

# The Fried Frailty Phenotype in Patients Undergoing Cardiac Surgery: A Systematic Review and Meta-Analysis

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## ABSTRACT

**Objective:** Frailty is an increasingly recognized marker of poor surgical outcomes in cardiac surgery. Frailty first was described in the seminal “Fried” paper, which constitutes the longest-standing and most well-recognized definition. This study aimed to assess the impact of the Fried and modified Fried frailty classifications on patient outcomes following cardiac surgery.

**Methods:** The PUBMED, MEDLINE, and EMBASE databases were searched from January 2000 until August 2021 for studies evaluating postoperative outcomes using the Fried or modified Fried frailty indexes in open cardiac surgical procedures. Primary outcomes were one-year survival and postoperative quality of life. Secondary outcomes included postoperative complications, intensive care unit (ICU) length of stay (LOS), total hospital LOS, and institutional discharge.

**Results:** Eight eligible studies were identified. Meta-analysis identified that frailty was associated with an increased risk of one-year mortality (Risk Ratio [RR]:2.23;95% confidence interval [CI]1.17 -4.23), postoperative complications (RR 1.78;95% CI 1.27 – 2.50), ICU LOS (Mean difference [MD] 21.2 hours;95% CI 8.42 – 33.94), hospital LOS (MD 3.29 days; 95% CI 2.19 – 4.94), and institutional discharge (RR 3.29;95% CI 2.19 – 4.94). A narrative review of quality of life suggested an improvement following surgery, with frail patients demonstrating a greater improvement from baseline over non-frail patients.

**Conclusions:** Frailty is associated with a higher degree of surgical morbidity, and frail patients are twice as likely to experience mortality within one-year post-operatively. Despite this, quality of life also improves dramatically in frail patients. Frailty, in itself, does not constitute a contraindication to cardiac surgery.

## INTRODUCTION

Cardiac surgery incurs a major physiological stress and may be associated with significant morbidity and mortality. A tight patient selection is therefore vital to mitigate excess surgical risk. However, aside from surgical morbidity, health-related quality of life (HRQoL) and functional independence outcomes are of equal importance and often are primary aims held by patients [Gavalaki 2020; Jokinen 2010]. There is a consequent need to not only identify patients at risk of operative morbidity, but also to understand the quality of life (QoL) trajectory in such patients who may elect for surgery. An understanding of both the potential risks and benefits of surgery is required for informed decision-making [Rumsfeld 2003].

Frailty conceptually represents a geriatric syndrome of reduced physiological reserve and susceptibility to stressors [Sundermann 2014; Chikwe 2010]. The geriatric phenotype of frailty was first described in 2001 in a seminal paper by Fried et al., which has since become known as the ‘Fried’ frailty definition [Fried 2001]. This phenotype includes five characteristics of unintentional weight loss, weak grip strength, poor endurance, slow gait, and a low level of physical activity [Fried 2001]. The presence of at least three criteria is descriptive of frailty, however, individuals fulfilling one to two criteria may be classified as pre-frail. A modified Fried index (Fried+) with an additional two assessment criteria of depression and cognitive impairment also has been used, recognizing the inability of some patients to complete the physical assessment [Theou 2015; Bergman 2007]. While related and frequently occurring together, frailty, aging, and comorbidity represent different clinical entities [Fulop 2010].

Mounting evidence suggests that frailty, measured by various assessment tools, is associated with poorer morbidity outcomes in cardiac surgical patients [Sepeshri 2014]. The impact of frailty on functional outcomes is less well defined. Without a standard definition of frailty, previous analyses have been subject to heterogeneity, due to the use of considerably different frailty measurement tools [Lee 2021]. This review aims to evaluate and summarize the current literature relating to the Fried indexes on both perioperative morbidity and quality of life to inform risk-stratification and assist in patient discussions regarding surgical expectations.

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**PATIENTS AND METHODS**

This review was written following the PRISMA guidelines for systematic reviews [Moher 2009]. Ethics approval was not required.

