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Frailty Index and Peri-operative Outcome

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ABSTRACT

As the population ages, increasing numbers of older adults are undergoing surgery. Frailty is prevalent in older adults and may be a better predictor of post-operative morbidity and mortality than chronological age. This thesis opens with a systematic review of the current literature on frailty and post-operative outcomes in older surgical patients (chapter two). Electronic databases from 2010 to 2015 were searched to identify articles which evaluated the relationship between frailty and post-operative outcomes in surgical patients with a mean age of 75 and older. Demographic data, type of surgery performed, frailty measure and impact of frailty on adverse outcomes were extracted from the selected studies. Quality of the studies and risk of bias was assessed by the Epidemiological Appraisal Instrument. Altogether 60 articles investigated the association between frailty and post-operative outcomes, 37 of them had patients with a mean age under 75 years old. The remaining 23 articles included in the review were assessed as medium to high quality. Participants ranged in age from 75 to 87 years, and included patients undergoing cardiac, oncological, general, vascular and hip fracture surgeries. There were 21 different instruments used to measure frailty. Regardless of how frailty was measured, the strongest evidence in terms of numbers of studies, consistency of results and study quality was for associations between frailty and increased mortality at 30 days, 90 days and one year follow-up, post-operative complications and length of stay. A small number of studies reported on discharge to institutional care, functional decline and lower quality of life after surgery, and also found a significant association with frailty.

Though many studies have confirmed that frailty is associated with increased adverse outcome in the surgical population, the time point when frailty was assessed in the current literature was unclear. Whether baseline frailty or inpatient frailty predicts adverse outcome in surgical patients has not been investigated previously. The third chapter of the thesis aimed to derive a baseline and an inpatient frailty index (FI) and examine whether each was associated with adverse outcomes in the surgical population. A retrospective analysis was undertaken which derived baseline and inpatient FI from comprehensive geriatric assessment of 208 general surgical and orthopaedic patients aged 70 and over admitted to four acute hospitals in Queensland, Australia. The association of the FIs with adverse outcomes was examined in logistic regression. The mean (SD) baseline FI was 0.19 (0.09) compared to 0.26 (0.12) on admission, with a predominant increase in domains related to functional status.

Both baseline and inpatient FIs were significant predictors of one year mortality, inpatient delirium, and a composite adverse outcome, after adjusting for age, sex and acuity of surgery. Baseline frailty and inpatient frailty, though distinct, are both predictive of adverse outcomes in surgical older patients. Frailty assessed at either time point is valid and useful in predicting adverse outcomes.

In the fourth chapter of the thesis, a prospective study evaluated the feasibility of FI-CGA (frailty index based on comprehensive geriatric assessment) in 246 surgical patients aged 70 years and over undergoing intermediate to high risk surgery in a tertiary hospital in Queensland, Australia. Frailty was assessed using a 57-item FI-CGA form, with fit, intermediate and frail patients defined as FI $\leq$0.25, >0.25-0.4, and >0.4 respectively. Logistic regression models assessed the relationship between FI and adverse outcomes, adjusting for age, gender and acuity of surgery. Adverse outcomes of interest were complications, prolonged length of stay, new discharge to residential aged care facility, deaths and unplanned hospital readmissions, ascertained intraoperatively, at 30 days and 12 months post-surgery. Mean age of the participants was 79 (SD 6.5), 52% were female, 91% were admitted from community, 65% underwent orthopaedic operations, and 43% underwent acute surgery. FI-CGA was a feasible tool which took on average 12 minutes to complete at the bedside. There were no statistically significant differences between fit, intermediate and frail groups in peri-operative (17.4%, 23.3%, 19.1% for fit, intermediate frail and frail patients p=0.577) and 30 day post-operative complications (35.8%, 47.8%, 46.8% p=0.183), which may have been a reflection of insufficient sample size. However, greater frailty was associated with increased 12 month mortality (6.4%, 15.6% and 23% for fit, intermediate frail and frail patients, p=0.01) and 12 month hospital readmissions (33.9%, 48.9%, 60%, p=0.004). Using FI-CGA peri-operatively may identify patients at high risk of poor long term outcome.

In conclusion, there is strong evidence in the current literature that frailty is a predictor of adverse outcomes in surgical older adults. Frailty both at baseline and during an acute illness is predictive of adverse outcomes. FI-CGA is a potentially useful tool for incorporating into routine pre-operative assessment to help with decision making and to identify vulnerable surgical patients who are at higher risk of adverse outcomes.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

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<u>Publications during candidature</u>

Peer reviewed papers:

1. Lin HS, Peel NM, Scott IA, et al. Peri-operative assessment of older surgical patients using a frailty index - feasibility and association with adverse post-operative outcomes. *Anaesthesia and Intensive Care Journal* 2017;45(6):676-682.
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None.

Research Involving Human or Animal Subjects

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Frailty, frailty index, baseline vulnerability, older adults, surgery, post-operative complications, adverse outcomes, morbidity, mortality

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List of Abbreviations

AAA: Abdominal Aortic Aneurysm

ACS NSQIP: American College of Surgeons National Surgical Quality Improvement Programme

ADLs: Activities of Daily Living

APACHE: Acute Physiology And Chronic Health Evaluation

AVFS: Addenbrooke's Vascular Frailty Score

CAF: Comprehensive Assessment of Frailty

CD: Clavien-Dindo

CFS: Clinical Frailty Scale

CGA: Comprehensive Geriatric Assessment

CHS: Cardiovascular Health Study

CSHA: Canadian Study of Health and Aging

CRGM: Centre for Research in Geriatric Medicine

EAI: Epidemiological Appraisal Instrument

EFS: Edmonton Frail Scale

ERAS: Enhanced Recover After Surgery

FI: Frailty Index

FI-CGA: Frailty Index derived from Comprehensive Geriatric Assessment

FORECAST: Frailty predicts death One year after Elective Cardiac Surgery Tests

GFI: Groningen Frailty Indicator

LOS: Length of Stay

MACCE: Major Cardiac and Cerebral Adverse Events

MFI: modified Frailty Index

MFS: Multidimensional Frailty Score

OR: Odds Ratio

OT: Operating Theatre

RACF: residential aged care facility

SD: Standard Deviation

STS: Society of Thoracic Surgeon

TAVR: Transcatheter Aortic Valve Replacement

TRST: Triage Risk Screening Tool

VES: Vulnerable Elder Survey

CHAPTER 1 INTRODUCTION

The population aged 65 and over worldwide is predicted to reach 1.6 billion by year 2050 [1]. In the United States, those aged 65 and over are projected to more than double from 40 million in 2010 to 89 million in 2050 [2, 3]. As the population ages, the rate of surgical procedures in older people is rising and the demand for surgical services is predicted to grow [4, 5]. In England, 2.5 million people over the age of 75 years underwent surgery between years 2014 and 2015, compared with just under 1.5 million between 2006 and 2007 [6, 7]. Nearly 30% of these 2.5 million adults were over 85 years old [6]. Similar trends were found in Australia. In years 2012-2013, those aged 65 and older represented a significant proportion of elective and emergency admissions involving surgery [8]. Furthermore, women aged 85 years and over represented the largest proportion in emergency surgical admissions in Australia in year 2012-2013 compared with all other age and gender groups [8]. As more elderly undergo surgery, more frailty is seen in the surgical patients.

1.1 Definition and prevalence of frailty

Frailty is a common term used by layman and some medical staff to describe an older person who appears weak, unsteady and vulnerable. This expression often implies some concerns about a person's future outlook [9]. More recently, frailty has been conceptually defined to describe a state of increased vulnerability; a syndrome of decreased physiologic reserve and resistance to stressors [10]. Frailty can lead to increased adverse outcome, such as loss of mobility and independence, triggered by relatively small physical insults, such as a new medication or minor infection [9].

The pathogenesis of frailty is thought to involve maladaptive response to stresses in multiple physiological systems, which leads to a loss of dynamic homeostasis [11]. The pathological processes hypothesised to be responsible for the development of frailty include chronic inflammation and immune activation, sarcopenia (loss of muscle mass and strength), and age-related changes to the endocrine system, such as a decrease in the sex hormones, higher levels of cortisol and vitamin D deficiency [12]. These interact together with risk factors, such as genetic and epigenetic factors, environmental and lifestyle stressors, acute and chronic diseases, to result in the clinical manifestation of frailty and adverse health outcomes [12].

Currently there is no unified method for measuring frailty. Abundant scales and instruments have been researched for identifying and quantifying frailty, however there is no standard tool for screening frailty in routine clinical practice. To date, clinicians rely on instinct and experience to identify frail patients. This "eyeballing" technique can be subjective and have large inter-observer variability [13]. Two major conceptual models of frailty have been proposed and from them stemmed other variations of frailty instruments.

In the "phenotype" model described by Fried *et al*, also known as the Cardiovascular Health Study (CHS) definition, frailty manifests as a decline in lean body mass, strength, endurance, walking performance and activity level [10]. The Fried criteria defines frailty as possessing three or more out of the five features of slowness, weakness, exhaustion, weight loss and low physical activity. Patients who have none of these five features are non-frail, those who have one or two of these features are deemed "pre-frail" and those with three or more are deemed "frail" [10].

The other model developed by Rockwood *et al* from the Canadian Study of Health and Aging (CSHA) is the "cumulative deficit" model [14]. This model conceptualises aging as the accumulation of deficits and views frailty as a multidimensional risk state quantified by the number of deficits rather than by the nature of the health problems [14]. Frailty is expressed as an index, calculated by counting the number of deficits present in an individual divided by the total number of deficits measured [15]. The deficits considered are from multiple domains, including co-morbidities, medications, physical and cognitive impairments, psychosocial risk factors and common geriatric syndromes [15]. The frailty index (FI) has a range between 0 and 1; a higher FI indicates a higher degree of frailty. FI represents a continuum, however, it can also be trichotomised to indicate low, intermediate and high level of frailty (FI$\leq$0.25, FI >0.25-0.4, FI >0.4) [16].

The prevalence of frailty ranges between 4%-59% with an overall weighted prevalence of 10.7% from a systematic review of 21 community based cohort studies involving 61,500 older adults [17]. The prevalence of frailty also increases with age; 4% in the 65-59 age group, 9% in the 75-79 age group and 26% in the older than 85 age group [17].

1.2 The importance of frailty in surgical patients

As more older adults undergo surgery, clinicians involved in surgery and peri-operative medicine will be encountering more frail surgical patients. Frailty has been shown in older medical patients to lead to worsening disability, falls, hospitalisation, admission to long term care facilities and increased mortality [10, 18, 19]. There has been a rapid increase in publications over the past 5 years on frailty in surgical patients and an increasing recognition that frailty is associated with higher post-operative mortality and morbidity in older surgical patients [20-22].

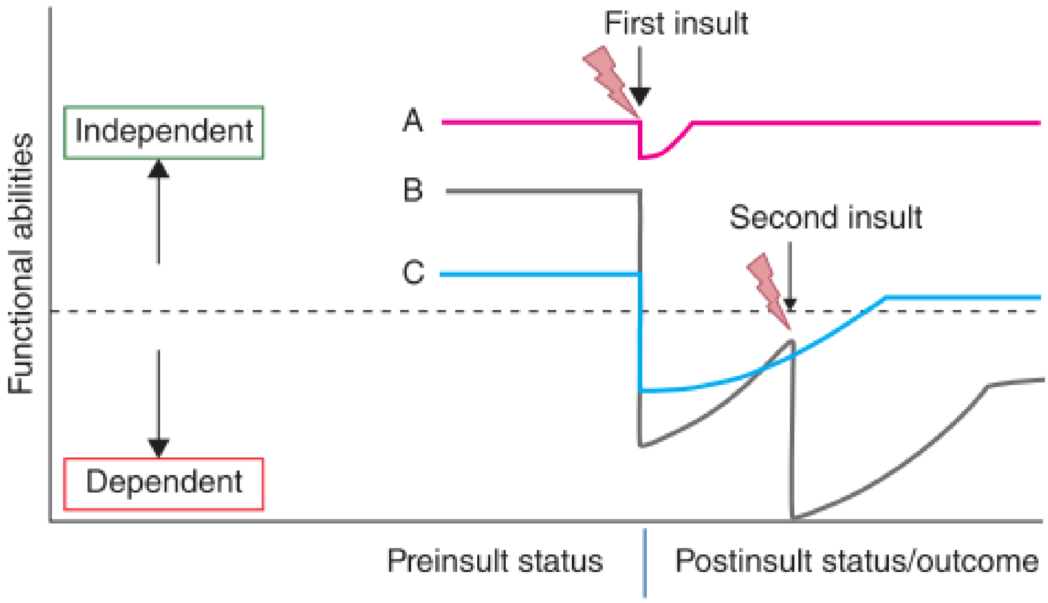

Figure 1 Role of frailty in recovery from surgery (taken from Desserud et al [22])

Adverse outcomes are an inter-play between the degree of frailty and the degree of insult or the invasiveness and complexity of surgery, as depicted in the diagram above (taken from Desserud et al [22]). Pathway "A" may be the journey of a fit individual who recovers quickly after a minor insult, such as appendicectomy from appendicitis, who returns to premorbid level of function after surgery. Pathway "C" illustrates a functionally independent individual with a degree of frailty, who suffers an intermediate insult, such as an emergency colon cancer surgery, who takes longer to recover but eventually returns to independent function with a reduced long term function compared with before surgery. Pathway “B” illustrates an independent individual with a degree of frailty, who suffers a major insult, such as strangulated small bowel, or perforated peptic ulcer with abdominal sepsis, leading to dependence. If this “B” individual suffers a second insult, such as postoperative pneumonia, cardiac event or anastomotic leak, further functional decline or even death may result, and recovery to independent function would be impossible.

As frailty is a predictor of poor outcome, early assessment of frailty can identify vulnerable surgical patients who may require more attention and tailored management plans. This has implications throughout a surgical patient’s hospital journey from admission to discharge. A frail patient is more likely to be medically unstable, needing medical optimisation prior to surgery, as well as early recognition and treatment of post-operative complications. A frail patient may lack capacity to consent for a surgical procedure, needing discussion with a substitute decision maker. With higher risk of complications, discussions regarding the ceiling of care and resuscitation status with the patient and family pre-operatively helps define treatment goals and improve informed consent. A frail patient is more likely to suffer adverse side effects from medications, which may affect the choice of anaesthesia and analgesics used intraoperatively and postoperatively. A frail patient is also more likely to be deconditioned after major surgery and early rehabilitation is crucial in restoring their function and facilitates discharge [23, 24].

This thesis opens with a literature review to examine the current evidence of the relationship between frailty and post-operative outcomes to determine if frailty is indeed a predictor of poor outcome in surgical patients. The literature review aims to summarise the tools which have been used for assessing frailty in surgical patients. This review also intends to explore whether there is a difference in frailty instruments used in acute versus elective surgical patients, and at what time point of a patient’s surgical journey frailty is measured.

CHAPTER 2 A SYSTEMATIC REVIEW OF THE IMPACT OF FRAILTY ON POST-OPERATIVE OUTCOMES

Abstract

As the population ages, increasing numbers of older adults are undergoing surgery. Frailty is prevalent in older adults and may be a better predictor of post-operative morbidity and mortality than chronological age. The aim of this review was to examine the impact of frailty on adverse outcomes in the ‘older old’ and ‘oldest old’ surgical patients. A systematic review was undertaken. Electronic databases from 2010 to 2015 were searched to identify articles which evaluated the relationship between frailty and post-operative outcomes in surgical patients aged 75 and older. Articles were excluded if they were in non-English languages or if frailty was measured using a single marker only. Demographic data, type of surgery performed, frailty measure and impact of frailty on adverse outcomes were extracted from the selected studies. Quality of the studies and risk of bias was assessed by the Epidemiological Appraisal Instrument. Twenty-three studies were selected for the review and they were assessed as medium to high quality. Participants ranged in age from 75 to 87 years, and included patients undergoing cardiac, oncological, general, vascular and hip fracture surgeries. There were 21 different instruments used to measure frailty. Regardless of how frailty was measured, the strongest evidence in terms of numbers of studies, consistency of results and study quality was for associations between frailty and increased mortality at 30 days, 90 days and one year follow-up, post-operative complications and length of stay. A small number of studies reported on discharge to institutional care, functional decline and lower quality of life after surgery, and also found a significant association with frailty. There was strong evidence that frailty in surgical patients aged 75 and over predicts post-operative mortality, complications, and prolonged length of stay. Frailty assessment may be a valuable tool in peri-operative assessment. It is possible that different frailty tools are best suited for different acuity and type of surgical patients. The association between frailty and return to pre-morbid function, discharge destination, and quality of life after surgery warrants further research.

2.1 Introduction

It has long been recognised that advanced age can carry increased risk of mortality and morbidity after surgery. However, new knowledge is emerging that frailty, an age-related cumulative decline in multiple physiological systems, is a better predictor of mortality and morbidity than chronological age [18, 25]. Patients of the same age do not all have the same risk. The identification and assessment of frailty may facilitate identification of vulnerable surgical patients so that appropriate surgical and anaesthetic management can be implemented.

Experienced clinicians may feel that they can identify frailty by end-of-bed ‘gestalt’ assessments. However, ‘eyeballing’ is subjective and tends to be inconsistent between different observers [13]. Currently there is no standardised method of measuring frailty, with more than 20 different frailty instruments identified in a systematic review [26]. These different scales are based on the two main models of frailty – the 'phenotype’ model described by Fried et al [10], and the cumulative deficit model or the frailty index described by Rockwood et al [14]. Which methods of measuring frailty are best suited for surgical patients have not been investigated.

There has been a significant increase in literature over the last five years on the subject of frailty in surgical patients. A search for articles on Pubmed published between the years 2011 to 2015 using search terms ‘frailty’ AND ‘surgical outcome’ identified 173 titles, whereas the same search for publications between 2006 and 2010 yielded only 34 titles. The majority of the current literature investigating frailty and surgery has defined ‘geriatric’ as those above 60 or 65 years old. However, there has been a change in who is thought of as ‘old’. Basing studies on someone 65 years old may not provide insight into appropriate treatment for the ‘new’ geriatric patient [27]. Despite frailty being more prevalent with increasing age, and the large proportion of those over 75 years old undergoing surgery, frailty in the ‘old old’ and the ‘oldest old’ (aged 75-85 and over 85 years) surgical patients has been less comprehensively explored. As literature on frailty in over 65 year old surgical patients is abundant, this review focuses on the ‘older old’ and ‘oldest old’ to provide more insightful summaries and reduce the heterogeneity of the study populations hence increase the comparability of the included studies.

The aim of this systematic review was to examine the association between frailty and adverse post-surgical outcomes in patients aged 75 years and over and to summarise how frailty is measured in this cohort of surgical patients.

2.2 Methods

1.2.1 Search Strategy

PUBMED, MEDLINE, EMBASE and Cochrane online databases were searched using search terms ‘frail*’ AND ‘surg*’ AND ‘outcome’ OR ‘morbidity’ OR ‘complication’. The search was conducted between October and December 2015 with filters applied to limit results to the English language, human research, and publications from year 2010 and onwards.

2.2.2 Publication Selection

The inclusion criteria for the search were: 1) the mean participant age was over 75 years; 2) the patient population had a surgical procedure; 3) frailty was assessed as a composite measure of more than one domain of health deficit, which accords with the current conceptualisation of frailty [28, 29] and was the main factor of interest in the study; and 4) the relationship between frailty and adverse outcomes was evaluated. Exclusion criteria were review articles, conference abstracts, and studies which measured frailty as a single item, such as a scan finding, a blood marker, or single physical performance test such as gait speed or hand grip strength alone.

2.2.3 Data extraction

Two reviewers (thesis author and JW) conducted the searches independently and compared results after assessing all identified abstracts for their compliance with the review criteria. Where agreement could not be reached a third independent reviewer (NP) was consulted. Reasons for exclusion were documented.

