Unadjusted mortality was higher among frail than non-frail patients, both for in-ICU (9.0% *v* 4.5%; $P < 0.001$) and all in-hospital deaths (17.6% *v* 8.2%; $P < 0.001$; unadjusted OR, 2.40; 95% CI, 2.17–2.64) (Box 5). In our multivariable analysis, frailty was significantly associated with in-hospital mortality after adjusting for sex, baseline severity of illness, and variation between regions and hospital types (adjusted OR, 1.87; 95% CI, 1.65–2.11) (Box 6). Frailty was also associated with higher mortality in sensitivity analyses in which sites were grouped by completeness of frailty coding (Supporting Information, table 5).

Rates of ICU re-admission were similar for frail and non-frail patients (4.4% *v* 4.1%); mean lengths of ICU and hospital stay were slightly longer for frail than non-frail patients, and frail patients

1 Selection of intensive care unit (ICU) patients for inclusion in our analysis

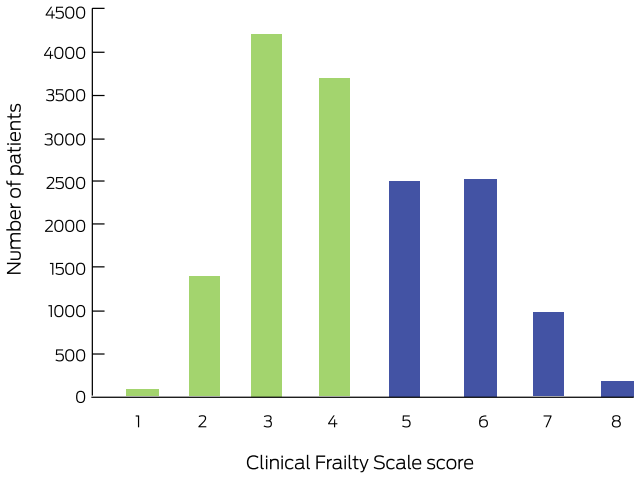


2 Baseline demographic characteristics of intensive care unit (ICU) patients included in study, by frailty status

Characteristic	All patients	Frail patients	Non-frail patients
Number	15 613	6203	9410
Age (years), median (IQR)	84.6 (82.1–87.8)	85.5 (82.8–89.0)	84.0 (81.8–87.0)
Sex (men)	8247 (52.8%)	2917 (47.0%)	5330 (56.6%)
APACHE II score, median (IQR)	16 (13–20)	17 (14–22)	15 (12–19)
APACHE III-j score, median (IQR)	58 (48–71)	62 (51–75)	56 (46–67)
ANZROD, median (IQR)	4.8% (1.6–16.2%)	9.2% (2.9–25.1%)	3.2% (1.2–10.3%)
ANZROD, mean (SD)	13.1% (18.8%)	17.9% (20.9%)	10.0% (16.5%)
Treatment limitations on admission	3013 (19.9%)	2039 (33.0%)	1064 (11.3%)
One or more chronic disease	5404 (34.6%)	2688 (43.3%)	2716 (28.9%)
Two or more chronic disease	1539 (9.9%)	850 (13.7%)	689 (7.3%)
Admission type			
Non-surgical	6878 (44.1%)	3330 (53.7%)	3548 (37.7%)
Elective surgical (planned ICU admission)	5988 (38.4%)	1683 (27.1%)	4305 (45.8%)
Emergency surgical	2747 (17.6%)	1190 (19.2%)	1557 (16.5%)
Hospital admission source			
Home	12 173 (81.4%)	4594 (75.5%)	7579 (85.5%)
Chronic care/palliative care/nursing home	476 (3.2%)	402 (6.6%)	74 (0.8%)
Transfer from other acute hospital	2153 (14.4%)	992 (16.3%)	1161 (13.1%)
Mental health	6 (< 0.1%)	4 (0.1%)	2 (< 0.1%)
Rehabilitation	138 (0.9%)	92 (1.5%)	46 (0.5%)
ICU admission source			
Operating theatre	8563 (55.4%)	2839 (45.8%)	5814 (61.8%)
Emergency department	3649 (23.4%)	1720 (27.7%)	1929 (20.5%)
Hospital ward	2554 (16.4%)	1320 (21.3%)	1234 (13.1%)
Direct transfer from other ICU	156 (1.0%)	54 (0.9%)	102 (1.1%)
Direct admission from other hospital	529 (3.4%)	243 (3.9%)	286 (3.0%)
Direct admission from home	72 (0.5%)	27 (0.4%)	45 (0.5%)

ANZROD = Australian and New Zealand Risk of Death; APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range. ◆

3 Distribution of Clinical Frailty Scale scores for 15 613 patients aged 80 years or more admitted to intensive care units in Australia and New Zealand, 2017–2018