The PUBMED, MEDLINE, and EMBASE databases were searched from January 1, 2000 through August 1, 2021. The MeSH search terms included frailty, heart diseases, surgery, coronary artery disease, valvular disease which were used in AND and OR configurations.

Inclusion criteria for this review had the following eligibility criteria: (1) any retrospective or prospective study using an observational or randomized control trial study design, (2) use of the Fried or modified Fried frailty indexes, (3) outcomes stratified by frailty status, (4) cardiac surgery defined as any operation involving the coronary circulation, cardiac valves or proximal aorta requiring a median sternotomy, (5) full text articles in English; and (6) publication date after January 2000. Results of the search strategy are presented in Figure 1. (Figure 1)

Two authors (MN and JC) independently searched the selected databases and screened titles and abstracts to identify eligible studies. These studies were then pooled and evaluated for inclusion by reading the full-text manuscript, independently performed by MN and JC. Data was extracted by MN and verified by JC. The primary outcomes were one-year mortality and quality of life (QoL) or functional outcomes. Secondary outcomes included 30-day mortality, society of cardiothoracic surgeons (STS) defined major adverse cardiac or cerebrovascular events (MACCE), intensive care unit (ICU)

of postoperative complications. All discrepancies were resolved by consensus discussion with a third author (AS).

**Risk of bias in studies:** Quality assessment for non-randomized studies was performed independently by two authors (MN and JC) using the Newcastle-Ottawa scale (NOS). This tool is validated in the setting of retrospective cohort and case-control studies [Margulis 2014].

**Statistical analysis:** A meta-analysis was performed to evaluate pooled outcomes using inverse variance weighting, and results have been summarized as risk ratios (RR) for binary outcomes (one-year mortality, postoperative complication rate, and institutional discharge) and mean difference (MD) for continuous outcomes (hospital LOS and ICU LOS). All outcomes were derived from raw cohort data. The methods described by Wan et al. 2014, Luo et al. 2018, and Shi et al. 2020 were used to approximate means and standard deviation from range, median and interquartile range where appropriate [Shi 2020; Luo 2018; Wan 2014]. A random-effects model was used to assess the pooled effect-estimates. Where frailty was trichotomized as ‘frail,’ ‘prefrail,’ and ‘robust,’ the prefrail and robust cohorts were combined to represent ‘non-frail’ patients. The Fried frailty index was used in analysis preferentially over the Fried+ if both were reported. Statistical significance was defined as a p-value less than 0.05. Tau2 and