The following data were extracted from the eligible studies: sample size, mean age, country of origin of the study population, study design, type of surgery performed, frailty measure, and impact of frailty on adverse outcome.

2.2.4 Assessment of study quality and risk of bias

Two reviewers (thesis author and JW) independently assessed the quality of the included studies using a modified version of the Epidemiological Appraisal Instrument (EAI), a valid and reliable tool for rating the quality of observational studies [30]. The EAI checklist addressed the following five domains of risk of bias: reporting, subject selection, measurement quality, data analysis, and generalisation of results. Each of the 23 questions in the EAI applicable to the selected studies was scored as yes (=2), partial (=1), no or unable to determine (=0) with the highest possible score being 46.

An *a priori* decision was made to divide the total possible score into quartiles. Quartile 1 (Q1) was 35-46 (the highest quality), quartile 2 (Q2) was 23-34, quartile 3 (Q3) was 12-23 and quartile 4 (Q4) was 0-11 (the lowest quality). Any disagreement regarding the assessment of the quality of a study was resolved by consulting a third reviewer (NP).

2.2.5 Grading the overall strength of the evidence

The overall strength of the evidence was evaluated using principles outlined by the Agency for Healthcare Research and Quality [31]. The key elements of evaluation were quality (based on study design according to the hierarchy of evidence and study execution), quantity (based on the number of studies) and consistency.

2.3 Results

The literature search identified 686 articles (187 from Pubmed, 169 from Medline, 300 from Embase and 28 from the Cochrane database). From these, 270 duplicate articles were removed. The titles, abstracts and the full texts of the articles were reviewed. Articles were selected based on inclusion and exclusion criteria. The references of selected articles were hand searched for further eligible articles. Altogether 60 articles investigated the association between frailty and post-operative outcomes. Of these, 37 studies with mean age under 75 years old were excluded (list of the studies, basic demographics and frailty measures and relationship with adverse outcomes were summarised in Appendix I), leaving 23 articles in the final analysis. The study selection process, as well as the reasons for exclusion, are shown in Figure 2.

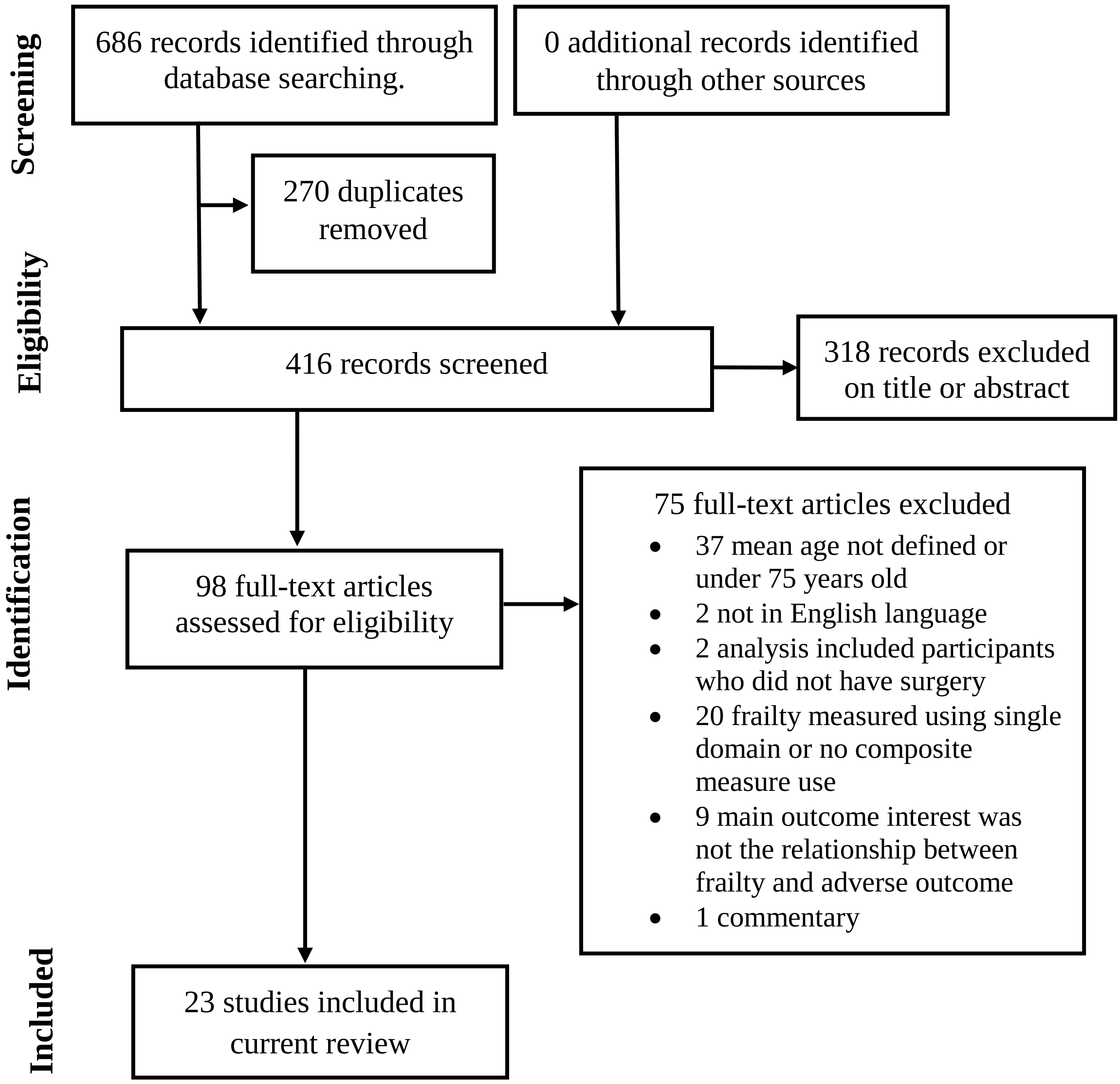

Figure 2. PRISMA flow diagram for study selection

In the 23 articles selected for this review, there were 16 cohorts of patients with a mean or median age ranging from 75 to 87 years. Twenty studies were of prospective design with sample sizes ranging from 30 to 450 [32-51], and three were of retrospective design [52-54], one of which contained a large sample size of nearly 13,000 participants [52]. Publications came from different countries, including USA [32, 33, 50, 52-54], UK [45, 47, 49, 51], Europe [34-43, 46], and Asia [44, 48]. The proportion of females ranged from 31% [49] to 83% [50]. Five studies did not report the gender distribution of the cohorts [37, 38, 44, 47, 53]. A meta-analysis was not conducted due to the heterogeneity of the frailty instruments used to measure frailty as well as the different cut offs and definition of frailty even if same instruments were used, the diversity of surgical types, the different timing of frailty measurement, and the heterogeneity of adverse outcomes which frailty was correlated with in the studies selected..

Nine studies measured frailty in cardiac surgery [32-39, 54], six in oncological surgery (predominantly focusing on colorectal cancer) [40-44, 52], three in general surgery [45, 46, 48], three in hip fracture surgery [50, 51, 53] and two in vascular surgery [47, 49]. Sixteen articles involved participants undergoing elective surgery [32-44, 48, 52, 54], five involved those undergoing acute surgery [45, 46, 50, 51, 53], while two included those undergoing both elective and acute surgery [47, 49]. Table 2.1, grouped by the type of surgery, describes the demographics, measurement of frailty and adverse outcome predicted by frailty for the selected studies.

2.3.1 Study quality and risk of bias

The EAI scores of the 23 studies ranged from 31 to 45, indicating they were in the upper two quartiles of study methodological quality. The EAI scores were in the in the second quartile for eight studies [33, 34, 37-39, 43, 44, 47] while the remainder 15 studies were in the first quartile [32, 35, 36, 40-42, 45, 46, 48-54]. There was a high level of agreement of quality assessment between the two independent reviewers. The most poorly reported items across all studies were: sample size calculation, adjustment for covariates and the report of losses to follow up. Study quality scores are incorporated into Table 2.1 and 2.3.

2.3.2 Frailty instruments

Of the 23 included studies, 21 different instruments were used to measure frailty. Variations of the Fried Criteria or instruments based on Comprehensive Geriatric Assessment (CGA), including the Frailty Index, were used in the majority of studies. Scales based on CGA are obtainable from patient interview as well as clinical notes without physical performance based measures, and were used in both acute and elective surgical cohorts. In contrast, the Fried frailty measure required physical performance-based tests, and was used exclusively in elective surgical cohorts. Four instruments, such as Multidimensional Frailty Score [48] and Comprehensive Assessment of Frailty [37-39] combined aspects of CGA with performance based tests (e.g. balance assessments, chair rise, stair climb) and medical investigations (e.g. blood test and respiratory function test). Details of measurement of frailty are presented in Table 2.2 as well as pros and cons of each frailty instrument.

2.3.3 Adverse outcomes predicted by frailty

Table 2.3 shows the adverse outcomes associated with frailty, grouped by the quality of the studies. Short, intermediate and long term mortality were assessed by 16 papers. Of ten studies evaluating the relationship between frailty and 12 month mortality, all found a significant relationship with frailty [33, 34, 36, 38, 39, 47, 48, 52-54]. Odds ratios ranged between 1.1 to 4.97 for the frail patients compared with those who were non-frail [33, 36, 38, 39, 53, 54]. This association was found regardless of the instruments used to measure frailty and irrespective of the type of surgery performed.

In the two papers that assessed long term mortality, frailty was associated with increased two year mortality with an odds ratio of 4.01 [53] and increased five year mortality with an odds ratio of 3.6 [42]. The association between frailty and 90 day mortality was evaluated in two studies [45, 52]. One found a significant association with an odds ratio of 10.4 [52] while the other did not find a significant association [45]. Thirty day mortality was evaluated in six studies [36, 37, 41, 45, 46, 51]; all but one [45] found a significant association, with odds ratios ranging between 1.4 to 8.33 [36, 41, 46]. This latter study included only a small proportion (31%, n=105) of patients who underwent surgery [45].

Table 2.1 Study demographics grouped by type of surgery

Author	**Sample size** **Country of origin** **Mean or median age** **% female** **Study design**	**Type of surgery**	**Frailty measure**	**Adverse outcome predicted by frailty**	**Association between frailty and adverse outcomes**
Cardiac					
Afilalo, J et al. (2012) [32] *	152 USA, Canada Mean age 75.9 34% female Prospective cohort study	Cardiac surgery (Elective)	Fried criteria Modified Fried criteria *Fried +cognitive impairment +depressed mood* 4-item MSSA frailty scale *gait speed, handgrip strength, inactivity, cognitive impairment* Gait speed	Composite end point of post-operative mortality or major morbidity	Fried criteria, non-sig Modified CHS frailty scale, non-sig 4 item MSSA frailty scale, non-sig Gait speed, OR 2.63 ($p<0.05$)
Green, P et al (2015) [54] *	244 USA Median age, %female - frail 87.1,53% - non-frail 85.4,45% Post-hoc analysis of PARTNER trial	Transcatheter Aortic Valve Replacement (TAVR) (Elective)	Fried criteria condensed into 4 domains *gait speed, grip strength, serum albumin, Katz index of ADL* Frail ≥6/12	1) Adverse clinical events at 30 days 2) 1 year mortality 3) Poor outcome (composite mortality & QoL assessed by KCCQ-OS) a) 6 months b) 1 year	Adjusted for covariates 1) non-sig 2) OR 2.5 (p=0.0002) 3) a) OR 2.21 (p=0.03) b) OR 2.4 (p=0.02)
Green, P. et al (2012) [33] ▪	159 USA Mean age 86 50% female Prospective cohort study	Transcatheter aortic valve replacement, (TAVR) (Elective)	Fried criteria condensed into 4 domains *gait speed, grip strength, serum albumin, Katz index of ADL* Frail >5/12	1) 1 year mortality 2) LOS 3) Procedural outcomes (any of major bleeding event, major vascular complications, stroke, acute kidney injury, 30day mortality)	Adjusted for covariates 1) OR 3.5 (p=0.006) 2) 9 vs 6 days (p=0.004) 3) OR 2.2 (p=0.04) for major bleeding but not other adverse outcomes
Kamga, M et	30	TAVI	Score Hospitalier d'Evaluation du Risque de		Adjusted for covariates

al (2013) [34] ▪	Belgium Mean age 86 47% female Prospective cohort study	(Elective)	Perte d'Autonomie (SHERPA-risk of functional decline) score *MMSE, age, perceived poor health, fall in the last year, number of iADL independently performed before admission* Identification of Seniors at Risk (ISAR) score *>3 medications, self reported memory problems, sensory problems, hospital admission within the last 6 months, increased need for help at home*	1)1 year mortality 2)Major cardiac and cerebral adverse events (MACCE)	1)SHERPA HR2.74 for every 1 point increase in score (p=0.004) ISAR non-sig 2)SHERPA non-sig ISAR non-sig
Schoenenberger, A.W. et al (2013) [35] *	119 Switzerland Mean age 83.4 55.5% female Prospective cohort study	TAVI (Elective)	*Mini Mental State Exam, Mini Nutritional Assessment, TUG, BADL, IADL, pre-clinical mobility disability* Frail ≥3	1) Functional decline (BADL ↓ ≥1 point) 2) Functional decline or death among all participants at 6 months	Univariate 1) OR 3.31 (p=0.02) 2) OR 4.46 (p=0.001)
Stortecky, S. et al. (2012) [36] *	100 Switzerland Mean age 83.7 60% female Prospective cohort study	TAVI (Elective)	*Mini Mental State Exam, Mini Nutritional Assessment, TUG, BADL, IADL, pre-clinical mobility disability* Frail ≥3	1) 30 day MACCE 2) 30 day mortality 3) 1 year MACCE 4) 1-year mortality	Univariate analysis 1) OR 4.78 (p=0.05) 2) OR 8.33 (p=0.03) 3) OR 4.89 (p=0.003) 4) OR 3.68 (p=0.02)
Sundermann S, et al (2011) [37] ▪	400 Germany Mean age 80.3 % female not reported Prospective cohort study	Cardiac surgery (Elective)	Comprehensive Assessment of Frailty (CAF) *Fried minus unintentional weight loss, plus balance assessment, albumin, creatinine, brain natriuretic peptide, FEV1 and Clinical Frailty Scale* moderately frail = 11-25 points severely frail = 26-35 points	30 day mortality	Severely frail vs non frail 21.7% vs 3.6% AUC=0.71 on logistic regression
Sundermann S, et al (2011) [38] ▪	213 Germany	Cardiac surgery (Elective)	CAF	1) 1 year mortality	Adjusted for EuroSCORE 1) OR 1.097 (p=0.001) AUC 0.70

	Mean age 80.1 % female not reported Prospective cohort study		FORECAST (Frailty predicts death One year after Elective Cardiac Surgery Tests)	2) Requirement for resuscitation 3) ICU stay 4) MACCE 1) 1 year mortality	Frail vs non frail 2) 16% vs 2% (p<0.05) 3) non-sig 4) non-sig 1) FORECAST AUC 0.76
Sundermann S, et al (2014) [39] ▪	450 Germany Mean age 79 50% female Prospective cohort study	Cardiac surgery (Elective)	CAF FORECAST *chair rise test, subjective weakness on questionnaire, stair climbing, Clinical Frail Scale and serum creatinine.*	1 year mortality	Adjusted for age CAF OR 1.091 (p<0.001) FORECAST OR 1.265 (p<0.001)
Oncologic					
Kristjansson S.R. et al (2010) [40] *	178 Norway Mean age 79.63 57% female Prospective cohort study	Colorectal cancer surgery (Elective)	Balducci Frailty Criteria from CGA *Cumulative Illness Rating Scale (CIRS), pADL, iADL, polypharmacy, MNA, MMSE, and GDS*	30 day post-operative complications (Clavian-Dindo grading)	Adjusted for covariates OR 3.13 (95% CI 1.65–5.92)
Kristjansson S.R. et al (2012) [41] *	176 Norway Mean age 80 57% female Prospective longitudinal study	Cancer surgery (Elective)	Balducci Frailty Criteria from CGA Modified Fried criteria	30 day mortality	Adjusted for cancer stage and age Balducci OR 3.39 (p<0.001) Modified Fried OR 2.67 (p=0.029)
Neuman, H.B. et al (2013) [52] *	12,979 USA Mean age 84.4 61.4% female Retrospective analysis of Surveillance, Epidemiology and End Results(SEER)-Medicare database	Colectomy for stage I to III colon cancer (Elective)	11 item frailty measure defined by the John Hopkins Adjusted Clinical Group case-mix system *Difficulty walking, weight loss, frequent falls, malnutrition, impaired vision, decubitus ulcer, incontinence (plus 4 additional unnamed conditions)* Frail $\geq$1/11	1) 90 day survival 2) 1-year survival	Adjusted for covariates 1) OR 10.4 (p<0.001) 2) OR 8.4 (p<0.001)

Ommundsen, N. et al (2014) [42] *	178 Norway Mean age 80 57% female Prospective cohort study	Colorectal cancer surgery (Elective)	Balducci Frailty Criteria from CGA	5 year mortality	Multivariate adjusted for TNM stage and sex OR 3.6 (p<0.001)
Ronning, B. et al. (2014)[43] ▪	84 Norway Median age 82 59% female Prospective cohort study	Colorectal cancer surgery (Elective)	Balducci Frailty Criteria from CGA	Post-operative functional status 1) Barthel Index↓ 2) NEADL ↓ 3) TUG ↑ 4) Grip strength ↓	Logistic regression (95%CI) 1) non-sig 2) non-sig 3) non-sig 4) non-sig
Tan, K-Y et al (2012) [44] ▪	83 Singapore and Japan Mean age 81.5 % female not reported Prospective cohort study	Colorectal cancer (Elective)	Fried criteria	Postop complications (Clavien-Dindo >II)	Bivariate analysis OR 4.08 (p=0.006)
General/abdominal					
Hewitt, J. et al (2015) [45] *	325 UK Mean age 77.6 57% female Prospective cohort study	General surgical patients (Acute) - only 31% underwent surgery	Clinical Frailty Scale (CFS) *7 frailty levels based on visual observation combined with an abbreviated review of medical records* Frail is >5	1) 30 day mortality 2) 90 day mortality 3) LOS 4) 30 day hospital readmission	Adjusted for age and polypharmacy, frail vs non frail 1) non-sig 2) non-sig 3) 19 vs 7 days (p=0.02) 4) non-sig
Kenig, J et al (2015) [46] *	184 Poland Mean age 76.9 53% female Prospective cohort study	Abdominal surgery (Acute)	Vulnerable Elder Survey (VES) *age, self-rated health, limitation in physical function and functional disabilities* Triage Risk Screening Tool (TRST) *cognitive impairment, difficulty walking/transferring/recent falls, >5 medications, ED use in previous 30 days or hospitalization in previous 90 days, lives alone and/or no available caregiver,*	1) 30 day post-operative complications (Clavien-Dindo grading)	Adjusted for covariates 1)VES: OR 2.4 (p<0.05) TRST: non-sig G8: OR 1.5 (p<0.05) GFI: OR 1.5 (p<0.05) Rockwood: non-sig Balducci: OR 1.7 (p<0.05) 2) VES: OR 2.4 (p<0.05)

			geriatric syndrome G8 *7 items from the Mini Nutritional Assessment (MNA) questionnaire and age* Groningen Frailty Indicator (GFI) *ADLs, sensory impairment, nutrition, polypharmacy, cognitive impairment, psychosocial wellbeing and subjective physical fitness* Rockwood's brief clinical instrument to classify frailty (4 frailty levels) Balducci Frailty Criteria	2) 30 day mortality	TRST: non-sig G8: OR 1.8 (p<0.05) GFI: OR 1.4 (p<0.05) Rockwood: non-sig Balducci: OR 1.4 (p<0.05)
Kim, S et al (2014) [48] *	275 Korea Mean age,% female - survivors 75.2, 46% - deceased 77.6, 32% Prospective cohort study	Intermediate or high risk general surgery (Elective)	Multidimensional Frailty Score (MFS) *Malignant disease, Charleston comorbidity Index, Albumin, ADLs, IADLs, dementia, risk of delirium, malnutrition, mid-arm circumference* Low risk ≤5 High risk >5	1) 1 year mortality 2) Discharge to residential care 3) Postoperative complications 4) LOS (median)	Adjusted for covariates, for every 1 point increase in MFS 1) OR 2.05 (p<0.001) 2) OR 1.42 (p=0.01) 3) non-sig 4) 14 vs 9 days for high vs low risk group (p<0.001)
Vascular					
Ambler, G.K. et al (2015) [47] ▪	410 UK Median age 77 % female not reported Prospective cohort study	Vascular surgery (Elective and Acute)	Addenbrooke's Vascular Frailty Score (AVFS; 6 items, score 0-6) *Not independently mobile on admission, depression, polypharmacy on admission (>8 medications), anaemia, Waterlow score >13 on admission, emergency admission*	1) 1 year mortality 2) Readmission-free survival 3) Discharge to residential care 3) Prolonged LOS	Univariate; most vs least frail 1) 58% vs 0%, AUC 0.83 2) 0% vs 68% (p<0·001), AUC 0.71 3) AUC 0.78 4) AUC 0.74
Partridge, J.S.L. et al (2015) [49] *	125 UK Mean age 76.3 31% female Prospective observational study	Vascular surgery (Elective and Acute)	Edmonton Frail Scale (EFS) *cognitive impairment, dependence in iADL, recent burden of illnesses, self-perceived health, depression, weight loss, medication issues, incontinence, inadequate social support and mobility difficulties.*	1) Composite measure post-operative complications 2) Composite measure	Multivariate, adjusted for significant baseline associations and age 1) non-sig 2) non-sig