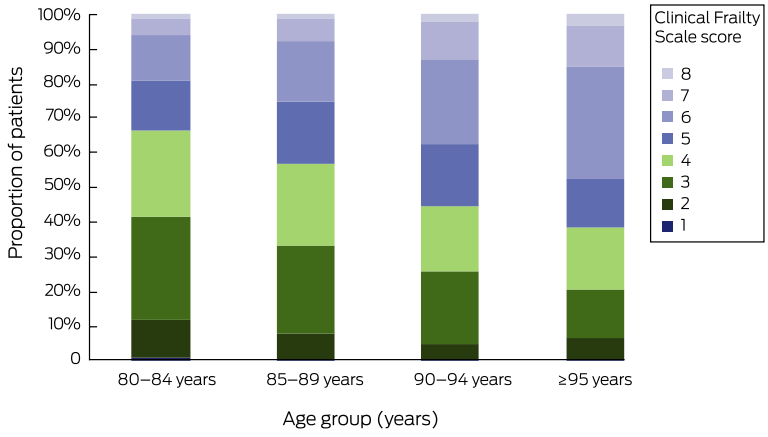


were more frequently discharged to a new nursing home or chronic care facility (4.9% *v* 2.8%) (Box 5). After adjusting for sex, baseline severity of illness, and variation between regions and hospital types, frailty in patients discharged alive from hospital was associated with an increased risk of discharge to new nursing home or chronic care (adjusted OR, 1.61; 95% CI, 1.34–1.95) (Box 6).

Discussion

We found that 39.7% of ICU patients in Australia and New Zealand aged 80 years or more are frail, or 6.1% of all adults admitted to ICUs. More than half these frail patients were women (53%); larger proportions of frail than non-frail patients were admitted to the ICU from emergency departments, or with sepsis or respiratory failure. Mortality among frail patients, after adjusting for sex, severity of illness, and regional and hospital variation, was almost twice as high as for non-frail patients, and frail patients were more frequently discharged to a new nursing home or chronic care admission than non-frail patients.

4 Distribution of Clinical Frailty Scale scores, stratified by 5-year age groups



Number of patients: 80–84 years, 8389; 80–84 years, 5132; 80–84 years, 1763; 95 years or more, 329. ◆

Comparison with earlier studies

The prevalence of frailty among our patients (39.7%) was comparable with that reported by a European study of 5000 ICU patients aged 80 years or more (43.1%);[4] the authors of the largest systematic review of frailty in critically ill adults (3030 patients aged 18 years or more) reported a lower pooled frailty prevalence (30%).[13] We found that frailty was more frequent among women than men (44.6% *v* 35.4%), as previously reported for various populations, including ICU patients;[3,14] various lifestyle, biological, and inflammatory factors have been invoked to explain this difference.[15]

Our adjusted odds ratio for in-hospital mortality (1.87) is similar to the in-hospital mortality relative risk reported by the large systematic review of frailty in adult ICU patients (1.71; 95% CI, 1.43–2.05).[13] Overall in-hospital mortality in our study (11.9%), however, was considerably lower than reported for other populations of critically ill older patients. In a 2014 study of 28 000 Victorian ICU patients aged 80 years or more, mortality was 24.1%;[16] in a 2009 study of 15 000 Australian and New Zealand ICU patients aged 80 years or more, it was 25%.[17] Mortality was 22.1% in a recent study of very old European ICU patients,[4] and 35% in a similar Canadian study.[18] The reason for the lower number of deaths in our study is unclear, but may be related to population differences (eg, the prevalence of sepsis was lower in our study than in other reports), the inclusion of patients with less severe illness (mean APACHE III score: our study, 61.3 *v* 2009 study, 67.5[17]), and recent improvements in ICU outcomes.

We found that the proportion of patients with limitations of medical treatment on admission was larger for frail than non-frail ICU patients, consistent with other studies,[3,4,19] suggesting that clinicians more frequently apply restricted goals of care to older critically ill patients who are frail.

Our finding that a greater proportion of frail than non-frail survivors of critical illness were discharged to residential care (7.6% *v* 3.1%) is consistent with the findings of the systematic review mentioned above (relative risk of home discharge [416 frail, 912 non-frail patients], 0.59; 95% CI, 0.49–0.71).[13] Our finding that the incidence of new residential care admission was higher for frail patients (4.9% *v* 2.8%), however, is novel.

The frailty measure we applied, the CFS, is the most employed frailty instrument in ICUs, and has been validated in a variety of hospital and community health care settings.[9,20] We have recently reported that the CFS can be used to measure frailty in critical ill patients across the spectrum of health domains, and its performance in ICU patients is comparable with that of comprehensive multidimensional frailty assessment tools.[21] Interest in using hospital coding data to generate automated frailty indexes is growing; for example, the Modified Frailty Index (mFI) was recently employed in a Brazilian study including more than 130 000 ICU patients.[22] Nine of 11 variables in the mFI, however, are comorbid conditions, and it does not include information on important domains of frailty, such as mobility impairment, malnutrition, and cognitive deficits. Before such screening tools can be adopted in ICUs, it is important that they are validated against accepted frailty scales.