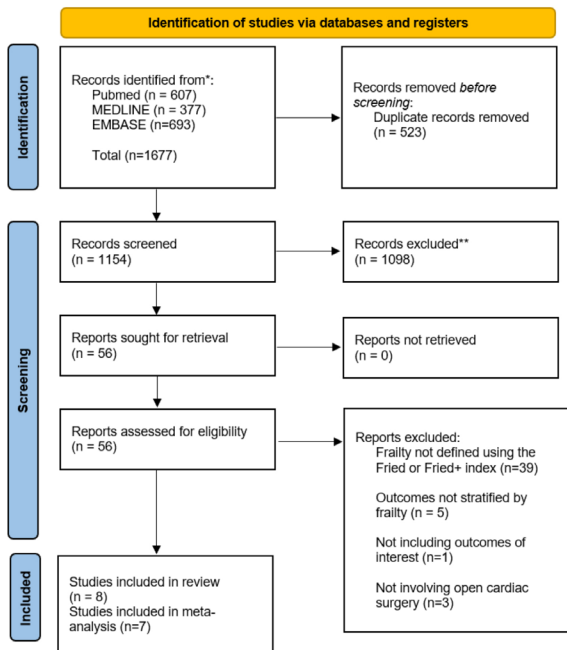


Figure 1. Results of database search and study inclusion

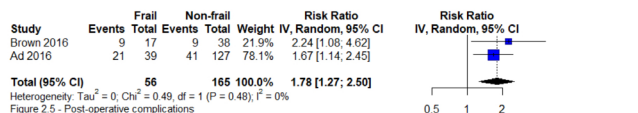
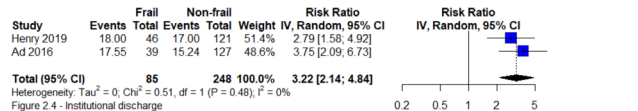
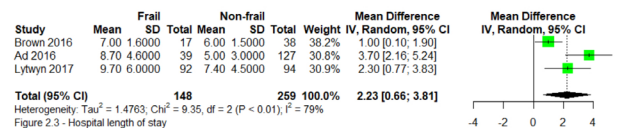
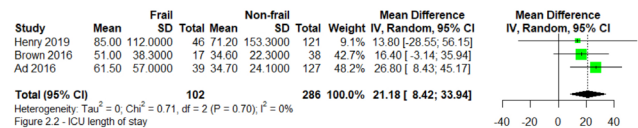
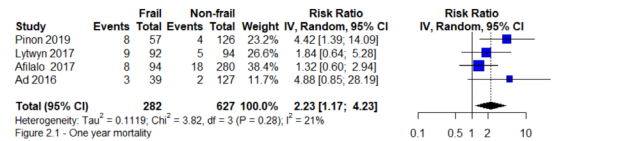


Figure 2. Meta-analysis of outcomes

length of stay (LOS), hospital length of stay, and development

I<sup>2</sup> values were used to assess heterogeneity [Higgins 2003].

I<sup>2</sup> values of 25%, 50%, and 75% indicate low, moderate, and high inter-study heterogeneity, respectively. Sensitivity analysis was performed by isolating pooled outcomes by strata of the Fried indexes individually. Additional sensitivity analysis was performed by separately evaluating each outcome after excluding studies with the largest weighting from the analysis.

All statistical analysis was performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and the ‘meta’ R package version 5.0.1, which is a software add-on for meta-analysis described by Balduzzi et al. [Balduzzi 2019].

## RESULTS

**Study selection and risk of bias:** A total of 1677 articles were identified from the database search (Figure 1). From these, 523 duplicate articles were removed. The remaining articles underwent a title and abstract screen, and 56 papers were evaluated by full text for inclusion. A total of eight articles were included in this systematic review and seven were analyzed in the meta-analysis.

Follow up ranged from one month up to three years postoperatively. Follow-up consistency was acceptable with a follow up rate of >80% achieved in all but one study [Ad 2016]. Methods of follow up included outpatient clinics, EMR records, and telephone contact. All studies were scored using the Newcastle-Ottawa scale (NOS) and deemed to be of an acceptable quality (Table 1). (Table 1)

**Study and cohort characteristics:** All studies included in this review were retrospective analyses of prospective cohorts. Five studies were performed at single centers [Ad 2016; Pinon 2019; Henry 2019; Lytwyn 2017; Brown 2016], while the remaining three were multicenter studies [Miguelena-Hycka 2019; Shi 2018; Afilalo 2017]. Investigations were performed

in multiple countries including the USA [Ad 2016; Henry 2019; Brown 2016; Shi 2018; Afilalo 2017], Canada [Lytwyn 2017; Shi 2018; Afilalo 2017], Spain [Pinon 2019; Miguelena-Hycka 2019], and France [Shi 2018; Afilalo 2017]. Cardiac surgical procedures included coronary artery bypass grafting (CABG), surgical aortic valve replacement (SAVR) and concomitant CABG and valvular surgery. Across all studies, 1,494 patients were assessed with a mean age ranging from 66 to 81 years. Study and cohort characteristics of the included articles are presented in Table 2. (Table 2)

**Definition of frailty:** Seven studies reported outcomes using the Fried index [Ad 2016; Pinon 2019; Henry 2019; Brown 2016; Miguelena-Hycka 2019; Shi 2018; Afilalo 2017], one of which also stratified cohorts using the Fried+ index [Afilalo 2017]. Only one study exclusively used the Fried+ index to report outcomes [Lytwyn 2017; Afilalo 2017]. Two studies made the distinction between frail, pre-frail, and robust [Miguelena-Hycka 2019; Shi 2018]. The cohort investigated by Shi et al. only included frail and pre-frail patients without any robust patients [Shi 2018]. Pre-frailty was described as meeting at one or two criteria and frailty as meeting three or more markers, regardless of whether the Fried or Fried+ index was used. Only one study in this meta-analysis exclusively used the Fried+ scale [Lytwyn 2017].