			Frail is >7/18	adverse functional outcomes 3) LOS ≥12 days	 3) non-sig
Hip fracture					
Kistler, E et al (2015) [50] *	35 USA Mean age 86 83% female Prospective cohort study	Hip fracture surgery (Acute)	Modified Fried Criteria	 1) Post-operative complications 2) Delirium 3) LOS 4) Time to surgery	Frail vs Non-frail 1) non-sig 2) non-sig 3) 7.3 vs 4.1 (p=0.038) 4) non-sig
Krishnan, M et al (2014) [51]*	178 UK Mean age 81 73.5% female Prospective cohort study	Hip fracture surgery (Acute)	FI (51 items)	 1) 30-day mortality 2) Inpatient mortality 3) LOS-failure to return home by 30 days	Frail vs Non-frail 1) 17.2% vs 0% (p<0.001) 2) 28.1% vs 0% (p<0.001) 3) AUC 0.82
Patel K.V. et al (2014) [53] *	218 USA Mean age 81.2 % female not reported Retrospective chart review	Hip fracture (Acute)	Modified FI (19 items)	1 year mortality 2-year mortality	OR 4.97 (p<0.001) OR 4.01 (p<0.001)

*indicates quartile 1 in the quality assessment
･indicates quartile 2 in the quality assessment
LOS = length of stay
MACCE = Major Cardiac & Cerebral Adverse Events
non-sig = no statistically significant association
AUC = area under the ROC curve for prediction of adverse outcomes

Table 2.2 Frailty instruments and their pros and cons

Frailty Instrument	Pros	Cons	Studies using the tool
Fried criteria *three or more out of the five features of slowness, weakness, exhaustion, weight loss and low physical activity*	Robust tool which has been validated in multiple studies across various surgical specialties	Relies on performance based tests which might limit its use in acute setting; does not take into account cognition	Afilalo, J et al. (2012) [32] Tan, K-Y et al (2012) [44]
Modified Fried criteria *Fried +cognitive impairment +depressed mood* 4-item MSSA frailty scale *gait speed, handgrip strength, inactivity, cognitive impairment*	Considers cognitive in addition to cognitive aspect of frailty	Relies on performance based tests	Kristjansson S.R. et al (2012) [41] Kistler, E et al (2015) [50]
Fried criteria condensed into 4 domains *gait speed, grip strength, serum albumin, Katz index of ADL* Frail ≥6/12	-	Relies on performance based tests	Green, P et al (2015) [54] Green, P. et al (2012) [33]
Mini Mental State Exam, Mini Nutritional Assessment, TUG, BADL, IADL, pre-clinical mobility disability Frail ≥3	-	Relies on performance based tests	Schoenenberger, A.W. et al (2013) [35] Stortecky, S. et al. (2012) [36]
Comprehensive Assessment of Frailty (CAF) *Fried minus unintentional weight loss, plus balance assessment, albumin, creatinine, brain natriuretic peptide, FEV1 and Clinical Frailty Scale* moderately frail = 11-25 points severely frail = 26-35 points	Comprehensive	Relies on performance based tests Can be time consuming as require results of spirometry and laboratory tests. Only validated by one research group	Sundermann S, et al (2011) [38] Sundermann S, et al (2014) [39]
FORECAST (Frailty predicts death One year after Elective Cardiac Surgery Tests) *chair rise test, subjective weakness on questionnaire, stair climbing, Clinical Frail Scale and serum creatinine.*	-	Relies on performance based tests Only validated by one research group	Sundermann S, et al (2014) [39]
Multidimensional Frailty Score (MFS) *Malignant disease, Charleston comorbidity Index, Albumin, ADLs, IADLs, dementia, risk of delirium,*	-	Only validated by one research group	Kim, S et al (2014) [48]

malnutrition, mid-arm circumference Low risk ≤5 High risk >5			
FI (51 items) *An index between 0 and 1 totalling the number of deficits present divided by the deficits measured. Denominator ranges from 30-71 covering multiple domains including co-morbidities, medications, physical and cognitive impairments, psychosocial risk factors and common geriatric syndromes.*	Comprehensive, multiple domains of health considered. Frailty measure can be taken from medical records and examined both prospectively and retrospectively Does not rely on performance based measures	Can be time consuming if deficits are manually collected	Krishnan, M et al (2014) [51]
Modified FI (19 items)	As above	-	Patel K.V. et al (2014) [53]
Balducci Frailty Criteria from CGA *Cumulative Illness Rating Scale (CIRS), pADL, iADL, polypharmacy, MNA, MMSE, and GDS*	-	Validated mainly in oncology surgical patients only, may not apply to other surgical subspecialty patients.	Kristjansson S.R. et al (2010) [40] Kristjansson S.R. et al (2012) [41] Ommundsen, N. et al (2014) [42] Ronning, B. et al. (2014) Kenig, J et al (2015) [46]
Addenbrooke's Vascular Frailty Score (AVFS; 6 items, score 0-6) *Not independently mobile on admission, depression, polypharmacy on admission (>8 medications), anaemia, Waterlow score >13 on admission, emergency admission*	-	Validated only in vascular surgical patients, may not apply to other surgical subspecialty patients.	Ambler, G.K. et al (2015) [47]
Edmonton Frail Scale (EFS) *cognitive impairment, dependence in iADL, recent burden of illnesses, self-perceived health, depression, weight loss, medication issues, incontinence, inadequate social support and mobility difficulties.* Frail is >7/18			Partridge, J.S.L. et al (2015) [49]
11 item frailty measure defined by the John Hopkins Adjusted Clinical Group case-mix system *Difficulty walking, weight loss, frequent falls, malnutrition, impaired vision, decubitus ulcer, incontinence (plus 4 additional unnamed conditions)*	Can be obtained from clinical notes.		Neuman, H.B. et al (2013) [52]

Frail ≥1/11			
Clinical Frailty Scale (CFS) *7 frailty levels based on visual observation combined with an abbreviated review of medical records* Frail is ≥5	Brief Pictorial and easily understood even in untrained assessor	Considers phenotypic/physical aspects of frailty only	Hewitt, J. et al (2015) [45]
Vulnerable Elder Survey (VES) *age, self-rated health, limitation in physical function and functional disabilities*	Brief	Measures only limited domains of frailty	Kenig, J et al (2015) [46]
Triage Risk Screening Tool (TRST) *cognitive impairment, difficulty walking/transferring/recent falls, ≥5 medications, ED use in previous 30 days or hospitalization in previous 90 days, lives alone and/or no available caregiver, geriatric syndrome*	Brief	Measures only limited domains of frailty	Kenig, J et al (2015) [46]
G8 *7 items from the Mini Nutritional Assessment (MNA) questionnaire and age*	Brief	Limited to nutritional aspect of frailty only, does not include other domains of frailty.	Kenig, J et al (2015) [46]
Groningen Frailty Indicator (GFI) *ADLs, sensory impairment, nutrition, polypharmacy, cognitive impairment, psychosocial wellbeing and subjective physical fitness*	-	Only validated by one research group	Kenig, J et al (2015) [46]
Score Hospitalier d'Evaluation du Risque de Perte d'Autonomie (SHERPA-risk of functional decline) score *MMSE, age, perceived poor health, fall in the last year, number of iADL independently performed before admission*	-	Only validated by one research group	Kamga, M et al (2013) [34]
Identification of Seniors at Risk (ISAR) score *>3 medications, self reported memory problems, sensory problems, hospital admission within the last 6 months, increased need for help at home*	-	Only validated by one research group	Kamga, M et al (2013) [34]

Table 2.3 Adverse outcome associated with frailty, grouped by the quality of studies

Outcome		Number of studies 1	2	3	4	5	6	7	8	9	10
Mortality											
1 year Mortality *n*=10	Quality [ref] N sample	Q1 [36] 100	Q1 [48] 275	Q1 [54] 244	Q1 [52] 12979	Q1 [53] 218	Q2 [33] 159	Q2 [34] 30	Q2 [38] 213	Q2 [39] 450	Q2 [47] 410
2 Year Mortality *n*=1	Quality [ref] N sample	Q1 [53] 218									
5 year Mortality *n*=1	Quality [ref] N sample	Q1 [42] 178									
30 Day Mortality *n*=6	Quality [ref] N sample	Q1 [36] 100	Q1 [41] 176	Q1 [46] 184	Q1 [51] 178	Q2 [37] 400	Q1 [45] 325				
90 Day Mortality *n*=2	Quality [ref] N sample	Q1 [52] 12979	Q1 [45] 325								
Post-Operative Complications											
Non-routine recovery *n*=10	Quality [ref] N sample	Q1 [40] 178	Q1 [46] 184	Q2 [33] 159	Q2 [44] 83	Q1 [32] 152	Q1 [48] 275	Q1 [49] 125	Q1 [50] 35	Q1 [54] 244	
Need for resuscitation *n*=1	Quality [ref] N sample	Q2 [38] 213									
Delirium *n*=1	Quality [ref] N sample	Q1 [50] 35									
MACCE *n*=3	Quality [ref] N sample	Q1 [36] 100	Q2 [38] 213	Q2 [34] 30							
Discharge											
Length of stay *n*=6	Quality [ref] N sample	Q1 [51] 178	Q1 [50] 35	Q1 [45] 325	Q2 [47] 410	Q2 [33] 159	Q1 [49] 125				
Discharge to Institution *n*=3	Quality [ref] N sample	Q1 [48] 275	Q2 [47] 410								
Functional Decline *n*=1	Quality [ref] N sample	Q1 [49] 125									
Post-Discharge											
Readmission rate: 1 year *n*=2	Quality [ref] N sample	Q2 [47] 410	Q1 [45] 325								
Functional Decline *n*=2	Quality [ref] N sample	Q1 [35] 119 *at 6 months*	Q2 [43] 84 *16-28 months*								
Quality of Life: 6 months, 1 year *n*=1	Quality [ref] N sample	Q1 [54] 244									

P: Prospective study, R: Retrospective study, Q1: Quartile one quality assessment, Q2: Quartile two quality assessment, MACCE: Major Cardiac & Cerebral Adverse Events, Dark/Light shade: significant/non-significant association (respectively). n: number of studies

Specific items of post-operative complications were also examined by several studies. An association between frailty and major cardiac and cerebral adverse events (MACCE) was reported by one of the three studies evaluating this outcome [34, 36, 38]. One study explored the association between frailty and delirium and did not find a significant association [50]. Of two studies evaluating frailty and readmission rate, one study found a significant association [47] while the other did not [45]. One study showed a significant association between frailty and the need for resuscitation [38].

Post-operative complications, as graded by the Clavien-Dindo severity classification [55] or pre-defined by the authors, were evaluated in nine papers [32, 33, 40, 44, 46, 48-50, 54]. Frailty was associated with increased post-operative complications in four studies with odds ratios ranging from 1.5 to 4.8 [33, 40, 44, 46]. The remaining five studies reported no significant association [32, 48-50, 54]. The definitions used for post-operative complications in these 10 studies were heterogeneous. Conditions pre-specified in the studies which counted as a post-operative complication included cardiac complications (namely myocardial infarction, heart failure, arrhythmia), pulmonary embolism, pneumonia, wound infection, major bleeding, renal failure, delirium, unplanned return to theatre and unplanned intensive care unit admission.

Of the six studies that included prolonged length of stay as an outcome, an association with frailty was found in five [33, 45, 47, 50, 51]. Three studies evaluated functional decline as an outcome, of which only one found a significant association [35]. Discharge to a residential care facility was found to be associated with frailty by both studies in which this outcome was evaluated [47, 48]. Quality of life was evaluated in one study and frailty was associated with the composite poor outcome of mortality or poorer quality of life [54].

Based on quality, quantity and consistency of the included studies, there is evidence for an association between frailty and adverse postoperative outcomes. Although cohort studies are lower on the hierarchy of evidence than randomised controlled trials, it is acknowledged that the cohort study design is entirely appropriate for investigating this particular research question. The literature search identified 23 studies that met the inclusion criteria and 15 of those were in the upper quartile of quality assessment, indicating the majority were methodologically sound. The consistency was evidenced by the finding that 20 of the included studies found evidence of an association between frailty and at least one adverse outcome.

2.4 Discussion

The reviewed studies consistently found that in patients aged over 75 years, frailty was associated with increased mortality, post-operative complications, prolonged length of stay and discharge to residential care facility. The strongest evidence of association was between frailty and one year mortality, supported by the greatest number of high quality positive studies. The association was consistent across different frailty instruments and regardless of the type of surgery performed.

Our findings are congruent with other reviews of frailty in surgical patients. Beggs et al found eight out of 19 articles demonstrating frailty to be significantly associated with mortality and post-operative complications [21]. Other systematic reviews have concentrated on specific surgical subspecialties, namely oncologic surgery [56], cardiac surgery [20] and thoracic surgery [57]. They also found frailty to impact negatively on post-operative outcomes. Two other reviews written on cardiac surgery also identified frailty as a risk factor that provided important prognostic information in older adults needing surgical or transcatheter aortic valve replacement [58] and found that frailty increased the predictive power of conventional risk scores [59].

The strength of this review is that it is inclusive of all types of surgery, both elective and acute, and focuses on those over 75 years old. This review provided insight into how frailty is measured and how it correlates with adverse outcomes in the 'old-old' and the 'oldest old' surgical population. Our search was limited to English publications and may have excluded relevant publications in other languages. Another limitation was that studies using single markers to determine frailty, such as measurement of muscle mass or gait speed, were excluded based on the consensus view of frailty being a multidimensional state of increased vulnerability. Finally, due to the differences in frailty instruments used and heterogeneity of the surgical patient population, meta-analysis could not be conducted, and the magnitude of the adverse impact of frailty on outcome could not be estimated.

There is evidence that frailty is associated with increased mortality and morbidity in the older surgical patients. As patients over 75 years old are presenting more commonly for surgery, frailty assessment may have considerable value as a tool for peri-operative assessment.

However, for the value of frailty assessment to be realised, it must not only predict outcomes but also be easily incorporated into routine assessment or created from existing information, without placing further resource burden on clinical staff and the patient. Once established, such a tool may offer a valuable addition to the risk assessment of older persons undergoing surgery, alongside the standard surgical and anaesthetic assessment tools. With the increasing focus on patient centred care, the ongoing development of frailty assessment has the potential to improve how well patients can be informed by their surgeons and anaesthetists prior to their procedures, thus enhancing informed consent.

This review found several important gaps in the current literature. Frailty in acute surgical patients is under-studied. Only 7 out of 23 studies assessed acute surgical patients and all of them used scales based on comprehensive geriatric assessment to measure frailty. In these seven studies with acute surgical patients, some assessed the frailty status on admission; others did not specify whether frailty reported in the study was on admission or pertaining to the pre-morbid period. Whether frailty in acute surgical patients differs in the pre-morbid period or on admission and the best timing of frailty measurement needs further evaluation.

Mortality and post-operative complications are the most commonly studied and reported outcomes in the 23 articles reviewed. Quality of life post-surgery was assessed in only one out of the 23 studies; similarly, functional decline and discharge to a care facility were only evaluated in three and two studies respectively. The association between frailty and functional outcome, discharge destination, and quality of life after surgery warrants further research. Factors and outcomes important to the individual elderly patient undergoing surgery must also be considered when performing pre-operative assessment, such as the consideration of premorbid status and return to the premorbid level of function.

The most well validated instruments in the 54 articles reviewed were the modified frailty index, frailty index, and Fried criteria. The rest of the scales were variations of the frailty index and Fried criteria, or a combination of features from both. Many scales have not been validated again after their initial development. The mFI having been validated in large cohorts of patients across many surgical sub specialities using retrospective analysis of an existing database has not been validated in prospective cohorts.

Fried’s model identifies frailty as a wasting disorder with sarcopenia as a key pathophysiologic feature and weakness and gait speed are important components of the criteria. However, there are pragmatic issues in applying the Frieds criteria as a clinical tool outside research setting in the surgical population, especially in the acutely admitted patients. Walking speed is not always possible to be measured, especially when patients are very frail and immobile. It is impractical to assess gait speed preoperatively in conditions such as lower limb fractures and trauma patients. Furthermore, hand grip measurement requires equipment which may not be universally available on the wards outside the research setting. Fried’s model does not take into account impairment in cognition and mood disorders which are important components of frailty.

The cumulative deficit model as evaluated by frailty index appears to be more advantageous in the peri-operative setting to measure frailty. It is comprehensive and takes into account all aspects of deficits which contribute to frailty, such as cognition, mood, mobility, falls, nutrition, sensory impairment, ADLs, co-morbidities, medications, continence and pressure ulcers. It can be assessed by interviewing patients or informants at the bedside in combination with medical charts without necessary physical performance tests. FI can also be obtained retrospectively from charts and established databases. While the FI has been evaluated in several studies to date, it requires further validation to confirm whether and how frailty measured by FI predicts post-surgical outcomes and its utility as a bedside frailty measurement tool.

Reliance on performance based tests may be impractical in the acute surgical patients. More research into how frailty impacts on surgical patients in the acute setting and how best to measure frailty in acute surgical patients is needed. An instrument which is robust and valid for measuring frailty in elective patients in a surgical pre-admission clinic may not be applicable to the acute patients. Despite the need to find a unified tool for measuring frailty, it is possible that different frailty tools are best suited for different acuity and type of surgical patients. Furthermore, these instruments need to be time-efficient and suitable for application at the bedside by staff who are not geriatricians.As FI does not rely on physical performance tests and can potentially be applied to both acute and elective patients, the next chapter of the thesis aims to derive FI from routinely collected data in comprehensive geriatric assessments in both acute and elective surgical patients, and to explore whether FI at baseline is different from FI on admission in surgical patients.