Implications of our findings

We found that frailty is prevalent among critically ill patients aged 80 years or more in Australia and New

5 Clinical characteristics and outcomes for 15 613 patients aged 80 years or more admitted to intensive care units (ICUs) in Australia and New Zealand, 2017–2018

Characteristic	Frail patients	Non-frail patients
Number	6203	9410
ICU diagnostic category		
Sepsis	742 (12.0%)	680 (7.2%)
Trauma	274 (4.4%)	357 (3.8%)
Cardiac surgery	196 (3.2%)	969 (10.3%)
Other cardiovascular	1148 (18.5%)	1739 (18.4%)
Respiratory	999 (16.1%)	1126 (12.0%)
Neurological	437 (7.0%)	885 (9.4%)
Gastrointestinal	1231 (19.8%)	1939 (20.6%)
Other	1176 (19.0%)	1715 (18.2%)
Re-admission to ICU	271 (4.4%)	382 (4.1%)
Length of stay (days), median (IQR)		
ICU	1.80 (0.93–3.31)	1.65 (0.90–2.97)
Hospital (including ICU)	10.0 (5.84–17.7)	8.86 (5.19–15.0)
Deaths		
ICU	554 (9.0%)	425 (4.5%)
Hospital (including ICU)	1090 (17.6%)	769 (8.2%)
Discharge destination		
Died	1090 (17.6%)	769 (8.2%)
Home	2831 (45.6%)	5604 (59.6%)
Nursing home/chronic care	472 (7.6%)	295 (3.1%)
New nursing home/chronic care	*302 (4.9%)*	*267 (2.8%)*
Rehabilitation	959 (15.5%)	1485 (15.8%)
Other hospital	789 (12.8%)	1177 (12.5%)
Other	62 (1.0%)	80 (1.0%)

IQR = interquartile range. ◆

6 Frailty and outcomes: summary of multivariable analyses

Analysis (frail *v* non frail patients)	Odds ratio (95% CI)	*P*	Area under receiver operating characteristic curve
In-hospital mortality (all patients)			
Univariable analysis	2.40 (2.17–2.64)	< 0.001	0.61 (0.60–0.62)
Multivariable analysis*	1.87 (1.65–2.11)	< 0.001	0.88 (0.88–0.89)
Discharge to new nursing home/chronic care (survivors only)			
Univariable analysis	1.96 (1.66–2.33)	< 0.001	0.58 (0.56–0.60)
Multivariable analysis*	1.61 (1.34–1.95)	< 0.001	0.82 (0.80–0.83)

*Mixed effects logistic regression adjusted for sex, region, hospital type, and severity of illness (ANZROD) at admission to the intensive care unit, with site as random effect. Full models are presented in the Supporting Information, tables 2–4.

Zealand, and that it is associated with higher rates of in-hospital mortality and discharge to residential care. That the risk of new residential care admission is 1.6 times as high for frail as for non-frail very old patients suggests that post-recovery impairment is greater for frail patients, a finding with major implications for health care and community resource planning for frail survivors of critical illness. We estimate that 9000 frail patients aged 80 years or more are admitted to participating ICUs in Australia and New Zealand each year, of whom 1600 die in hospital and 450 are discharged to new nursing home or chronic care.

Strengths and limitations

Our study is the largest to have applied the Clinical Frailty Scale to very old critically ill patients, and the first large scale study of frailty in ICUs in Australia and New Zealand. The binational database upon which the study is based is large, and its data are regularly audited and validated, ensuring their high quality. However, we reviewed medical records to assign frailty scores, whereas previous CFS-based studies have interviewed patients or their relatives.[3,10] Inaccurate CFS scoring was therefore possible, although substantial inter-rater reliability in CFS scores assigned on the basis of ICU medical records has been reported.[23] Further, CFS scores based on chart review are comparable with scores based on direct ICU patient interview;[24] the accuracy of retrospective CFS scores obtained in this manner, when compared with scores assigned after comprehensive geriatric medical assessments, has also been reported.[25]

A further limitation was that frailty status was not available for most ICU patients, as CFS reporting, a relatively recent addition to the ANZICS dataset, was not mandatory in the participating ICUs. However, differences in baseline characteristics and outcomes between patients with and without known frailty status were small and not clinically relevant. For example, overall in-hospital mortality (11.9% *v* 12.9%), median APACHE III scores (58 *v* 59), and Australian and New Zealand Risk of Death score (4.9 *v* 5.0) were all similar for patients with and without frailty scores, and the distributions of diagnostic categories were also similar (Supporting Information, table 1). Further, frailty was associated with higher in-hospital mortality both overall and when assessed in groups of ICUs classed by the degree of completeness of frailty score recording (except for ICUs with completion rates below 10%; however, the small proportions of patients with frailty data in these ICUs renders comparison difficult) (Supporting Information, table 5).

Conclusion

A large proportion of very old critically ill patients in Australia and New Zealand are frail, and frailty is associated with considerably poorer health outcomes, including increased risks of in-hospital death or new admission to residential care. These findings have important public health implications. Routine screening of older ICU patients for frailty could improve outcome prediction and inform intensive care and community health care planning on discharge.

Acknowledgements: Sean Bagshaw is supported by a Canada Research Chair in Critical Care Nephrology.

Competing interests: No relevant disclosures.

Received 31 May 2019, accepted 31 July 2019

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Supporting Information

Additional Supporting Information is included with the online version of this article.