**Quality of life measures:** Quality of life represents an individual’s overall emotional and physical wellbeing, as well as engagement in social and functional aspects of life [Study Protocol WHO 1993]. Translating subjective patient experiences into objective measures requires detailed and sensitive assessment tools. Generic tools aim to assess QoL across several domains for comparability between different diseases and cohorts.

Validated generic HRQoL tools reported included the Short-form 12 survey (SF-12), EuroQoL 5-dimension index

Table 1. Quality assessment of studies included

Author, year	Selection			Demonstration that outcome of interest was not present at start of study	Comparability		Outcome	
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure		Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts
Piñón 2019	★	★	★	★	★	★	★	★
Henry 2019	★	★	★	★	★	★	★	★
Miguelena-Hycka 2019	★	★	★	★	★	★	★	
Lytwyn 2017	★	★	★	★	★	★	★	
Afilalo 2017	★	★	★	★	★	★	★	★
Ad 2016	★	★	★	★	★	★	★	
Brown 2016			★	★	★	★	★	★
Shi S (2018)		★	★		★	★	★	

Table 2. Study characteristics

Author, year (study period)	Study characteristics			Patient demographics	Study precision	
	Patients: frail vs. non-frail	Study design and location	Frailty tool (frailty groups)	Cohort demographics (Total or Non-frail vs. frail)	Method of follow up	Follow-up consistency
Piñón, 2019 (2010 – 2015)	N = 183, Frail: 57, Non-frail: 126	Prospective, single center, Spain	Fried frailty index, (frail and non-frail)	Age:80.8± 3.6, Female:50%, DM:36.1%, HTN:81.4%, HCL:61.7%, COPD:19.1%, CRF:13.7%, PVD:8.7%, CVA:8.2%, BMI: NR%, Albumin:4.2± 0.7	Baseline: NR Follow up: outpatient clinics, EMR records, tele- phone contact	PR: NR RR: 100%
Henry, 2018 (2012-2013)	N = 167, Frail: 46, Non-frail: 121	Prospective, single center, USA	Fried frailty index, (frail and non-frail)	Age: (73.0 vs 77.2), Female (19% vs 39.1%), Diabetes Mellitus: (26.4% vs 37.0%), HTN: (72.7% vs 82.6%), HCL: NR, COPD: NR, CRF: NR, PVD: (7.4% vs 13.0%), CVA (18.2% vs 21.7%), BMI: (28.3 ± 5.6 vs 30.4 ± 7.0), Albumin: NR%	Baseline: NR Follow up: NR	PR: 78% RR: 100%
Miguelena- Hycka, 2019 (2015-2016)	N = 137, Robust: 26, Pre-frail: 73, Frail: 38	Prospective, multicenter, Spain	Fried frailty index, (frail, prefrail and robust)	Age:78.4 ± 4.2, Female:65%, DM:38%, HTN:80.3%, HCL:59.1%, COPD:19.7%, CRF:NR%, PVD:NR%, CVA:NR%, BMI: 27.7 ± 3.9, Albumin: NR%	Baseline: NR Follow up: NR	PR: 96% RR: 80%
Lytwyn, 2017 (2012-2013)	N = 186, Frail: 92, Robust: 94	Prospective, single center, Canada	Modified fried frailty index, (frail, non-frail)	Age:(70 vs 73), Female:(22.3% vs 35.9%), DM:(24.5% vs 39.1%), HTN:(77.7% vs 90.2%), HCL:(71.3% vs 73.9%), COPD:(6.5% vs 18.9%), CRF:(2.1% vs 8.7%), PVD:(6.4% vs 16.3%), CVA:(6.4% vs 18.5%), BMI:(28.3 (25.3-33.1) vs 28.4 (25.1-31.3)), Albumin:(38 (35-40) vs 37 (34-39)	Baseline: NR Follow up: questionnaire during in clinic follow up or by telephone, 3 attempts	PR: 80% RR: 99%
Afilalo, 2017 (2012-2016)	N = 374, Frail: 94, Non-frail: 280	Prospective, multicenter (14), USA, Canada, France	Fried frailty index, modified fried frailty (frail, non-frail)	Age:77, Female:33%, DM:30%, HTN:NR%, HCL:NR%, COPD:12%, CRF:NR%, PVD:11%, CVA:5%, BMI:28.1, Albumin:4.0(g/DL)	Baseline: NR Follow up: medical records, death certificates, administrative records, contact with patient or family	PR: NR RR: 100%
Ad, 2016 (2012-2013)	N = 166, Frail: 39, Non-frail: 127	Prospective, single center, USA	Fried frailty index, (frail, non-frail)	Age:(73.1 vs 77.6), Female:(21% vs 39%), DM:(27% vs 39%), HTN:(74% vs 82%), HCL:NR%, COPD:(23% vs 44%). CRF: NR%, PVD:(7% vs 15%), CVA:(18% vs 23%). BMI:(28.4± 5.6 vs 30.7 ± 6.9), Albumin:(4.0 ± 0.4 vs 3.9 ± 0.4) (g/DL)	Baseline: NR Follow up: NR	PR: 51% RR: NR
Brown, 2016 (2010-2013)	N = 55, Frail: 17 (17), Non-frail: 38	Prospective, single center, USA	Fried frailty index, (frail, non-frail)	Age (64.7±5.6 vs 67.7±8.4), Female:(21% vs 35.3%, HTN:(84.2% vs 82.4%), DM:(29.0% vs 47%), COPD: (10.5% vs 29.4%), CRF: (7.9% vs 0%), PVD:(2.6% vs 0%), CVA:(5.3% vs 5.9%), BMI: NR, Albumin: NR	Baseline: Trained research assistant Fol- low up: Inpatient chart review	PR: 34% RR: 92%
Shi S, 2018 (2014-2018)	N = 91, Pre- frail: 56, Frail: 35	Prospective, multicenter (14), Canada, USA, France	Fried frailty index, (frail, pre-frail)	Age (77.8 ± 5.3), female:44.0%, DM:28.6%, HTN:NR%, COPD:24.2%, CRF:29.7%, PVD: NR, CVA:6.6%, BMI: NR, Albumin: NR	Baseline: trained research assistant or nurse interview, Follow up: telephone	PR: NR RR: 88%