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CHAPTER 3 BASELINE VULNERABILITY AND INPATIENT FRAILTY STATUS IN OLDER SURGICAL PATIENTS – A RETROSPECTIVE STUDY

Abstract

This study aimed to derive measures of baseline vulnerability and inpatient frailty in elderly surgical patients and to study their association with adverse post-operative outcomes. Data from comprehensive geriatric assessment of 208 general surgical and orthopaedic patients aged 70 and over admitted to four acute hospitals in Queensland, Australia, were analysed to derive a baseline and inpatient Frailty Index (FI). The association of these indices with adverse outcomes was examined in logistic regression. The mean (SD) baseline FI was 0.19 (0.09) compared to 0.26 (0.12) on admission, with a predominant increase in domains related to functional status. Both baseline and inpatient FI were significant predictors of one year mortality, inpatient delirium, and a composite adverse outcome, after adjusting for age, sex and acuity of surgery. In summary, detecting baseline frailty pre-hospitalisation may be useful to trigger the implementation of supportive and preventative measures in hospital.

3.1 Introduction

The systematic review in the previous chapter highlighted a shortage of studies on frailty in acute surgical patients, due to the nature that many frailty instruments rely on performance based tests which may preclude their application in those who are acutely unwell or bedridden due to the surgical diagnosis, for example hip fracture. Frailty index quantifies the degree of frailty in a continuum and can be generated either retrospectively from the medical chart or prospectively by patient interviews. It is advantageous in that performance based tests such as proximal muscle strength and hand grip strength are not compulsory in assessing frailty if they cannot be measured at the time of assessment. It is a potentially useful tool in both elective and acute surgical patients.

There is also a lack of literature on whether frailty should be assessed at baseline or at the admission to hospital; whether frailty at two time points are the same or different and which or both are associated with adverse outcomes. While frailty status may be the same at baseline and on admission to hospital for elective surgical patients, that for acute surgical patients is likely to be different. Previous studies on frailty and adverse outcomes in surgical patients had not specified whether frailty was assessed at baseline or on admission and sometimes they may be used interchangeably. While frailty was originally conceptualised as baseline vulnerability in community-dwellers [10, 60], the risk status of older people in the hospital setting has also been reported in terms of levels of frailty [47, 61]. It is intuitive that people will be more ‘frail’ during admission to hospital than in the pre-morbid period due to the impact of acute illness; yet the relationship between these two prognostic indicators and their association with adverse outcomes has been incompletely explored.

The aim of this retrospective study was to derive and evaluate baseline and inpatient frailty index in a cohort of older surgical patients.

3.2 Methods

3.2.1 Study design, participants and setting

This study was a secondary analysis of data collected for a prospective observational study [62], which recruited 493 patients aged $\geq$70 years admitted to general medical, surgical and orthopaedic wards of four acute hospitals in Queensland between 2008 and 2010. Experienced research nurses performed comprehensive geriatric assessments using the interRAI Acute Care (interRAI AC) instrument [63] within 48 hours of admission [62]. These assessments included data on demographics and health deficits on domains such as cognition, communication, mood and behaviour, activities of daily living, continence, nutrition, skin condition, falls, medical diagnosis, and medications. If a patient had surgery requiring a general anaesthetic within 36 hours of admission, the assessment was completed 72 hours following surgery [62]. This information was collected for the current state (in the first 24 hours of admission) and the premorbid period (pertaining to the three days prior to the onset of the acute illness). The premorbid or baseline health status was arbitrarily chosen in the interRAI instrument to be the health status three days prior to the onset of symptoms related to the acute illness, to reflect the most recent health status prior to acute illness leading to hospital admission. This definition of baseline was not based on previous research (no current research on how to define baseline health status) but aims to capture an older person's most recent health condition prior to the impact of the acute illness. Patients were followed up daily during their hospital stay, at 28 days and 12 months post discharge for adverse outcomes. Of the 493 patients, 214 patients were extracted from the database using inclusion criteria of having a "procedural date" or "admitted to a surgical or orthopaedic ward". After excluding six medical outliers, 208 surgical patients were included in the final analysis.

3.2.2 Measures

Frailty Index (FI)

Using a well-defined methodology [64], the inpatient FI was derived from the interRAI AC by summing health deficits across multiple domains and dividing it by the total number of deficits measured (56). The baseline FI was derived similarly by summing health deficits pertaining to the premorbid period divided by 54 (total items of deficits collected for this period). Medications related to inpatient hospital treatment and diagnoses recorded as the primary reason for admission were excluded when calculating the baseline FI.

Treatment received

Patients were categorised as being managed conservatively (no surgery or having a low risk procedure), or having surgery (acute or elective) by reviewing their primary diagnoses and the procedure undertaken.

Outcome Measures

Adverse outcome measures captured in the original prospective study available for analysis were in-hospital, 28 day and 12 months mortality, length of stay, discharge to a higher level of care, in-hospital falls, delirium diagnosed by a geriatrician and psychogeriatrician according to DSM IV criteria, functional decline, and hospital readmission within 28 days of discharge. A composite adverse outcome as an inpatient was constructed for patients who recorded a fall, delirium, discharge to a higher level of care or inpatient mortality.

3.2.3 Statistical analysis

Frequency distributions were used to describe the characteristics of the population. Correlation or comparison of means (or medians) tests were used to examine the association of baseline or inpatient FI with outcomes. Significant associations found in univariate analysis were tested in logistic regression models, adjusting for age, sex and acuity of surgery, and reported as an Odds Ratio (OR) with 95% Confidence Interval (CI). For logistic regression models, the FI was multiplied by 10 for ease of OR interpretation [16]. McNemar's test was used to examine which components of the FIs changed from the baseline to inpatient state. SPSS version 22 was used for statistical analysis.

3.2.4 Ethics Approval

Ethics approval was obtained from each participating hospital's Human Research and Ethics Committee and the University Medical Research Ethics Committee when the data were collected.

3.3 Results

The mean age of the study population was 79 years, with 59% being female and 45% receiving surgery (Table 3.1). The mean (SD) baseline FI in this cohort was 0.19 (0.09) while that for inpatient FI was 0.26 (0.12). Both FIs followed a normal distribution and were strongly correlated ($r=0.824$; $p<0.001$). Both FIs were moderately correlated with length of stay ($r=0.22$; $p <0.01$ and $r= 0.32$; $p<0.001$ respectively).

In univariate analysis, greater frailty both at baseline and as an inpatient was predictive of one year mortality, longer length of stay, inpatient delirium, discharge to a higher level of care, and a composite adverse outcome as an inpatient. Neither FI measure was predictive of inpatient mortality, inpatient falls, functional decline or readmission within 28 days of discharge. In logistic regression models, adjusting for age, sex and acuity of surgery, higher levels of both baseline and inpatient FI remained significant predictors of one year mortality, inpatient delirium, and a composite adverse outcome (Table 3.2).

Table 3.1 Patient demographics and clinical outcomes

Demographics, N=208	
Age (years)	
- Mean (SD)	79 (6)
- Median (IQR)	78 (73-84)
- Range	70-96
Gender, N, (%)	
- Male	86 (41%)
- Female	122 (59%)
Length of stay (days)	
- Median (IQR)	8(4-13)
Frailty index	
- Premorbid, mean (SD)	0.19 (0.09)
- Admission, mean (SD)	0.26 (0.12)
Treatment received	
Conservative management or procedure	114 (54.8%)
Surgery	94 (45.2%)
- Acute surgery	40 (19.2%)
- Elective surgery	54 (26.0%)
Mortality	
- In hospital	4 (1.9%)
- Additional deaths by 28 day follow up	4 (1.9%)
- Additional deaths by 12 months	37 (17.8%)
Admitted from	
- Community	189 (91%)
- Another hospital	1 (0.5%)
- RACF	18 (8.5%)
Discharge destination (N, %)	
- Community	158 (76.0%)
- RAC	17 (8.2%)
- Transfer to rehabilitation	21 (10.1%)
- Other (death, palliative unit, hospice)	12 (5.8%)

Adverse outcomes	
- Inpatient falls	10 (4.8%)
- Inpatient delirium	33 (16.2%)
- Discharge to a higher level of care excluding deaths	30 (14.7%)
- Length of stay ≥14 days *	49 (23.6%)
- Hospital readmission at 28 days	45 (22.3%)
- Composite adverse outcome as inpatient	58 (28.4%)

* Length of stay greater than the 75th percentile

RAC= residential aged care

Table 3.2 Logistic regression models for baseline FI, admission FI and outcomes†

	Baseline FI Odds Ratio (95% CI)	P value	Inpatient FI Odds Ratio (95% CI)	P value
1 year mortality	1.76 (1.19-2.59) ‡	0.004	1.69 (1.19-2.39)	0.003
Inpatient delirium	1.67 (1.09-2.56)	0.018	1.66 (1.13-2.45)	0.011
Composite Adverse Outcome	1.54 (1.00-2.37)	0.049	1.73 (1.19-2.51)	0.004

† Logistic regression models adjusting for age, sex and acuity of surgery.

‡ An odds ratio of 1.76 means that every increase of 0.1 in the premorbid FI is associated with 76% increased risk for 1 year mortality.

On McNemar's test, there is a significant increase in the deficits in activities of daily living items in the functional status domain from baseline to inpatient status ($p<0.001$) indicating a deterioration, as well as significantly increased medication count ($p<0.001$), increased need for modified diet ($p<0.001$), bowel incontinence ($p<0.001$), urinary incontinence ($p=0.028$) and report of pain ($p=0.049$), showing that the increased FI from baseline to inpatient status are contributed by these items. Cognitive domains and health condition domains (including falls, fatigue and dyspnoea) showed no significant increase in the number of deficits from baseline to inpatient status.

3.4 Discussion

This study showed that a frailty index derived from comprehensive geriatric assessment can be used to quantify deterioration in health status for elderly surgical patients on admission to hospital compared with their baseline vulnerability. Both baseline and inpatient FIs were predictive of one year mortality, inpatient delirium and a composite inpatient adverse outcome.

Baseline and inpatient FIs are distinctive, and the frailty index increases from baseline to admission due to increased functional dependence, incontinence and pain. Baseline and inpatient FIs are strongly correlated, suggesting that a person who is frail at baseline is more likely to be frail on admission. Measurement of frailty at both time points is important, as both are predictive of adverse short and long term outcomes. A person may be robust at baseline, however if a significant surgical illness, procedure or complication in an admission made them frail, this person still carries a risk of poor short and long term outcome.
To our knowledge, this study is the first to investigate the difference between baseline vulnerability and inpatient frailty status. Detecting frailty at baseline level pre-admission may be useful to trigger the implementation of supportive or preventative measures in hospital. This study also highlighted the importance of recognising frailty in older surgical patients in the inpatient setting as it is significantly associated with mortality and adverse post-operative outcomes.

Many studies have shown an association between frailty as measured by the cumulative deficit model and adverse post-surgical outcome. Krishnan et al found a 51 item frailty index to be predictive of increased inpatient and 30 day mortality and prolonged length of stay in hip fracture patients [51]. Similarly, Kenig et al found frailty as measured by the Groningen Frailty indicator and Balducci Frailty Criteria to be predictive of 30 day post-operative complications and mortality in older patients undergoing acute abdominal surgeries [65].

The main limitation of this study is the retrospective design. Because data were retrospectively examined, certain assumptions had to be made, such as excluding the acute medications related to the inpatient stay, and that no surgery was performed if there was no surgical date documented. The adverse outcome of interest in relation to frailty was limited to inpatient falls, delirium, mortality, length of stay, hospital readmission and discharge to higher level of care, as those were the outcomes previously determined in the original study. Other adverse outcomes, such as medical and surgical complications, could not be studied due to analysis being restricted to the data available in the existing dataset. The sample size was small and 55% of the subjects had conservative management, hence the impact of surgery on the adverse outcomes cannot be assessed and those who received and those who did not undergo surgery could not be analysed separately. A larger sample size may have detected a statistically significant association between frailty and other adverse outcomes not found in the current study. The retrospective study design did not allow comparison between the predictability of baseline versus inpatient FI; which is better at predicting adverse outcomes and whether one was better at predicting certain outcomes than the other.

Future studies could measure baseline and inpatient frailty prospectively to confirm their differences and relationship. If the role of baseline FI becomes established, it can be built into existing assessment tools and utilised in the community setting to aid clinical decision-making and inform risk stratification.

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Since both premorbid frailty and inpatient frailty statuses are important and predictive of poor outcomes, the next chapter of the thesis presents a prospective evaluation using a premorbid FI to assess its association with adverse outcomes in older surgical patients.

CHAPTER 4 FEASIBILITY OF FRAILTY INDEX IN PERI-OPERATIVE ASSESSMENT OF OLDER SURGICAL PATIENTS AND ITS ASSOCIATION WITH POST-OPERATIVE OUTCOMES – A PROSPECTIVE STUDY

Abstract

Increasing numbers of frail older adults are undergoing surgery. This study aimed to examine the feasibility of using a frailty index (FI) based on comprehensive geriatric assessment (CGA), termed FI-CGA, to assess the level of frailty in older surgical patients peri-operatively and evaluate the association of FI with adverse post-operative outcomes. 246 patients aged 70 years and over undergoing intermediate to high risk surgery in a tertiary hospital in Queensland, Australia, were recruited. Frailty was assessed using a 57-item FI-CGA form, with fit, intermediate and frail patients defined as FI $\leq$0.25, >0.25-0.4, and >0.4 respectively. Adverse outcomes were ascertained peri-operatively and at 30 days and 12 months post-surgery. Logistic regression models assessed the relationship between FI and adverse outcomes, adjusting for age, gender and acuity of surgery. Mean age of the participants was 79 years (SD 6.5), 52% were female, 91% were admitted from community, 43% underwent acute surgery, and 19% were frail. FI-CGA is a feasible tool for frailty assessment in surgical patients, especially if it can be derived from routinely collected data. There were no statistically significant differences between fit, intermediate and frail groups in peri-operative (17.4%, 23.3%, 19.1% for fit, intermediate frail and frail patients p=0.577) and 30 day post-operative complications (35.8%, 47.8%, 46.8% p=0.183), which may have been a reflection of insufficient sample size. However, greater frailty was associated with increased 12 month mortality (6.4%, 15.6% and 23% for fit, intermediate frail and frail patients, p=0.01) and 12 month hospital readmissions (33.9%, 48.9%, 60%, p=0.004). Using FI-CGA peri-operatively may identify patients at high risk of poor long term outcome.

4.1 Introduction

Population ageing has led to increasing numbers of older patients undergoing surgery [5, 66]. Many of these patients are frail, manifesting as deficits in one or more domains of physical and mental function and homeostasis. Frailty increases with age, and is associated with decreased survival, increased hip fractures, hospitalizations and institutionalization [18, 19, 67]. Depending on how frailty is defined and measured, prevalence varies from 4%-59%, with a weighted average of 10.7%[17].

Emerging evidence suggests an association between frailty in surgical patients and post-operative mortality and morbidity [20, 21, 68]. The systematic review in chapter two of the thesis found 10 studies demonstrating association between greater frailty and increased mortality rates at 12 months, although associations with other short term outcomes such as 30-day post-operative complications varied between studies. These findings have implications for informed consent for surgical procedures, choice of anaesthesia, pain management, and rehabilitation post-surgery [23, 24]. However, tools for measuring frailty that is brief, time efficient, valid and practical for clinical application at the bedside are lacking, and none have been developed for predicting post-operative outcomes. Frailty assessment is additional and complementary to the current surgical risk prediction tools [69, 70].

The phenotypic measure of frailty developed by Fried *et al* comprises three or more of the following five features: slowness, weakness, exhaustion, weight loss and low physical activity [10]. Although widely cited, Fried criteria does not consider cognitive and psychosocial aspects of frailty, and is reliant on patients undergoing tests of physical performance. To date, such testing has not been applied to older acute surgical patients who may be in pain, bed bound or otherwise unable to perform physical tests.

The commonly used Frailty Index (FI) developed by Rockwood *et al* is based on the cumulative deficit model which views frailty as a multidimensional risk state quantified by the number of health deficits rather than by the nature of the health problems [15]. The FI is calculated by dividing the number of deficits present in an individual by the total number of possible deficits measured across broad health domains, such as medical co-morbidities, physical and cognitive impairments, psychosocial risk factors and common geriatric syndromes [15]. The FI assumes values between zero (no frailty) and one (extreme frailty) [15].

The FI has been generated from comprehensive geriatric assessment (CGA) [71], and the ability of this FI-CGA method (Frailty Index derived from Comprehensive Geriatric Assessment) to predict adverse outcomes has been validated in acute hospitalised patients [71, 72] and outpatients with chronic kidney disease [73]. Accordingly, it may serve to assess the degree of frailty and predict risk of adverse outcomes in surgical patients in the peri-operative setting.

The aims of this study were to investigate the feasibility of using FI-CGA in the peri-operative setting and evaluate whether a higher FI was associated with higher risk of several short and long term adverse outcomes.

4.2 Methods

4.2.1 Study design, setting and participants

This prospective cohort study conducted in a tertiary hospital in Queensland, Australia, between July 2014 and January 2015 recruited patients aged 70 years and over who were planned to undergo, or had undergone within the previous ten days, intermediate or high risk surgery as defined by established guidelines [74] (See Appendix B). Exclusion criteria were those having low risk surgery (such as superficial procedures and cataract surgery) and/or unable to speak English with no interpreter available. Preadmission clinic patient lists were screened for eligible elective surgical patients, while the admission lists from the emergency department and inpatient lists from the surgical wards were screened for eligible acute surgical patients. Four data collectors, comprising two senior medical registrars (HL and DV) and two medical students (JM and MN), shared a roster to approach eligible patients pragmatically on a daily basis to obtain consent. Time constraints precluded every eligible patient from being approached or consented. Legally authorized substitute decision makers provided consent for patients lacking capacity. Patient information and consent forms are included in Appendix C.

4.2.2 Measurement of frailty and operative risk

Consenting participants were interviewed by data collectors using a previously designed and validated one-page FI-CGA form [71] (form included in Appendix D). Data collectors underwent a one hour training session on how to assess frailty using the form prior to study commencement, with several sessions within three weeks after study commencement discussing and resolving any further queries. Data was captured and coded on health deficits at baseline comprising self-rated health, cognition, communication, mood and behaviour, social engagement, activities of daily living (ADLs), continence, nutrition, falls, mobility, polypharmacy and medical comorbidities. ADLs were self-reported and pertained to the period before the onset of the surgical diagnosis. Information from medical notes and patients' next of kin supplemented patient interviews.

The FI was calculated for each patient by dividing the total number of reported deficits by the total number of deficits assessed (maximum 57 items). In the case of items unable to be assessed, the denominator was recalculated as 57 minus the number of missing items, with precision being acceptable if the total deficits in the denominator were 30 or more [75]. Patients were categorized into fit (FI $\leq$0.25), intermediate frail (FI $>$0.25, $\leq$0.4) and frail (FI$>$0.4) using previously validated FI cut-offs [76].

Traditional pre-operative risk stratification tools comprising the American Society of Anaesthesiologists (ASA) physical status classification [77] and Lee's revised cardiac risk index [78] were also collected for each participant.

Feasibility of the FI-CGA tool was evaluated according to three aspects: its practicality, acceptability, and implementation/adaption. With regards to practicality, time taken for the tool application, time taken for the training and feedback from the four assessors regarding its ease of use was assessed. With regards to acceptability, qualitative feedback from the assessors of whether the tool was acceptable was sought, as well as the number of refusal and reasons for refusal by patients. With regards to implementation and adaption, proportion of missing data and the completion rate of FI-CGA was assessed.