DM, diabetes mellitus; HTN, hypertension; HCL, hypercholesterolaemia; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; PVD, peripheral vascular disease; CVA, cerebrovascular accident; BMI, body mass index; NR, not reported; PR, participation rate; RR, response rate; P, prospective



Table 3. Quality of life and functional outcomes

Author, year	Results
Miguelena-Hycka 2019	Six month follow up (preop vs. postop), Frail: EQ5D-index: 0.65 vs 0.775 *, Prefrail: EQ5D-index: 0.775 vs 0.84 *, Robust: EQ5D-index: 0.870 vs 0.9, Frail: EQ5D VAS: 46% vs 60%*, Prefrail: EQ5D VAS: 60% vs 67%*, Robust: EQ5D VAS: 71% vs 75%
Henry 2019	Baseline vs six months vs. 12-month follow up, Frail: SF12 PCS, 34.0 vs 38.6 vs 37.9, Non-frail: SF12 PCS, 46.4 vs 49 vs 50, Frail: SF12 MCS: 52.1 vs 52.1 vs 50.8, Non-Frail: SF12 MCS: 55.4 vs 56 vs 52
Shi 2018	Death vs poor recovery vs partial recovery vs good recovery (6 month follow up), Frail: 3% vs 11% vs 34% vs 51%, Prefrail: 4% vs 2% vs 30% vs 64%, Six-month mortality or poor recovery A (frail vs pre-frail): OR: (2.9 (0.7 – 13.2), $P = 0.16$ ), Six-month mortality or poor recovery A (frail vs pre-frail) OR: (2.7 (0.6 – 13.6), $P = 0.22$ )
Lytwyn 2017	1-year postoperative EuroQoL-VAS score (frail vs not-frail) (74(50-83) vs 80(70-87), $P < 0.01$ ), 1-year poor functional survival B (frail vs not-frail) 38.0% vs 14.9%, $P < 0.01$ (OR 3.51 (1.73-7.11)), 1-year poor functional survival B (frail vs not-frail) 38.0% vs 14.9%, $P < 0.01$ (OR 3.44 (1.69-7.00))