4.2.3 Outcome variables

Outcomes of interest were listed below:

- Peri-operative adverse events (occurring during surgery or in the immediate post-operative period in recovery room): transfusion of blood products (any of packed red blood cells, platelets, fresh frozen plasma, or cryoprecipitate), unplanned return to operating theatre (OT), unplanned admission to the intensive care unit (ICU), surgical complications (such as bowel perforation, peri-prosthetic fracture), new arrhythmia, hypotension requiring treatment, massive blood loss, and new onset delirium as documented by treating clinicians in the medical record.
- Post-operative complications within 30 days of surgery: any major cardiac events (cardiac arrest, acute myocardial infarction, complete heart block, congestive heart failure, pulmonary oedema, and arrhythmia), venous thromboembolism, sepsis, pneumonia, wound infection, stroke, acute kidney injury, transfusion of blood products, delirium, unplanned return to OT, unplanned ICU admission or death.
- Post-operative disposition outcomes: prolonged length of stay in acute care (longer than the 75th percentile), new discharge to residential aged care (RAC), unplanned hospital readmission within 30 days of surgery.
- Deaths within 12 months of surgery (inclusive of deaths within 30 days of surgery)
- Unplanned hospital readmissions within 12 months of surgery (inclusive of readmissions within 30 days of surgery)
- Composite 12 month adverse outcomes: deaths or unplanned hospital readmission within 12 months of surgery.

Outcomes were ascertained from electronic medical records (for in-hospital events) and by telephone call (for post-discharge events) at 30 days. Patients un-contactable by telephone were sent a follow up letter for reporting any complications up to 30 days. Death and hospital readmission between 30 days and 12 months post-surgery were ascertained from medical records and Queensland death registry.

4.2.4 Statistical analysis

Assuming the proportions of frail (FI >0.25) to fit (FI≤ 0.25) patients were 1:1, a sample size of 250 patients was estimated as providing 90% power in detecting a twofold difference in adverse outcomes between frail and fit patients, assuming 10% loss to follow-up. This was based on published data from 208 surgical patients within a cohort of 1418 inpatients aged >70 where the prevalence in the fit group of a composite adverse outcome of inpatient fall, delirium, discharge to higher level of care and death was 20% [79].

Distributional statistics comprised proportions for categorical variables, means and standard deviation for normally distributed continuous variables and medians and interquartile range for non-normally distributed continuous variables. Patient characteristics and outcomes were compared according to frailty status (fit, intermediate frail and frail) using ANOVA for continuous variables and Chi-Square tests for categorical variables. Adverse outcomes that varied significantly in frequency between groups in univariate analysis were entered into a logistic regression model that adjusted for confounders (age, gender and whether surgery was acute or elective) and risk of outcomes at specific time points was expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Subgroup analyses compared adjusted mortality and hospital readmission rates at 12 months between acute and elective surgery patients. Significance levels were set at $p<0.05$ and all analyses were performed using IBM SPSS Version 23.0 (Armonk, NY).

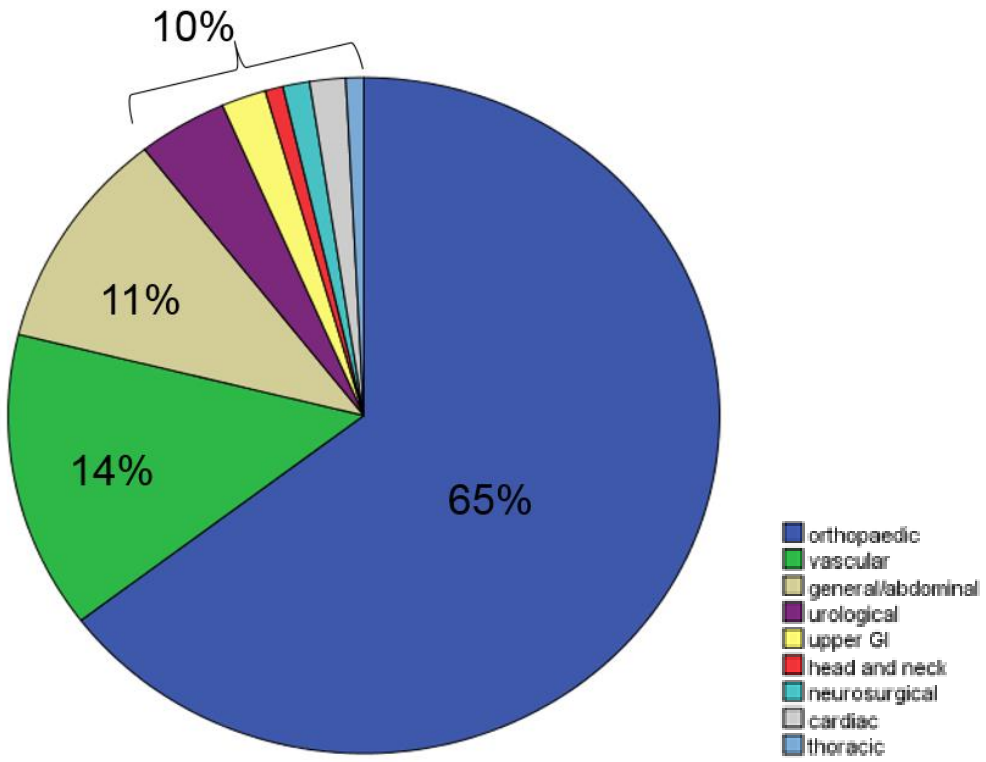
4.2.5 Ethics approval

Approval was granted by the hospital Human Research and Ethics Committee and Site Governance (HREC/14/QPAH/215 and SSA/14/QPAH/216). Ethics and site specific approval are attached in Appendix E.

4.3 Results

Of 267 screened patients, six refused participation and 15 demonstrated exclusion criteria. Reasons for refusal were subjective fatigue and feeling unwell post-surgery (2), limited English language communication (3), and previous negative experience with research (1). 246 participants were included in the final analysis, with a mean age of 79 (SD 6.5) years and mean FI of 0.29 (SD 0.14, range 0.04 to 0.74). Baseline characteristics of the participants are shown in Table 4.1. Almost half (43%) underwent acute surgery; 65% underwent orthopaedic surgery, 14% vascular surgery, and 11% abdominal surgery. Distribution of the types of surgery which the participants underwent is shown in Figure 3. The majority (73%) had an ASA classification of three or four representing severe or incapacitating systemic diseases. Compared to fit and intermediate frail patients, frail patients were older, more likely to have ASA class of three or more, more likely to undergo acute surgery and more likely to be admitted from a residential aged care facility (Table 4.1).

Figure 3. Distribution of types of surgery in study participants



Ascertainment of 30-day and 12 month outcomes was complete in 98% and 100% of participants respectively. Mean length of stay in acute care was 8 days (SD 7 days). Perioperative adverse events occurred in 49 participants (20%), and 30 day postoperative complications occurred in 104 (42%). Thirteen patients (5.3%) were discharged to RAC having been admitted from home. (Table 4.2) At 12 months, 32 participants (13%) had died while 110 (44.7%) had unplanned hospital readmissions (Table 4.2).

Table 4.1 Baseline characteristics

	Total N=246	Fit n=109 (44.3%)	Intermediate frail n=90 (36.6%)	Frail n=47 (19.1%)	p value
Mean age (SD)	79 (6.5)	77 (6)	79 (6)	81 (7.6)	0.002
Female gender, n (%)	128 (52)	46 (42.2)	55 (61.1)	27 (57.4)	0.021
Mean FI (SD)	0.29 (0.14)	0.17 (0.05)	0.31 (0.04)	0.52 (0.10)	<0.001
ASA classification $\geq$3, n (%)	179 (73.7)	67 (62.6)	70 (77.8)	42 (91.3)	0.001
Revised Cardiac Risk index $\geq$2, n (%)	44 (17.9)	15 (13.8)	17 (18.9)	12 (25.5)	0.202
High risk surgery, n (%)	20 (8.1)	13 (11.9)	5 (5.6)	2(4.3)	0.181
Acute surgery, n (%)	105 (42.7)	38 (34.9)	41 (45.6)	26 (55.3)	0.047
Admitted from home, n (%)	224 (91.1)	108 (99.1)	82 (91.1)	34 (72.3)	<0.001
Admitted from RAC, n (%)	21 (8.5)	0 (0)	8 (8.9)	13 (27.7)	<0.001

RAC=Residential Aged Care; ASA=American Association of Anaesthesiologists.

Table 4.2 Adverse outcomes

	Total N=246	Fit n=109	Intermediate frail n=90	Frail n=47	p value
Peri-operative adverse events, n (%)	49 (19.9)	19 (17.4)	21 (23.3)	9 (19.1)	0.577
Postoperative complications at 30 days, n (%)	104 (42.3)	39 (35.8)	43 (47.8)	22 (46.8)	0.183
Unplanned hospital readmission within 30 days, n (%)	26 (10.6)	11 (10.1)	10 (11.1)	5 (10.6)	0.973
Prolonged length of stay in acute care (>75th percentile), n (%)	69 (28)	34 (31.2)	20 (22.2)	15 (31.9)	0.302
New discharge to RAC, n (%)	13 (5.3)	1 (0.9)	7 (7.8)	5 (10.6)	0.009
Mortality at 12 months, n (%)	32 (13)	7 (6.4)	14 (15.6)	11 (23.4)	0.010
Unplanned hospital readmission within 12 months, n (%)	110 (44.7)	37 (33.9)	44 (48.9)	29 (61.7)	0.004
Composite 12 month adverse outcomes, n (%)	124 (50.4)	40 (36.7)	50 (55.6)	34 (72.3)	<0.001

RAC=Residential Aged Care

4.3.1 Feasibility of FI-CGA

The FI-CGA form was acceptable on interview with the four data collectors who applied the FI-CGA in the study participants. This tool was also acceptable and well received by patients, with a low rate of refusal (2.2%). In terms of practicality of the tool, the average time taken to complete the form was 12.5 minutes (SD 4.1, range 5-30 minutes)in 175 assessments sampled (71% of all assessments). The FI-CGA form was self-explanatory, and the training involved before its use was one hour. In the feedback from the four data collectors, the majority of items on the FI-CGA form were easy to rate, However items such as motivation can be difficult to elicit from participants, and grip strength assessment can be subjective without a dynamometer. Inter-rater reliability was not assessed in this study due to time restraint.

The completion rate of the FI-CGA forms was 45%, with the majority (91%) of the incomplete forms having minimal amount of data missing – fewer than four items. The form with the highest number of missing data (11 out of 57 health deficits could not be assessed) still had a denominator of 46 which was sufficient for deriving a valid FI. The rate of missing data was highest for proximal muscle strength (36.6%) where the patient was asked to rise from a chair without the help of arms, which may not be possible with post-operative states or surgical diagnoses such as hip fractures. Other variables associated with missing data were self-rated health (8.9%), motivation (8.5%) and grip strength (8.5%), which relied on the cooperation of participants. Answers to these items may be precluded by dementia or delirium, as opposed to items obtainable from next of kin. All other domains had less than 3% missing data.

4.3.2 Association of frailty with adverse outcomes

There were no statistically significant differences between the fit, intermediate frail and frail participants in the incidence of peri-operative adverse events, 30 day postoperative complications or post-operative disposition outcomes. (Table 4.2) However, there is a significant relationship between frailty and 12 month mortality (6.4%, 15.6% and 23% for fit, intermediate frail and frail patients, p=0.01), 12 month hospital readmission (33.9%, 48.9%, 60%, p=0.004) and new discharge to RAC (0.9%, 7.8%, 10.6%, p=0.009).

Applying logistic regression methods, every 0.1 increase in FI was associated with 36% greater odds of death at 12 months (OR 1.36 [95% CI 1.04-1.79], p=0.026), 53% greater odds of unplanned hospital readmission at 12 months (OR 1.53 [95% CI 1.24-1.90], p<0.001) and 68% greater odds of either death or readmission combined (OR 1.68 [95% CI 1.34-2.10], p<0.001). Frailty was not associated with new discharge to RAC in logistic regression after adjusting for confounders.

Subgroup analyses of acute versus elective patients revealed that the rise in 12 month mortality with increasing frailty was greater among the former (OR 1.49 [95%CI 1.03-2.15] for every 0.1 increment of FI), but no significant association was seen between mortality and FI in elective patients. In contrast, the rise in unplanned 12 month readmissions with increasing frailty was seen in both acute (OR 1.37 [95%CI 1.03-1.83]) and elective patients (OR 1.89 [95%CI 1.34-2.66]) with the effect being greater among the latter.

4.4 Discussion

4.4.1 Key results

This study investigated the feasibility of using FI-CGA in the peri-operative setting and evaluated the association between FI and incidence of adverse peri-operative, post-operative and longer term outcomes. In regards to feasibility, while the FI-CGA form was acceptable and easy to use, with low rate of missing data, the requisite one hour training period and the time to complete it (12 minutes on average) may limit its application in busy surgical wards and preadmission clinics.

Our results indicate that higher levels of frailty were associated with higher rates of death and unplanned readmissions at 12 months, with a 68% increase in this combined end-point for every 0.1 increase in FI. However, somewhat counterintuitively, frailty was not associated with peri-operative (17.4%, 23.3%, 19.1% for fit, intermediate frail and frail patients p=0.577) and post-operative complications at 30 days (35.8%, 47.8%, 46.8% p=0.183), nor disposition outcomes (hospital readmission within 30 days, length of stay and new discharge to RAC).

4.4.2 Strengths and limitations

To our knowledge, this is the first study that has assessed the feasibility of using FI-CGA in acute and elective surgical patients. Study strengths were the targeting of older patients undergoing either acute or elective surgery (most studies only include the latter), prospective data collection, assessment of multiple domains of physiological and functional reserve, low rates of missing data, and multiple end-points up to 12 months. Study limitations include small sample size which may have underpowered analyses of associations between frailty and adverse outcomes occurring peri-operatively and at 30 days post-operatively. The power calculation was based on a two-fold difference in adverse outcomes between fit and frail participants; however, in our cohort there was only a 1.5 fold increase, hence a bigger sample size would be required to show an association. While our sample is representative of older Australians undergoing intermediate and high risk surgery, our results may not apply to those under 70 years old and those undergoing low risk surgery.

4.4.3 Feasibility of using FI-CGA

The FI-CGA tool was found to be an acceptable tool both for the assessors and for participants. It is easy to use, however may not be practical for using at bedside in busy surgical wards and clinics as it requires on average twelve minutes to complete. Despite 55% of the assessments not being 100% completed, the number of missing fields in the incomplete assessments was very small, which would not affect its implementation and adaption in clinical practice. Despite not being able to measure performance based tests (such as proximal muscle strength or grip strength) or self-rated items in some acutely unwell surgical patients, sufficient data was obtained from the next of kin and the medical chart to generate a valid FI, making this tool applicable to both acute and elective surgical patients.

Barriers to implementing the FI-CGA in routine clinical practice were the time involved to conduct a single assessment and the labour and time intensive process in manually entering the data from paper assessment forms into an excel spreadsheet to generate the FIs. These can be overcome by building FI-CGA into the electronic medical records and generating FIs from routinely collected data using automated methods.

Other tools based on comprehensive geriatric assessment trialled in surgical patients include Balducci Frailty Criteria [40] used in oncology surgery, and a 51 item frailty index [51] applied to hip fracture patients. Whilst not specifically stated in their respective studies, these tools will likely take as long as FI-CGA. Brief tools such as the 7-point clinical frailty score (derived from visual observations combined with review of medical records) [45], G8 and Vulnerable Elder Survey (VES) [46] would take less time to perform and be potentially more practical, but are less comprehensive than FI-CGA. A very recent study describes a frailty score (Risk Analysis Index) consisting of a two-minute nursing survey combined with routinely collected medical information that was validated in a cohort of surgical patients [80] who were considerably younger than our cohort (mean age 60.7 ± 13.9 versus 79.0 ± 6.5 years).

4.4.4 Association between frailty and adverse outcomes

The significant association between higher levels of frailty and higher rates of death and readmissions at 12 months seen here confirms the findings of other investigators. The systematic review in chapter two of the thesis found that a significant association between frailty (variously defined) and long term 12 month mortality [68]. However, only two studies evaluated the association with 12 month unplanned readmissions, which was confirmed in one. Only four out of nine studies which measured post-operative complications found a significant association with frailty [68] which suggests our failure to confirm this relationship is in keeping with the majority of evidence. It is possible that frailty reflects a baseline vulnerability which leads to poorer long term outcomes with less effect on short term outcomes, which are more influenced by the acuity of the underlying illness and the level of invasiveness of the surgery.

Frailty being associated with poorer longer term outcomes may have clinical implications. Early identification of at risk elders undergoing surgery followed by early mobilisation and early detection and management of geriatric syndromes may prevent de-conditioning and consequential poor long term outcomes. In elective surgery, pre-operative assessment of frailty may help identify those at risk of poorer long term outcomes who could then be better informed of this risk and who, in response, may elect to adopt more conservative management aimed at symptom management and improving quality of life.

We found no significant relationship between frailty and prolonged length of stay in acute care and new discharge to RAC on multivariate analysis, which is contrary to other studies. In the systematic review in this thesis, five out of six studies which evaluated prolonged length of stay showed a significant association with frailty, and two out of two studies showed an association between frailty and discharge to RAC [68]. As institutionalisation could be the most undesirable outcome for some older patients, confirming the relationship between frailty and this outcome in future studies will enable discussion around the risk of institutionalisation post-surgery and result in better informed consent.

4.4.5 Future directions

The associations between FI and adverse outcomes observed in this study as well as frailty being a predictor of poor long term outcomes need to be replicated in future studies involving larger surgical cohorts, including sub-cohorts of specific surgery types, prior to its use as a validated predictive tool for informing patients and surgeons of long term outcomes in relation to individual frailty status. Future studies could investigate how to build FI-CGA into digital hospital systems in optimising its efficient use and enabling it to be used for large scale frailty screening in surgical patients. Interventional studies are necessary to demonstrate whether prehabilitation or geriatrician input before surgery for optimisation could improve frailty and reduce postoperative outcomes.

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CHAPTER 5 OVERALL CONCLUSION

5.1 Summary of Findings

Frailty is a syndrome of decreased physiologic reserve and resistance to stressors. As the population ages, more frailty is seen in older adults undergoing surgery. There has been a surge of published literature in the last 5 years examining the impact of frailty on adverse outcomes. In the systematic review, 23 studies examined the relationship between frailty and adverse outcomes in surgical patients with a mean age of 75 and above. The strongest evidence was found for associations with increased mortality at 30 days, 90 days and one year from surgery, post-operative complications and length of stay. A small number of studies found associations between frailty and discharge to institutional care, functional decline and lower quality of life after surgery. Of the numerous frailty measures, frailty index was an instrument which can be potentially applicable to both acute and elective surgical patients.

In the retrospective study, FI increased from baseline to inpatient status, showing that these two are distinct entities and the increased frailty as an inpatient is contributed mainly by increased functional dependence. This study was not able to quantify the impact of acute illness, the severity or type of surgery which may also contribute to the increase in FI on admission. Both baseline and inpatient FI were predictors of one year mortality, inpatient delirium, and a composite adverse outcome (consisting of inpatient falls, delirium, discharge to a higher level of care or inpatient mortality), after adjusting for age, sex and acuity of surgery. Frailty assessed at either time point is valid and useful in predicting adverse outcomes.

In the prospective study, FI-CGA was applied to 246 surgical patients aged 70 years and over undergoing intermediate to high risk surgery. FI-CGA although time consuming and labour intensive, was an acceptable tool to patients. Greater frailty was associated with increased 12 month mortality (6.4%, 15.6% and 23% for fit, intermediate frail and frail patients, $p=0.01$) and 12 month hospital readmissions (33.9%, 48.9%, 60%, $p=0.004$), however there were no statistically significant differences in the peri-operative and 30 day post-operative complications.

5.2 Strengths and Weaknesses

This thesis reviewed and summarised the large body of evidence in frailty and adverse outcomes in older surgical patients, with a particular focus on the "older-old" and the "oldest old". This is valuable and relevant because this group of patients are the most susceptible to adverse outcomes post-surgery and the most in need of frailty assessment. This review outlined the instruments which had been used in this older population and was comprehensive in summarising the various adverse outcome endpoints in both acute and elective patients. This thesis is also novel in exploring whether frailty status differs between baseline status and on admission to hospital and demonstrated that frailty measured at both time points is associated with post-operative adverse outcomes. The application of FI-CGA tool in older surgical patients was a pragmatic trial assessing its suitability for usage clinically at bedside. The endpoints collected for assessment of association with frailty were comprehensive and inclusive of both short and long term outcomes.

One of the limitations of this thesis is that meta-analysis of the selected studies in the systematic review could not be conducted due to the heterogeneity of the study populations, frailty instruments and outcome measures; hence the effect size of the impact of frailty on adverse post-operative outcomes could not be established. In order to obtain the effect size, smaller subsets of studies using the same frailty instrument and measuring the same outcome of interest will need to be selected. Out of those articles for the "older-old" and the "oldest old", the number of articles on one instrument measuring comparable outcomes was insufficient for this analysis. It was also out of the scope of this systematic review to synthesise the evidence in the literature in the "younger-old" frail population, however an attempt was made in listing out these studies and the main findings (included in Appendix A). In addition, single markers for frailty such as inflammatory markers, gait speed alone, or psoas muscle size were not evaluated, as frailty in this thesis is viewed in the multi-dimensional approach. Neither were traditional risk predictive tools reviewed, such as EuroScore, STS score (Society of Thoracic Surgeon) or APACHEII (Acute Physiology And

Chronic Health Evaluation). How effective or useful these traditional tools or single markers of frailty are for predicting adverse outcomes in older surgical patients and how they compare with the multi-dimensional frailty tools need further evaluation.

The retrospective study was limited by the quality of the data which was collected for a study with other aims. The conclusions are based on certain assumptions and would need prospective studies to confirm. The prospective study was limited by time and resource constraints, where the data collectors were not full time researchers but collected data in addition to their clinical and academic duties and for a limited data collection period of seven months. Hence convenience sampling was used and not every eligible patient could be recruited. The sample size might have under-powered the analysis between frailty and the short term adverse outcomes. Because of the small window of opportunity for seeing acute surgical patients before surgery, the frailty assessment on these patients occurred mainly after surgery, which introduces possible recall bias when reporting their baseline frailty status. Testing inter-rater reliability of the FI-CGA tool is needed but was beyond the scope of this study.

5.3 Clinical Application

Recognition of the importance of frailty in surgical patients is reflected in the rapid emergence of publications on this topic over the past five years. There is strong evidence that frailty leads to poorer outcomes in surgical patients, however the lack of a unifying tool which is time-efficient and practical for measuring frailty has limited its current usage in surgical pre-admission clinics. Detection of frailty at baseline in surgical preadmission clinics and detection of frail patients after acute surgery could aid identification of high risk patients with potential poor outcomes. Instituting supportive and preventative measures during their hospital admission may optimise their outcomes.

The frail elderly surgical patients would benefit from early recognition and treatment of surgical complications, post-operative infections, monitoring of adequate hydration and nutrition, and early mobilisation and rehabilitation to prevent de-conditioning [22]. Evaluation of cognition which is not currently a routine practice but part of frailty assessment could also lead to preventive measures to decrease the incidence of post-operative delirium. Surgical patients at high risk of post-operative delirium would benefit from multi-disciplinary team input, early mobilisation, sleep hygiene, avoidance of restraints, adequate nutrition, fluids, oxygen and adequate pain control while minimising use of opioids [81]. Many of these strategies have been incorporated into the optimal perioperative management of the geriatric patient practice guidelines from the American College of Surgeons [82].

Older people presenting with hip fractures are some of the frailest surgical patients [83]. The ortho-geriatric care model where patients are co-managed by geriatricians and orthopaedic surgeons has led to reduced mortality [84] and has now become the standard of care in most first world countries. Several service improvement models have also been developed and trialled in elective surgical patients, such as the 'POPS' (proactive care of older people undergoing surgery) [85] and the PSH (perioperative surgical home) [86, 87] with a focus on coordinated, multi-disciplinary and patient-centred care. The latter model however is led by anaesthetists and has not yet incorporated geriatric assessment. ERAS (Enhanced Recovery After Surgery) protocols have several components addressing frailty, such as optimisation of nutrition pre-operatively and early mobilisation post-operatively, however may not address all components of frailty such as cognitive impairment [88]. In a systematic review, pre-operative comprehensive geriatric assessment (CGA) has also been shown to improve post-operative outcomes such as complication rate and length of stay [89]. A recent randomised controlled trial of elective vascular surgical patients aged 65 years or older showed that preoperative CGA and optimisation was associated with a shorter length of hospital stay, fewer complications and were less likely to be discharged to a higher level of care [90]. Similarly, a cluster randomised controlled trial of a Hospital Elder Life Programme with orientating communication, nutritional assistance and early mobilisation in 577 elective abdominal surgical patients showed reduced rates of delirium and length of stay [91]. Another prospective cohort quality improvement project involving 9153 patients showed that widespread frailty screening preoperatively reduces mortality. FI-CGA validated in our study has great potential to be used for frailty screening in surgical patients.

For elective surgical patients, prehabilitation or reversal of frailty may make them a fitter candidate for surgery. Studies have suggested that prehabilitation before surgery with a multimodal programme consisting of exercise training and nutritional and psychological support may lead to better functional capacity post-operatively than rehabilitation after surgery [92, 93]. A systematic review of pre-operative exercise intervention in cancer patients showed significant improvement in the rate of incontinence, functional walking capacity and cardiorespiratory fitness [94]. A pilot study of health coaching and wellness plans through the Community Actions and Resources Empowering Seniors (CARES) model showed that this initiative decreases frailty status in the primary care setting [95]. In a very small cohort study of frail lung cancer patients (n=14), preoperative high intensity training program could reduce post-operative complications [96]. In frail pre-transplant patients, prehabilitation through fitness based interventions with wearable fitness tracking devices can mitigate frailty and decrease length of hospital stay and post-operative complications [97]. More large scale intervention studies on frailty in pre-operative patients are needed to confirm its effectiveness in reducing morbidity and mortality.

Knowing surgical patients' frailty status is also highly essential in communication with patients, families and in informed consent. Explaining the higher risk of post-operative outcomes will pre-empt potential adverse outcomes and give patients and families realistic expectations after surgery. Those who are extremely frail may accept the high risk of morbidity and mortality while undergoing a palliative surgery with the goal of improved quality of life, however they may wish to opt for conservative treatment over a curative surgery, which may treat a disease but not necessarily improve life quality after surgery. Risk of discharge to a residential care facility and not being able to maintain independence post-surgery can be a significant adverse outcome for many older patients and their decision to receive surgical treatment may change if this risk is disclosed and discussed pre-operatively.

5.4 Evolution of the Field

Since the commencement of this MPhil, publications in frailty and perioperative outcomes have surged. In Figure 4, the arrow indicates when the literature search was conducted for this the systematic review in chapter 2 of the thesis and the number of subsequent publications. Frailty intervention trials are also increasing, although the numbers are small compared with the number of studies evaluating the relationship between frailty and adverse peri-operative outcomes.

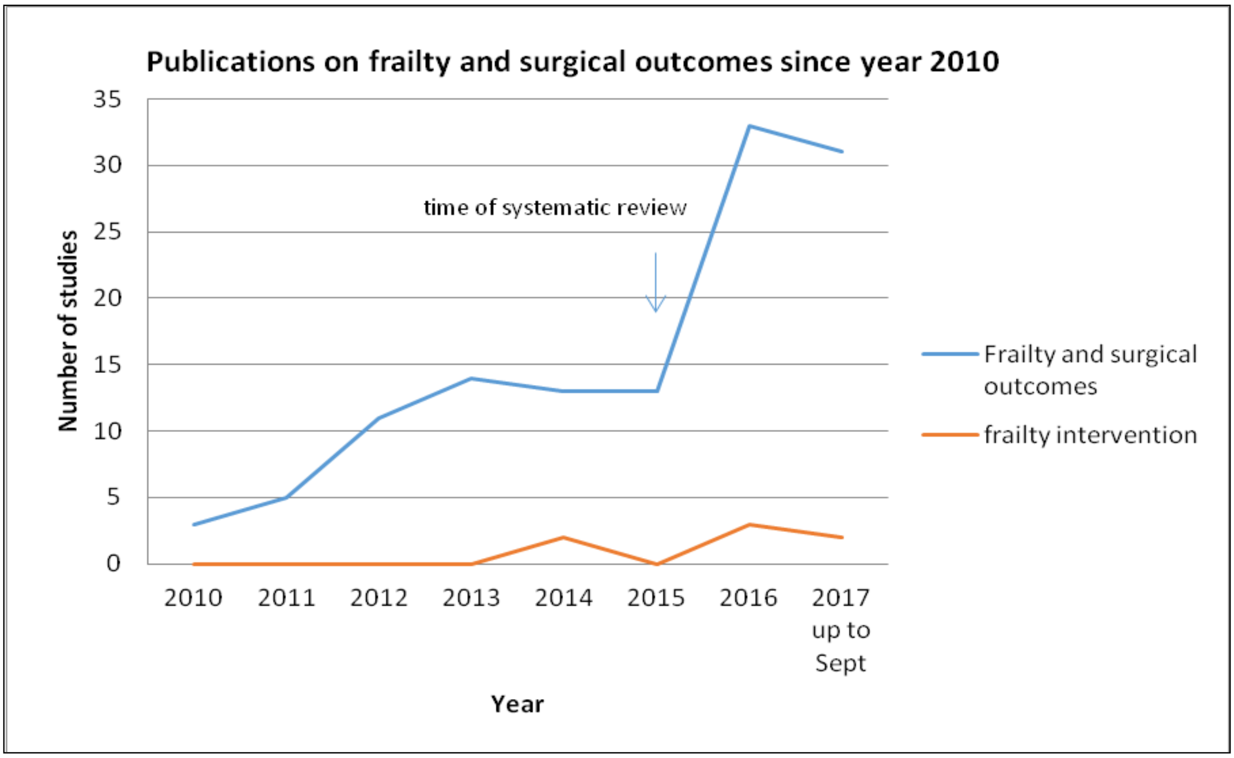

Figure 4. Publications on frailty, surgical outcomes and frailty interventions since year 2010

Appendix F summarises the study population, surgical types and main findings from studies which examined the relationship between frailty and surgical outcomes published after January 2016 not included in the systematic review. The majority of the studies are in the “younger old” population (mean age of the study populations ranged from 60 to 75 years) with several studies involving populations with a mean age in the fifties. There are a large number of studies (n=24) evaluating modified frailty index (mFI) retrospectively in various surgical subspecialties in relation to adverse outcomes using the ACS NSQIP (American College of Surgeons National Surgical Quality Improvement Program) database. The mFI was derived from mapping the deficits captured by NSQIP database with the 70 items studied in Canadian Study of Health and Aging (CSHA). The 11 deficits in the mFI encompassed domains of functional status, impaired sensorium, cardiovascular co-morbidities, COPD and pneumonia. The mFI has different cut off values in different studies for the definition of frailty; some studies also used the number of deficits out of 11 to define frailty rather than an index. Even though mFI is the most frequently evaluated and published tool to date, it heavily relies on medical co-morbidities to determine frailty, does not incorporate cognitive impairment and has not been validated in prospective studies as a bedside screening tool. In elective cardiac surgery, Fried criteria and its variation are the most commonly tested tools, while in non-cardiac surgery, the cumulative deficit model and tools which can be incorporated into medical records and routinely collected data seem to be gaining popularity.

5.5 Future Direction and Research

As the surgical population is heterogeneous, future reviews focusing on each single surgical sub-speciality or focusing on similar frailty tools and adverse outcomes will allow meta-analysis to quantify the risks and calculate the predictive value of the tools. The optimal time point for assessing frailty requires further study. Our results of screening frailty at baseline and on admission being equally valid require confirmation by larger prospective studies. Future research could also investigate whether building the FI-CGA into electronic medical records would reduce its assessment time. Finally, further research comparing the frailty index, its optimal cut off value and its predictability with that of the other frailty instruments as well as traditional risk assessment tools in surgical patients will help identify the best instrument for frailty screening. The ultimate goal would be to find a tool which is universal, time efficient and applicable to all surgical patients regardless of whether surgery is acute or elective and regardless of the type of surgery.

Not only is detection of frailty important but also the management and intervention of frailty where a paucity of evidence lies. A large amount of work is urgently needed to determine whether pre-operative intervention on frailty improves post-operative outcome and whether knowing surgical patients' frailty status alters clinical decision making by surgeons and anaesthetists.

5.6 Personal Reflection

My MPhil study has equipped me with a wide range of new research skills. I have learnt how to conduct a systematic review including comprehensive literature search, critically looking at the quality of studies, assessing risk of bias, and synthesising evidence. I have acquired skills in data handling and basic analysis using the SPSS statistical program and have attended bio-statistical teaching sessions. I have become proficient in EndNote and sharpened my skills in scientific writing by attending an eight week Academic writing course. I have experienced working with researchers from other disciplines, such as Anaesthesia and Internal Medicine, where I learnt the leadership skills needed to co-ordinate a study involving multiple investigators. The learning processes which I have passed through in the production of the thesis are invaluable.

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183. Wilson, M.E., et al., *Pretransplant frailty is associated with decreased survival after lung transplantation.* J Heart Lung Transplant, 2016. **35**(2): p. 173-8.

APPENDICES

APPENDIX A

Studies evaluating frailty and adverse outcomes in surgical patients under 75 years olds grouped by type of surgery

Cardiac surgery

Reference	Sample size, population, and age group	Study design	Type of surgery	Measures of frailty	Adverse outcomes predicted by frailty	Odds ratio for mortality or morbidity
Jung, P et al (2015)[98]	133 Canada Mean age not reported	Prospective cohort study	Cardiac surgery, elective	1. MFC (Modified Fried Criteria), 2. 35 item frailty index 3. SPPB (Physical Performance Battery)	Postoperative delirium	5.05 (p=0.0015) 3.72 for FI score ≥0.3 (p=0.0021) 8.26 (p=0.0007)
Ganapathi, A et al (2014) [99]	574 USA Average age 56	Retrospective analysis of a prospectively maintained database	Proximal aortic root surgery, elective, urgent and emergency	Frailty score of 6 components: age>70, BMI<18.5km/m2, anaemia, hypoalbuminaemia, history of stroke, total psoas volume in the bottom quartile of patient population	30-day and 1-year mortality LOS >14 days, discharge destination other than home	5.0 at 30 day (p<0.01) 4.5 at 1 year (p<0.01)
Dunlay, S.M. et al (2014)[100]	99 USA Mena age 65.1	Prospective cohort study	LVAD	31 item deficit index	1 year mortality 30 day hospital readmission	2.31 for deficit index of >0.25 (p=0.014)
Robinson, T.N. et al (2013) [101]	201 USA Average age 74	Prospective cohort study	Cardiac (64%) and colorectal (36%) surgery, elective	Simple Frailty Score	Postoperative complications, LOS, 30-day readmission rate	Not mentioned
Herman C.R. et al (2013)[102]	4270 Canada Median age 67	Retrospective cohort study	Cardiac surgery	Any deficiency in the Katz index of ADL, or impaired ambulation, or diagnosis of	Composite end point of in-hospital death, stroke, acute renal failure,	1.7

				dementia	infection.	
Lee, D.H. et al (2010) [103]	3826 Canada Median age 71 in the frail group, 66 in the non frail group	Prospective pilot study	Cardiac surgery, Elective and emergency	Any deficiency in the Katz index of ADL, or impaired ambulation, or diagnosis of dementia	In-hospital mortality, midterm all-cause mortality, discharge to an institution or skilled nursing facility, in-hospital outcomes^	1.8 for in hospital mortality (p=0.03) 1.5 for mid-term mortality (p=0.01)

Oncologic surgery

Reference	Sample size, population, and age group	Study design	Type of surgery	Measures of frailty	Adverse outcomes predicted by frailty	Odds ratio for mortality or morbidity
Reisinger, K.W. et al (2015)[104]	310 The Netherlands Median age not reported. 51.3% of patients were >70	Prospective cohort study	Colorectal cancer surgery	1.GFI 2.Sarcopenia 3.SNAQ (short nutritional assessment questionnaire)	30 day and/or in-hospital mortality Sepsis	43.3 by sarcopenia (p=0.007) 3.96 by GFI $\geq$5 (p=0.03)
Uppal, S et al (2015)[105]	6551 USA Mean age not reported	Retrospective analysis of NSQIP database	Gynaecologic cancer surgery, elective	MFI	Clavian IV/V complications	12.5 for MFI>4
Choi, J-Y et al (2015) [106]	281 Korea Mean age 74 (females only)	Retrospective cohort study	Cancer surgery, elective	MFS (Multidimensional Frailty Score)	Postoperative Complications (pneumonia, urinary tract infection, delirium, PE, and unplanned ICU admission) Institutionalisation	1.412 for every 1 point increase in MFS (p=0.042) or 8.513 for MFS$\geq$7 vs <7 (p=0.002) 1.377 for every 1 point increase in MFS (p=0.105) or 1.291 for MFS$\geq$7 vs <7 (p=0.717)
Tegels, J.J.W et al	180 (only 127	Retrospective	Gastric cancer surgery,	GFI	In-hospital mortality,	3.96

(2014) [107]	completed GFI) Netherlands Mean age 69.8	cohort study	elective and emergency	(Groningen Frailty Indicator)	postoperative complications (Clavien-Dindo grade ≥3a)	(p=0.03) Or 4.64 in curative intent cohort (p=0.05)
Dale, W. et al (2014)[108]	76 USA Mean age 67	Prospective cohort study	Pancreaticoduodenectomy	4 components of Frieds criteria VES-13 SPPB	Major postoperative complications (Clavien-Dindo grade ≥3)	4.06 (p=0.01) for exhaustion component of Fried criteria
Courtney-Brooks, M et al (2012) [109]	37 USA Age ≥65 Mean age 73	Prospective pilot study	Gynaecologic oncology surgery	Fried criteria	30-day postoperative complication	Not reported. 67% in frail group vs 24% non frail group P=0.04

General surgery

Reference	Sample size, population, and age group	Study design	Type of surgery	Measures of frailty	Adverse outcomes predicted by frailty	Odds ratio for mortality or morbidity
Revenig, L.M. et al (2015) [110]	351 USA Median 63	Prospective cohort study *excluded patients unable to ambulate poor manual dexterity or inability to grip	Major intra abdominal surgery	Fried criteria ASA, ECOG, CCI, biochem and FBC developing into a model most predictive of outcome – grip strength, shrinking, ASA <3, low Hb	30 day post operative complications	1.97 for 1-2/5 and 4.89 for >3/5 (p=0.048, p<0.001)
Amrock, L.G. (2014) [111]	76,106 USA Mean age 74.4	Retrospective analysis of NSQIP database	Lower GI surgery, elective	Predictive models using following domains: CCI, BMI, demographics, creat, albumin, Hct, ASA, functional status, impaired sensorium	30 day mortality and morbidity	2.30 for albumin <3.4g/dL 3.45 for CCI >0.5 3.66 for functional status being totally dependent (P<0.001)
Lasithiotakis, K et al (2013)[112]	57 Greece Median age 73	Prospective cohort study	Laparoscopic cholecystectomy, elective	Comprehensive geriatric assessment (CGA)	30 day Postoperative complications, >2 days of post op	6 (p=0.026) 4.2

					stay	(p=0.023)
Farhat, J.S. et al (2012) [113]	35,334 USA Mean age not reported, >60 year old (inclusion criteria)	Retrospective audit from NSQIP database	General surgery, emergent	MFI	30-day mortality, wound infection, wound occurrence, any infection, any occurrence	11.7 (p<0.001)
Obeid N.M. et al (2012)[114]	58,448 USA Mean age not reported	Retrospective analysis of NSQIP database	Laparoscopic and open colectomy, elective and emergent	MFI	30 day mortality, postoperative complications (Clavian 4)	Combined 14.4 (p=0.001)
Cohen, R-R et al (2012) [115]	102 USA Mean age 72.2	Retrospective cohort study	Abdominal surgery	Braden Scale (six domains: sensory perception and communication, moisture, activity, mobility, nutrition, and skin friction and shear) DAI (Deficit Accumulation Index)	30 day postoperative complication LOS, discharge to institution DAI not associated with outcome	1.3 for every 1 point decreased in Braden score. (p=0.001) 3.63 if more than 18.
Saxton, A et al (2011) [116]	226 USA Average age 61	Retrospective cohort study	Major general surgery, elective	Canadian Study of Health and Aging 70 Item Frailty Index (FI)	30 day post operative complications	2.71 (p=0.03)