A, poor recovery defined as NRHA 3/4 and functional decline defined in study; B, poor functional survival defined as EuroQoL-Visual Analogue Scale score  $\leq 60$ ; EQ5D- index, EuroQoL 5-dimension index; EQ5D- VAS, EuroQoL 5-dimension visual analogue score; SF12 MCS, short form 12 mental component score; SF12 PCS, short form 12 physical component score; \*indicates significance

score (EQ5D-index) and visual analogue component (EQ5D-VAS) [Johnson 1998]. The EQ5D-index score is calculated from a questionnaire, describing quality of life while the EQ5D-VAS is a numerical value given by a patient for their perceived overall quality of life. One further study reported an institutional functional status score based on patient activities of daily living and New York Heart Association class [Gallagher 2019]. A summary of QoL outcomes is presented in Table 3. (Table 3)

**Morbidity and mortality outcomes:** A summary of all clinical outcomes is presented in Figure 2. (Figure 2) Frail patient status was associated with an increased risk of one-year all-cause mortality over non-frail patients (RR: 2.23; 95% CI 1.17 – 4.23;  $P = 0.01$ ). Frail patients also experienced worse outcomes in several perioperative domains, including a longer ICU length of stay (MD 21.18 hours; 95% CI 8.42 – 33.94;  $P < 0.01$ ), total hospital length of stay (MD 2.23 days; 95% CI 0.66 – 3.81;  $P < 0.01$ ), institutional discharge (RR 3.29; 95% CI 2.19 – 4.94;  $P < 0.01$ ), and any postoperative complication (RR 1.78; 95% CI 1.27 – 2.50;  $P < 0.01$ ). An analysis of perioperative mortality and STS defined major adverse events was unable to be conducted due to limited available data.

A sensitivity analysis was performed by analyzing the outcome variables by strata of the Fried index separately. One-year mortality remained significant (RR 2.59; 95% CI 1.01 – 6.60;  $P = 0.05$ ). Outcome variables, including postoperative complications, ICU admission duration and institutional discharge, were calculated only using the Fried index and remained significant, however, hospital LOS was no longer significant after index stratification (MD 2.28; 95% CI -0.37 – 4.92;  $P = 0.09$ ). Additional sensitivity analysis was performed by omitting the study with the largest weighting from each outcome given the limited number of articles. One-year mortality remained significant (RR 3.01; 95% CI 1.47 – 6.14;  $P < 0.01$ ), as did hospital LOS (MD 3.00 days; 95% CI 1.63 – 4.37;  $P < 0.01$ ), postoperative complications (RR 2.24; 95%

CI 1.08 – 4.62;  $P = 0.03$ ), and institutional discharge (RR 2.79; 95% CI 1.58 – 4.92;  $P < 0.01$ ). The duration of ICU admission showed borderline significance (MD 15.9 hours; 95% CI -1.79 to 33.69);  $P = 0.08$ ).

**Health-related quality of life:** Health-related quality of life outcomes were reported in four studies (Table 3) [Henry 2019; Lytwyn 2017; Miguelena-Hycka 2019; Shi 2018]. Due to heterogeneous quality of life tools and QoL assessment at variable follow-up intervals (range: three to 12 months), a meta-analysis was not conducted.