Vascular surgery

Reference	Sample size, population, and age group	Study design	Type of surgery	Measures of frailty	Adverse outcomes predicted by frailty	Odds ratio for mortality or morbidity
Arya, S. et al (2015)[117]	23,027 USA Mean age 73.4	Retrospective analysis of NSQIP database	Endovascular and open AAA repair, elective and emergency	MFI	30 day mortality postoperative complications (Clavian 4)	2.0 for those who are severely frail 1.7 for those who are severely frail

Karam, J. et al (2013) [118]	67,308 USA Mean age of 68	Retrospective analysis of NSQIP database	Vascular surgery, elective and emergency	MFI	30 day mortality, postoperative complications (Clavian 4)	2.058 (p<0.001)
Pol, R.A. et al (2011)[119]	142 The Netherlands Mean age 68	Prospective cohort study	Vascular surgery, elective	GFI (Groningen Frailty Indicator)	Postoperative delirium based on geriatrician assessment	1.9 (p=0.05)

Mixed surgical specialities

Reference	**Sample size, population, and age group**	**Study design**	**Type of surgery**	**Measures of frailty**	**Adverse outcomes predicted by frailty**	**Odds ratio for mortality or morbidity**
Revenig, L.M. et al (2014) [120]	80 USA Mean age 60	Prospective cohort study	Minimally invasive surgery (endoscopic, laparoscopic, robotic procedures)	Fried criteria	30 day postoperative complications	5.91 (p=0.025)
Revenig, L.M. et al (2013) [121]	189 USA >18 years old Mean age of 62	Prospective cohort study	Major general, urological and oncological surgery, elective	Hopkins Frailty Score	30 –day postoperative complications	2.07 (p=0.036)
Velanovich, V. et al (2012) [122]	971,434 USA Mean age not reported	Retrospective analysis of NSQIP database	Cardiac, general, gynaecological, neurosurgical, orthopaedic, ENT, plastic, thoracic, urologic, vascular surgery.	MFI	30 day mortality and morbidity	Stepwise increase of mortality with each unit increase in FI, OR ranged from 1.33-46.33,highest for low risk surgery
Leung, J.M. et al (2011)[123]	63 USA Mean age 71.9 in the no-delirium group and 74.2 in delirium group	Prospective cohort study	Non cardiac surgery	Fried's criteria	Postoperative delirium based on CAM assessment	1.84 (P=0.028)
Makary, M.A el al (2010) [124]	594 USA Mean age 71.3 in the non frail group (majority), 76.3 in the frail group	Prospective cohort study	Any surgery at John Hopkins hospital, Elective	Hopkin's Frailty Score	30-day surgical complications Increased LOS Discharge to skilled or assisted living	2.54 (CI:1.12–5.77) (p<0 .01). 1.69 (CI:1.28–2.23) (p<0.001) 20.48 (CI:5.54–75.68) (p<0.001)

Miscellaneous

Reference	**Sample size, population, and age group**	**Study design**	**Type of surgery**	**Measures of frailty**	**Adverse outcomes predicted by frailty**	**Odds ratio for mortality or morbidity**
McAdams-DeMarco, M.A. et al (2015)[125]	534 USA Median age 53	Prospective cohort study	Kidney transplant, elective	Fried criteria	1,3, and 5 year mortality	2.17 (p=0.047)
Joseph, B et al (2014) [126]	250 USA Mean age 77.9	Prospective cohort study	Trauma 7.2% only underwent operative intervention	Frailty index using 50 preadmission frailty variables	In-hospital complications, adverse discharge disposition.	2.5* (p=0.001) 1.6* (p=0.001) For FI of $\geq$0.25
Joseph, B et al (2014)[127]	200 USA Mean age 77	Prospective observational study	Trauma patients May not have had surgery	TSFI (Trauma Specific Frailty Index) 15 variable	Unfavourable discharge disposition	1.8* (p=0.01) for frailty index >0.27
Hodari, A et al (2013) [128]	2095 USA Age not stated	Retrospective analysis of NSQIP database	Esophagectomy, elective and emergency	MFI	Postoperative complications (Clavian 4), mortality	31.84 (p=0.015)
Adams, P et al (2013) [129]	6727 USA Age not stated	Retrospective analysis of NSQIP database	Head and neck surgery, Elective and emergency	MFI	30-day Postoperative complications (Clavian 4), 30-day mortality	Not mentioned
Tsiouris, A et al (2013) [130]	1940 USA Average age 66	Retrospective analysis of NSQIP database	Lobectomy, Elective and emergency	MFI	Postoperative complications (Clavian 4), mortality	9.3 for MFI >0.27 (p=0.002)
Masud, D. et al (2013) [131]	42 UK Mean age 76.9	Retrospective analysis of a prospectively maintained database	Burns patients (50% underwent surgical debridement)	Clinical Frailty Score (1-7)	1 year mortality	2.1 for CFS>3 (p=0.0003)
Johnson, M.S. et al (2013)[132]	100 USA Median age of 64	Case series with chart review	Tracheostomy	RAI (risk analysis index)	6 month mortality	Risk of mortality was predicted to be 40.5% in the non

						survivors vs 25.4% in the survivors (p=0.001)
McAdams-DeMarco, M.A. et al (2013)[133]	383 USA Mean age 53.5	Prospective longitudinal study	Kidney transplant, elective	Fried criteria	Early hospital readmission (within 30 days)	1.61 P=0.002
Garonzik-Wang, J.M. et al (2012)[134]	183 USA Mean age 53	Prospective cohort study	Kidney transplant, elective	Hopkins frailty score (Fried criteria)	Delayed graft function	1.94* (p=0.02)

APPENDIX B

Cardiac Risk* Stratification for Non-cardiac Surgical Procedures

Risk Stratification	**Procedure Examples**
High (reported cardiac risk often more than 5%)	Aortic and other major vascular surgery Peripheral vascular surgery
Intermediate (reported cardiac risk generally 1% to 5%)	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopaedic surgery Prostate surgery
Low† (reported cardiac risk generally less than 1%)	Endoscopic procedures Superficial procedure Cataract surgery Breast surgery Ambulatory surgery

*Combined incidence of cardiac death and nonfatal myocardial infarction.
†These procedures do not generally require further preoperative cardiac testing.

Adapted from Table 4 of Fleisher LA, Beckman JA, Brown KA et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2007;50(17):e159-241.

APPENDIX C

Patient information sheet and consent form

Metro South Health

Princess Alexandra Hospital

Frailty and Postoperative Outcomes

Information Sheet Version 1, April 2014

Older people sometimes have to undergo surgery. Determination of suitability for surgery can be difficult in older people. Older people can often be described as being frail. Frailty does not have a precise meaning but 'frail' patients have sometimes lost weight, become weaker, able to exercise less or have problems with their memory. Frailty is important because people who become frail often do less well than other people and need more care from relatives and medical services.

It is not known why some people become frail and others do not. It may be the result of a combination of changes in the body due to age or illness. For example, muscles tend to waste in frail people and they tend to lose muscle strength. Some things seem to slow down like the production of blood cells or the body's ability to break down medicines. It is likely to be a combination of all these factors.

About the Study

We are carrying out a study in the Princess Alexandra Hospital, looking at how frailty as measured using a questionnaire might help predict outcomes after moderate or high intensity surgery. We think that by asking questions about different aspects of health (medical problems, ability to look after oneself, mood, sleep, thinking) we can determine how frail a person is.

We would like to include you in this study. We are trying to test if the questionnaire works. Therefore we want to include a whole range of people – from those who are very fit to those who are very frail.

If you consent to taking part in the study, we will ask you some questions about your medical history and medications. You will also be asked questions about memory, quality of life and current level of functioning, for example whether you are able to wash and dress yourself independently. The questions take about 10 minutes to 15 minutes to answer.

Additional information regarding your health/ medical conditions and the operation you undergo will be collected from your medical records.

We will follow up people who take part in the study at 30 days after the operation (with a telephone call if they have left hospital) and at 12 months after the operation with a further phone call to determine how they have fared after their surgery.

Important

There is no obligation for you to take part in the study. A decision not to take part will have no effect on your medical care.

If you do consent to take part, you may change your mind at any time and withdraw your consent.

All information gathered during the study is confidential, will be safely stored and will be presented anonymously.

If you have any questions relating to the study, we will do our best to answer them.

If you do decide to take part, the study co-ordinators (who gave you this form) will go through the questionnaire with you.

If you have any further questions about the study, you can contact:

Dr Ruth E.Hubbard
Senior Lecturer in Geriatric Medicine
Deputy Director, Centre for Research in Geriatric Medicine
Level 2, Building 33
The Princess Alexandra Hospital
Ipswich Road, Woolloongabba
Brisbane, Queensland 4102
Telephone – 07 3176 5330
Email – r.hubbard1@uq.edu.au

If you have any complaints, please contact:
HREC Coordinator
Phone – 07 34338049
Email – Ethicsresearch.pah@health.qld.gov.au

Thank you for your time

Office Use Only
- Data Input_______________
- Form scanned_______________

Princess Alexandra Hospital

PARTICIPANT ID#

FRAILTY AND POSTOPERATIVE OUTCOMES

Consent Form Version 1, April 2014

I,...

of ....

give consent to be part of the above named study.

I have read / have had read to me the contents of the Information Sheet.

I have had the opportunity to ask questions, and received adequate answers. I have had enough time to decide whether I want to take part in the study.

I understand that I will not be given any form of treatment as a part of the study.

I understand that I am under no obligation to take part in the study, and that refusal will not affect my medical care. If I do take part in the study I may withdraw at any stage, and it will have no effect on my medical care.

Signed:.. Date: ....

Witnessed:... Date: ....

Study investigator: ....Date: ....

OR

If the Participant is unable to sign:

Consent of Authorised Person who can sign for the Participant

Patient name: ………………………………………….

Hospital no:………………………………………………

Address:……………………………………………………………………

Phone Number:…………………………………………………………

I………………………………………………… give consent on behalf of

……………………………… to be included in the above named study.

My relationship to the patient named above is …………………… and my understanding is that I may give consent on his/her behalf. To the best of my knowledge this decision is not going against the wishes of other family members. I understand that the patient cannot give his/her own consent at the moment, but that if that situation changes, his/her wishes will be respected.

I have read / have had read to me the Patient Information Sheet. I have had the opportunity to ask questions, and received adequate answers. I have had enough time to decide whether I feel my relative would want to take part in the study.

I understand that he/she will not be given any form of treatment as a part of the study.

I understand that I am under no obligation to allow inclusion of my relative in the study, and that refusal will not affect his/her medical care. I understand that consent may be withdrawn at any stage of the study and it will have no effect on my relative's medical care.

Signed:……………………………………………… Date: ………………………

Witnessed:……………………………………………… Date: ………………………

Study investigator: ………………………… Date: ………………………

APPENDIX D

FI-CGA Form

A table consisting of the following domains and questions of assessment:

1. How would you rate your motivation to recover from your surgery? (high, usual, or low)
2. How would you rate your health? (excellent, good, fair, poor, couldn't say)
3. Cognition (normal, mild cognitive impairment, dementia). 1 additional point if patient has agitation/wandering, delusions/hallucinations or delirium (1 point for each symptom present).
4. Emotional (normal, anxiety, bereavement, depression, fatigue)
5. Sleep (normal, poor or disrupted sleep, daytime drowsiness)
6. Communication - speech, hearing, vision (normal, impaired)
7. Strength – grip strength (normal, weak), proximal muscle strength (normal, weak), hemiparesis (no, yes)
8. Mobility – transfer, walking, (independent, assist, dependent), aids used (nil, walking stick, frame), slow (no, yes), low activity level (no, yes)
9. Balance (normal, impaired), falls in the last 6 months (no, yes)
10. Elimination – bowel, bladder (continent, occasional accident, incontinent)
11. Nutrition – weight change (stable, loss, gain), appetite (normal, fair, poor), BMI (normal, <18. >30)
12. ADLs – feeding, bathing, dressing, toileting (independent, assist, dependent)
13. IADLs – cooking, cleaning, shopping, medications, transport, banking (independent, assist, dependent)
14. Medical history – 1 point each for hypertension, COPD, TIA/stroke, angina/MI, CCF, diabetes, cancer, alcohol excess, hip fracture, OA/RA, osteoporosis, PVD, dyslipidaemia
15. Number of different medications in 24 hours (up to 4 points for > 20 medications)
16. Social engagement (frequent, occasional, rarely)

Total number of deficits (denominator) was 57 with intermediate impairment weighing half of a point (eg assistance for ADLs and mobility being half a point, dependence being one point).

APPENDIX E

Ethics approval

Metro South Health

Enquiries to: Centres For Health Research
Research Governance
Phone: (07) 3443 8050
Fax: (07) 3443 8003
Our Ref: HREC/14/QPAH/215 – SSA/14/QPAH/216
E-mail PAH-Research@health.qld.gov.au

Dr Ruth Hubbard
Centre for Research in Geriatric Medicine
Level 2, Bldg 33
Princess Alexandra Hospital
199 Ipswich Rd
Woolloongabba QLD 4102

HREC APPROVAL AND SSA AUTHORISATION
PRINCESS ALEXANDRA HOSPITAL
METRO SOUTH HOSPITAL AND HEALTH SERVICE

HREC Reference number: HREC/14/QPAH/215
SSA reference number: SSA/14/QPAH/216
Project title: Evaluation of perioperative frailty to determine post operative outcomes in elderly patients undergoing elective and emergency surgery

I am pleased to advise that the above protocol has been recommended for approval by the Low and Negligible Risk Sub Committee of the Metro South Human Research Ethics Committee. The Committee is duly constituted, operates in accordance and complies with the current National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research 2007.*

	Version	Date
LNR Form		07/04/2014
PAH Participant Information and Consent Form	1	April 2014
Frailty Assessment Form		
Post-operative Frailty Assessment Form – 30 days		
Post-operative Frailty Assessment Form – 365 days		

On the recommendation of the Human Research Ethics Committee approval is granted for your project to proceed.

The duration of approval is 1 years from the date of this letter.

This approval is subject to researcher(s) compliance throughout the duration of the research with certain requirements as outlined in the *National Statement on Ethical Conduct in Human Research 2007* and *Australian Code for the Responsible Conduct of Research.*

The following links have been provided for your convenience:
http://www.nhmrc.gov.au/publications/synopses/e72syn.htm
http://www.nhmrc.gov.au/publications/synopses/r39syn.htm

Office
Centres for Health Research
Princess Alexandra Hospital
Metro South Hospital and Health Service

Postal
37 Kent St
Woolloongabba Q 4102

Phone
61 7 3443 8050

Fax
61 7 3443 8003

Some requirements are briefly outlined below. Please ensure that you communicate with the HREC on the following:

- ***Protocol Changes:*** Substantial changes made to the protocol require HREC approval http://www.health.qld.gov.au/pahospital/research/amendments.asp
- ***Problems and SAEs:*** The HREC must be informed of any problems that arise during the course of the study which may have ethical implications. Serious adverse events must be notified to the HREC as soon as possible http://www.health.qld.gov.au/pahospital/research/adverse_events.asp
- ***Lapsed Approval***: If the study has not commenced within twelve months approval will lapse requiring resubmission of the study to the HREC.
- ***Annual Reviews:*** All studies are required by the NHMRC to be reviewed annually. To assist with reporting obligations an Annual Report template is available on the MSHSD HREC website. This form is required to be completed and returned to the HREC within the 12 month reviewing period http://www.health.qld.gov.au/pahospital/research/monitoring.asp

If this research involves the recruitment of patients from the Metro South Hospital and Health Service (MSHHS), it is my responsibility to remind you of your ongoing duty of care for all people recruited into projects or clinical trials whilst public patients. All conditions and requirements regarding confidentiality of public information and patient privacy apply. You are required to comply at all times with any application requirements of Australian and Queensland Laws including the Health Services Act, the Privacy Act, Public Health Act (2005) and other relevant legislation, ethics obligations and guidelines which may be applicable to the MSHHS from time to time including, without limitation, any requirement in respect of the maintenance, preservation or destruction of patient records.

When the study involves patient contact, it is your responsibility as the principal investigator to notify the relevant consultant and request their approval.

Should you have any problems, please liaise directly with the Chair of the HREC early in the program.

A copy of this letter should be presented when required as official confirmation of the approval of the Metro South Human Research Ethics Committee.

We wish you every success in undertaking this research.

Yours sincerely,

Ken Ho

Professor Ken Ho
Chair, Centres for Health Research
METRO SOUTH HEALTH

10 / 6 / 14

Office
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Princess Alexandra Hospital
Metro South Hospital and Health Service

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Metro South Health

Enquiries to:	Metro South Human Research Ethics Committee
Phone:	07 3443 8049
Fax:	07 3443 8003
HREC Ref:	HREC/14/QPAH/215
E-mail:	Ethicsresearch.pah@health.qld.gov.au
Amendment	AM01

A/Prof Ruth Hubbard
Centre for Research in Geriatric Medicine
Princess Alexandra Hospital
199 Ipswich Road
Woolloongabba QLD 4102

Dear A/Prof Hubbard,

HREC Reference number: HREC/14/QPAH/215
Protocol title: Evaluation of perioperative frailty to determine post operative outcomes in elderly patients undergoing elective and emergency surgery

The Office of the Metro South Human Research Ethics Committee noted and approved the following:-

Document	Version	Date
MSF49 Notification of Amendment in respect to a request for extension of ethical approval until 30 June 2017		25 February 2016
Original HREC Approval and Governance Authorisation Letter		10 June 2014

The Metro South Hospital and Health Service HREC is constituted and operates in accordance with the National Health and Medical Research Council's *"National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007)* and the "*CPMP/ICH Note for Guidance on Good Clinical Practice"*.

This will be ratified by the HREC at its 5 April 2016 meeting.

Please provide a copy of this approval letter to the Research Governance Office.

It should be noted that all requirements of the original approval still apply. Please continue to provide at least annual progress reports until the study has been completed.

If you have any queries please do not hesitate to contact the Human Research Ethics Committee office on +617 3443 8049.

Yours sincerely,

A/Prof Richard Roylance
Chair
Metro South Hospital and Health Service
Human Research Ethics Committee (EC00167)
Centres for Health Research
Princess Alexandra Hospital
Woolloongabba QLD 4102
3/3/2016

C.c. Nancye Peel, Centre for Research in Geriatric Medicine

Queensland Government

APPENDIX F

Publications on relationship between frailty and surgical outcomes between January 2016 and 2017

Studies using modified Frailty Index (mFI)

Reference	Sample size, population, average age and gender distribution	Type of surgery	Adverse outcomes predicted by frailty	Odds ratio for mortality or morbidity
Abt et al 2016[135]	1193 Mean age 63 68% male	Head and neck cancer surgery	1: Clavien-Dindo Grade IV-V complications 2: morbidity, readmission, and reoperation	Increased from 4.6% to 100% non frail vs most frail p<0.01. Death 0.8% to 3.6% p0.42 OR 1.65p0.007 for CD IV complications NS
Ali et al 2016[136]	18,294 Mean age not reported 52% male	Spinal surgery	30 day adverse events	mFI 0 vs >0.27 at least 1 adverse events: 8.1% vs 24.3% (p < 0.001). mortality: 0.1% vs 2.3% for an mFI (p < 0.001). surgical site infection: 1.7% vs 4.1% (p < 0.001) Clavien IV complications: 0.8% vs 7.1% (p < 0.001)
Ali et al 2017 [137]	4,704 Mean age 68 64% males	Lower limb bypass surgery	group 1 mFI 0-0.09, group 2 mFI 0.18-0.27, group 3 mFI 0.36-0.45, group 4 mFI 0.54-0.63 mortality postop complications (MI, stroke, renal failure, graft failure)	Comparing 4 frailty groups 0.6%, 1.4%, 4%, 7.4%. Similar patterns
Arya et al 2016[138]	15,843 Mean age 69.7 35% female	Elective vascular surgery	Non-home discharge mFI>0.25 is frail	OR 1.6, 95%CI 1.4-1.8, p<0.01 after adjusting for other covariates.
Augustin et al 2016[139]	13,020 Mean age ranged	Pancreatectomy	CD IV complications 30 day Mortality	mFI of 5 or more vs mFI of 0 27.8% vs 3.4% (p<0.001)

	from 58-68.7% 48-66% female			11.1% vs 0.6% (p<0.001) Every 1-point increase in modified frailty index was associated with 6 times increase in complications, 10 times increased mortality, adjusted for age, sex, body mass index, albumin, weight loss, and type of pancreatectomy
Brahmbhatt et al 2016[140]	24,645 Mean age 67-69	Infra-inguinal vascular surgery	30 day mortality 30 day CD IV complications	OR 1.74 OR 1.2
Chimukangara et al 2016[141]	885 Inclusion criteria ≥60yro 76% female	Para-oesophageal hernia repair	 30 day CD ≥III complications 30 day Mortality Discharge to facility other than home Re-admission	mFI scores of 0, 1, 2, and ≥3 3.2%, 4.7%, 9.8%, and 23.3% (p<0.0001) OR 3.51; CI 1.46–8.46 0.0%, 0.9%, 1.8%, and 2.3% (p 0.0974) 4.4%, 10.9%, 15.7%, and 31.7% (p<0.0001) OR 4.07; CI 1.29–12.82 8.9%, 6.8%, 8.5%, and 16.3% (p=0.1703) OR 1.01; CI 0.36–2.84
Cloney et al 2016[142]	243 Mean age 73 Gender not specified	Glioblastoma patients	LOS Complications Survival	Significant association on log rank test for trend P=0.0061 (median LOS for frailest cf rest 6 vs 4 days P= 0.0123; OR, 1.40; 95% CI, 1.08- 1.83) Reduced overalls survival P=0.0028
Dayama et al 2016[143]	3121 Mean age 77.3 760% female	Hip fracture surgery	CD IV complications Failure to rescue (likelihood of death from inpatient complications)	OR 1.6, 95%CI1.15-2.25, p=0.006 for mFI >0.18 OR 2.1 95%CI 1.12-3.93 p=0.02 for mFI >0.18 Multivariate analysis adjusting for condounders
Ehlert et al 2016[144]	72,106 Mean age range 67-75 Male 57-80%	Carotid revascularization, abdominal aortic aneurysm (AAA) repair, and lower extremity revascularization for peripheral arterial disease (PAD)	30day mortality CD IV complications	The mFI was a better discriminator of mortality than other risk indices. The mFI was also a better discriminator of class IV complications for the open and endovascular AAA repair groups.
Fang et al 2017[145]	379 Mean age 55.1 64% male	Major lower limb amputation	30 day readmission	OR 1.510, 95%CI 1.245-1.832, p <.0001

Flexman et al 2016[146]	53,080 Mean age 56 years 52% male	Degenerative spine surgery	CD >II complications Prolonged LOS Discharge to a new facility	OR 1.15 for every 0.10 increase in mFI, 95%CI 1.09–1.21, p<.0005 OR 1.27, 95%CI 1.19–1.35, p<.0005 OR 1.32, 95%CI 1.24–1.40, p<.0005
George et al 2016[147]	66,105 20% 60 years of older	Hysterectomy	 Wound infection CD IV complications Overall complications Mortality	mFI 0 vs mFI >0.5 2.4% vs 4.8% (P < 0.0001) 0.98% to 7.3% (P < 0.0001) 3.7% to 14.5% (P < 0.0001) 0.06% to 3.2% (P < 0.0001)
Leven et al 2016[148]	1001 Mean age 59 54% female	Spinal fusion	 Any complications Any blood transfusion Mortality Return to OT	mFI of >0.18 is an independent predictor of: OR 1.6, 95% CI 1.1-2.4 p=0.01 OR 1.6 95%CI 1.1-2.4 p=0.013 OR 95% CI 0.8-71.1 p=0.085 OR 2.3, 95%CI 1.2-4.5 p=0.017 a superior predictor than age and obesity
Louwers et al 2016[149]	10,300 Mean age 58 49% male	Hepatectomy	CD IV complications Mortality Extended length of stay	5% vs 15.8%, OR = 40.0, (95% CI = 15.2 to 105.0) P < .001 1.5% vs 9.1% OR = 26.4, (95% CI = 7.7 to 88.2) P < .001 7.6% vs 43.0% P < .001 for mFI 0 vs 0.33 Use of the mFI allows for feasibility of data collection in a busy clinical setting.
Mogal et al 2017[150]	9986 Mean age 64.1 48.8% female	Pancreaticoduodenectomy	 CD III-IV complications 30-days mortality	Adjusting for age, sex, ASA classification, albumin level, and body mass index (BMI), mFI of >0.27 is associated with increased adverse outcomes. OR 1.544; 95% CI 1.289-1.850; p < 0.0001) OR 1.536; 95% CI 1.049-2.248; p = 0.027).
Mosquera et al 2016[151]	232,352 Mean age 65 46% female	High risk surgery	1 year mortality	OR 6.01; 95% CI, 5.47–7.03 for mFI>3 vs mFI 0
Shin et al 2016[152]	14,583 Mean age 65 55.6% female 25,223 Mean age 67 63.5% female	Total hip arthroplasty Total knee arthroplasty	CD IV complications	Adjusting for demographics, age>75, BMI >40, ASA>4 and non-clean wound status, mFI>0.45 was shown to be the strongest independent predictor of complications OR5.140 95%CI 1.400-18.871 p=0.0136 for THA OR 4.183 95%CI 1.464-11.948 p=0.0075 for TKA
Shin et al 2017[153]	6965 Mean age 52.9-59.8 43.9-49.7% female	Cervical spine fusion	CD IV complications	0.8% vs 9.0% for mFI 0 to 0.27 mFI of 0.27 is an independent predictor of CD IV complications with OR 4.67, 95% CI 2.27– 9.62, P<0.001, adjusting for age, obesity, ASA

Vermillion et al 2017[154]	41,455 mean age 72.4 47.4% female	GI cancer resection (69.3% were CRC)	LOS Major complications (CD III/IV) 30 day mortality	Frail vs non frail 11.7 vs 9.0 days (P < 0.001) 29.1% vs 17.9% (P < 0.001) 5.6% vs 2.5% (P < 0.001) Multivariate analysis found mFI to be an independent predictor of major complications (OR 1.52, 95%CI 1.39-1.65, P < 0.001) and 30-day mortality (OR 1.48, 95%CI 1.24-1.75, P < 0.001), adjusting for age, gender, BMI, ASA, and albumin level.
Vu et al 2017[155]	36,424 Mean age 79.5 years 27.8% male	Orthopaedic trauma	30 day mortality	adjusted for age, sex, race, BMI, total length of stay, operative time, region of injury, any occurrence of complication OR 2.6, 95% CI: 1.7–3.9, p < 0.001 Better predictor than ASA and age
Wachal et al 2017[156]	343 Mean age 63 81% male	Total laryngectomy	Any postop complications LOS Require skilled care after discharge	mFI of 3 vs 0 50.0%vs 16.7%; OR, 3.83; 95%CI, 1.72- 8.51 14.2 vs 9.5 days; difference, 4.7; 95%CI, 1.3-8.1 days (33.3%vs 3.2%; difference, 30.1%; 95%CI, 7.4%-52.9%).
Wahl et al 2017[157]	236,957 procedures (VSQIP) Mean age 64 90% male	High volume surgical specialities (orthopaedic, general and vascular surgery)	30 day unplanned readmission 2 outcomes: (30 day complications, 30 day mortality, 30 day ED visit)	odds ratio [OR], 1.11; 95%CI, 1.10-1.1
Wen et al 2017[158]	272	Ileostomy closure	Discharge within 48 hours of surgery	mFI of 0 is associated with successful discharge within 48 hours but not mFI of 1 or 2.

Cardiac surgery

Reference	**Sample size, mean age and gender**	**Type of surgery**	**Frailty measure**	**Adverse outcomes predicted by frailty or main findings of the study**
Ad et al 2016[159]	167 (prospective cohort study) Mean age 74.1 25% female	Elective CABG or valve surgery	CHS frailty index (Fried criteria)	STS defined complications Non sig on multivariate analyses Readmission to hospital within 30 days Non sig on multivariate analyses Discharge to intermediate care facility

				OR3.13, 95%CI: 1.24–7.91,p=0.016
Afilo et al 2017[160]	1020 Median age 82	TAVI and surgical aortic valve replacement	Fried criteria Fried+ MMSE + GDS Rockwood CFS Short Physical Performance Battery Bern scale – composite score of gait speed, mobility, cognition, nutrition, ADL and IADL disability Columbia scale - gait speed, grip strength, albumin, and ADL disability Essential Frailty Toolset (EFT) – five chair rises, presence of cognitive impairment, albumin, haemoglobin	Frailty as measured by the EFT was the strongest predictor of death at 1 year (adjusted odds ratio [OR]: 3.72; 95% confidence interval [CI]: 2.54 to 5.45) with a C-statistic improvement of 0.071 ($p < 0.001$) and integrated discrimination improvement of 0.067 ($p < 0.001$). Moreover, the EFT was the strongest predictor of worsening disability at 1 year (adjusted OR: 2.13; 95% CI: 1.57 to 2.87) and death at 30 days (adjusted OR: 3.29; 95% CI: 1.73 to 6.26)
Chauhan et al 2016[161]	342	TAVI	15-ft walk test, Katz ADL, preoperative, albumin, and dominant handgrip strength	Patients with frailty score of 3/4 or 4/4 had increased all-cause mortality ($P = .015$ and $P < .001$) and were more likely to be discharged to an acute care facility ($P = .083$ and $P = .001$). 4/4 frail patients had increased post-operative length of stay ($P = .014$) when compared to less frail patients.
Esses et al 2018 [162]	3088	Aortic Valve Replacement	mFI Risk analysis index Ganapathi index	Frailty was a better predictor of mortality than morbidity, and it was not markedly different among any of the 3 indices. Frailty was associated with an increased risk of 30-day mortality and longer lengths of stay.
Huded et al 2016[163]	191	TAVI	Modified Fried criteria	There was no difference in post-TAVI 30-day mortality, stroke, major vascular injury, major or life-threatening bleeding, respiratory failure, mean hospital length of stay, 30-day hospital re-admission, or overall survival between groups. Frailty was independently associated with discharge to a rehabilitation facility (odds ratio 4.80, 95% confidence interval 1.66 to 13.85, $p = 0.004$).

Lytwyn et al 2017[164]	188	Cardiac surgery	Modified Fried criteria SPPB CFS	Poor 1 year functional survival OR 3.44 OR 3.47 OR 2.08
Marshall et al 2016[165]	123 Mean age 77.1	Open cardiac surgery	Cumulative score from 11 different frailty measures	Frail patients had higher incidence of an unfavorable composite outcome (52.9%) compared to their borderline (28.3%) and robust (13.3%) counterparts (p = 0.003). Greater 6 month mortality in the frail cohort.
Okoh et al 2017[166]	75 Mean age 92 65% female	TAVI	Frailty score consisting grip strength, gait speed, serum albumin, and ADLs. ≥3 is frail	All cause mortality OR 1.84, 95%CI: 1.06–3.17, p=0.028
Rodrigues et al 2017[167]	221	Cardiovascular surgery	CFS	Pre-frail patients showed a longer mechanical ventilation time, LOS at ICU, higher number of adverse events and in-hospital death and higher number needing home care services compared with non frail patients.
Shimura et al 2017[168]	1215 Mean age 83-85 20-40% male	TAVI	Clinical Frail Scale	Cumulative 1 year mortality Increase per 1 point increase in CFS OR 1.28, 95%CI 1.10–1.49, p<0.001

Non cardiac surgery

Reference	**Sample size, population, and age group**	**Type of surgery**	**Frailty measure**	**Adverse outcomes predicted by frailty or main findings of the study**
Driver et al 2017[169]	Mean age 68.5	Stage I-IV endometrial cancer	Any of: Albumin <3.5 mg/dL, haemoglobin< 10 mg/dL, BMI<20 kg/m2, unintentional weight loss, ECOG performance status ≥2, history of osteopenia or osteoporosis	Cancer recurrence OR = 2.21; 95% CI:1.02–4.8 when adjusted for age, stage, grade of cancer and Charlson score Death OR = 2.34; 95% CI 1.08–5.03
Gani et al 2017[170]	2714 Median age 60 51.6% female	Elective Major Hepatectomy	Revised frailty index (rFI): ASA class, BMI, serum albumin, 110dmonton110it, underlying pathology, and type of liver	postoperative complication or death prolonged LOS Predictive ability AUROC= 0.68

			resection	
Hall et al 2017[80]	2785 mean age 60.7 3.6% female	Elective surgery	Risk Analysis Index – Administrative (RAI –A)	Predictive ability with C statistics, AUC 30day mortality 0.901 (0.861-0.940) 180day mortality 0.823 (0.763-0.883) 365day mortality 0.797 (0.750-0.843) CD IV complications 0.577 (0.510-0.644)
Isharwall et al 2017[171]	42,715 Mean age and gender not reported	Urology surgery	RAI: scoring system comprising age, gender, admission to nursing home in last 3 months, unintentional weight loss within 3 months, renal failure, chronic heart failure, poor appetite, shortness of breath, active cancer diagnosis, deteriorated cognitive skills within 3 months and activity of daily living score	Postoperative complication - Significant increase with increasing RAI score p<0.0001 Mortality - Significant increase with increasing RAI score p<0.001 Rate of return to operating room - Significant increase with increasing RAI score p<0.0001 hospital readmission rate - Significant increase with increasing RAI score p<0.001 Discharge to home - Significant decrease with increasing RAI score
McIsaac et al 2016[172]	202,811 Mean age 74 vs 77 in frail and non frail groups Female 58% vs 55%	Elective non cardiac surgery	Johns Hopkins Adjusted Clinical Groups (12 clusters of frailty-defining diagnoses)	Adjusting for age, sex, neighbourhood income quintile, and procedure 1-year mortality risk OR 2.23; 95% CI 2.08-2.40
Nieman et al 2017[173]	159,301 mean age 62 years 30% female	Head and neck cancer surgery	Johns Hopkins Adjusted Clinical Groups	in-hospital death OR 1.6, 95% CI 1.1–2.4, p=0.011 postoperative surgical complications OR 2.0, 95% CI 1.7–2.3 p<0.001 acute medical complications OR 3.9, 95% CI 3.2–4.9 <0.001 increased mean LOS

				4.9 days
Choi et al 2017[174]	481 Median age 80.2 72% female	Hip fracture surgery	Hip-MFS (Hip multidimensional frailty score): Sex, Charlson Comorbidity Index, Albumin, g/dL, Koval grade Dementia (MMSE-KC), Risk of falling, MNA, Midarm circumference >8 point =frail	adjusted hazard ratio per 1 point increase in Hip-MFS 6-months mortality OR 1.458, 95% CI: 1.210–1.75 P < 0.001 postoperative complications OR 1.239 95% CI: 1.115–1.377 P < 0.001 prolonged total hospital stay OR 1.156 95% CI: 1.031–1.296 P < 0.01 AUC for predicting 6 month mortality was 0.784, better than age and ASA.
Kua et al 2016[175]	144 Mean age 79.1 66% female	Hip fracture surgery	Reported Edmonton frail scale (REFS): gait speed substituted by "In the last 2 weeks, were you able to (i) climbbone flight of stairs (ii) walk 1 km Modified fried criteria (MFC) not predictive in multivariate logistic regression	Postoperative complications OR 3.42, p = 0.04 Dependence in basic ADL function OR 6.19, p = 0.01
Gleason et al 2017[176]	175 Mean age 82.3 75% female	Trauma surgery	FRAIL scale: short 5 question assessment of fatigue, resistance, aerobic capacity, illnesses, and loss of weight Score 1-2=prefrail Score 3-5=frail	Multiple regression analysis, adjusted by age, sex, and Charlson index, robust vs prefrail vs frail groups LOS 4.2 vs 5.0 vs 7.1 days, p=0.002 Any complications 3.4% vs 26% vs 39.7%, p=0.03 Discharged home 31% vs4.2% vs 4.1%, p=0.008
Goeteyn et al 2017[177]	98 Mean age 74 36% female	Emergency general surgery	7 point Clinical Frailty Scale	90 day mortality OR 10.828, 95%CI 1.343–87.296, p=0.025 for fit vs frail Other outcomes no statistically sig difference
Joseph et al 2016 [178]	220 Mean age 75.5	Emergency general surgery	50 item Rockwood Preadmission FI FI≥0.25 is frail	in-hospital complications OR 2.13; 95% CI, 1.09-4.16; p = 0.02 major complications OR 3.87; 95% CI, 1.69-8.84; p = 0.001

				Age and ASA score were not predictive of postoperative and major complications. 80% sensitivity, 72% specificity, and area under the curve of 0.75 in predicting complications.
Li et al 2016[179]	189 Mean age 62 60% male	Major intra-abdominal surgery	Fried criteria	1 year mortality OR 3.6 95%CI 0.86-12.46, p=0.082 for frailty score 2-4 vs 0-1 Frailty in addition to ECGO, ASDA, age improves the predictability of 1 year mortality from 0.797 to 0.866
McAdams-DeMarco et al 2016[180]	74,859	Kidney transplant	Novel registry augmented methods	Frailty was independently associated with longer LOS [relative risk = 1.15, 95% confidence interval (CI): 1.03-1.29; P = 0.01] and LOS ≥2 weeks (odds ratio = 1.57, 95% CI: 1.06-2.33; P = 0.03) after accounting for registry-based risk factors, including delayed graft function.
Sridharan et al 2017[181]	1,496 Mean age 71.3	Carotid endarterectomy	Accumulated deficit model – 7 items from CSHA-FI	≥4 deficits was more predictive of perioperative major adverse events (odds ratio [OR] = 3.62, P < 0.001) than symptomatology within 6 months (OR = 1.57, P = 0.08) or octogenarian status (OR = 2.00, P = 0.02). Kaplan-Meier analysis showed significantly decreased survival over time with accumulating deficits (P < 0.001). Patients with >/=4 deficits have a hazards ratio for death of 2.6 compared to patients with ≤3 deficits (P < 0.001). Overall survival is estimated at 79.5% (95% confidence interval [CI]: 0.77-0.82) at 5 years in patients with ≤3 deficits versus 52.4% (95% CI: 0.46-0.58) in patients with ≥4 deficits.
Srinivasan et al 2016[182]	184 Median age 77 85% male	Ruptured AAA surgery	Ruptured Aneurysm Frailty Score - Katz score, Charlson score, number of admission medicines, visual impairment, hearing impairment, hemoglobin level, and statin use	12 month mortality AUC 0.84
Wilson et al 2016[183]	144	Lung transplant	32 item frailty deficit index Frail = FI>0.25	Frail patients had an increased risk of death. Adjusted OR 2.24, 95%CI 1.22-4.19; p = 0.0089.