Non-frail patients displayed higher levels of preoperative quality of life over their frail counterparts. Overall HRQoL improved across all frailty statuses at the six-month mark, although with a maximal follow up of one year, there is insufficient evidence to conclude if this is sustained in the long-term. Miguelena-Hycka et al. suggested robust patients preoperative QoL exceeds national age-matched QoL averages (EQ-5D index 0.87 vs. national average 0.78, VAS 71% vs. national 62.2), and remains unchanged following surgery at six months [Miguelena-Hycka 2019; Janssen 2014]. Comparatively, frail and pre-frail patients experienced a significant increase in HRQoL, with outcomes slightly inferior to national averages as measured by the VAS score. Lytwyn et al. did not report specific HRQoL scores for patients but identified postoperative QoL was significantly greater in non-frail patients (EQ5D-VAS, frail vs. not-frail 74(50-83) vs. 80(70-87),  $P < 0.01$ ) [Lytwyn 2017]. Physical improvements in QoL were the greatest beneficiaries of surgery suggested by results from Henry et al., finding only the physical component of the SF-12 survey showing improvement at six months for patients, while the mental domain showed no changes post-operatively [Henry 2019]. One year post-operatively, the mental domain scored worse than pre-operatively for both groups of patients, while the physical score did not change appreciably. Shi et al. only noted that frail patients have higher rates of poor recovery with reduced improvement in activities of daily living in comparison with pre-frail patients [Shi 2018].

## DISCUSSION

Frail patients undergoing cardiac surgery have significantly higher perioperative risk and poorer survival outcomes. This meta-analysis demonstrates that frailty is associated with worse operative outcomes including one-year mortality, ICU length of stay, hospital length of stay, institutional discharge, and the development of postoperative complications. Despite this, quality of life improves substantially following surgery even amongst frail patients. The identification of frailty therefore should not represent a contraindication to surgical candidacy in of itself. Frailty may assist in discussions between patients and health care providers regarding the risks are surgery and expected quality-of-life trajectory.

To the authors' knowledge, this is the first meta-analysis on the clinical impact of the 'Fried' and 'modified Fried' frailty criteria following cardiac surgery. Previous analyses of frailty, measured by multiple assessment criteria, have demonstrated poorer morbidity outcomes but have been subject to significant inter-study heterogeneity warranting a more detailed analysis of individual frailty measures [Sepehri 2014; Li 2018; Abdullahi 2017]. This review explores the archetype of frailty first described by Fried et al., in conjunction with the modified Fried index, which use the same five features of physical decline to reduce study heterogeneity in this analysis. Consistency in the patient characteristics identified by frailty assessment is reflected in the low  $I^2$  values suggesting a low level of inter-study heterogeneity. Heterogeneity was only present in the assessment of hospital length of stay ( $I^2$  79%) while all other outcome variables had a low degree of heterogeneity ( $I^2$  range 0-25). An influential analysis was performed in consideration of the limited number of studies present, whereby each study with the largest weighting was excluded and the outcomes separately re-evaluated. Significance was maintained for all outcomes excluding ICU admission duration, which showed borderline significance (MD 15.9 hours; 95% CI -1.79 to 33.69);  $P = 0.08$ ). Larger samples may more definitively identify this association. The Fried+ index was considered eligible in this analysis due to the common physical evaluation of frailty. The addition of cognitive domains in the Fried+ index theoretically allows frail patients who, due to mental factors, would otherwise be unable to complete physical assessment [Bieniek 2016]. To account for possible underlying heterogeneity due to inclusion of the Fried+ criteria, a further analysis was performed which excluded these studies. Significance of all outcome variables aside from hospital LOS was maintained ( $P = 0.09$ ), substantiating Fried frailty alone as independently associated with negative operative outcomes. Existing preoperative risk assessment tools, including EuroSCORE II and the STS-PROM, are used in assessing preoperative surgical risk and candidacy. These were not directly controlled for within available studies preventing subgroup analysis. As such, while no consistent imbalances were seen between frail and non-frail cohorts among included studies, the benefit of frailty as an additive element or use as a separate assessment tool remains uncertain. This article also discusses functional outcomes in frail patients following cardiac surgery which has not been the subject of any prior systematic reviews.

While quality of life was unable to be analyzed in-depth, this review nonetheless highlights some important aspects of QoL in cardiac surgery patients. Preoperative quality of life is substantially higher in non-frail patients and baseline QoL in robust patients is comparable with national age-matched quality of life averages [Henry 2019; Miguelena-Hycka 2019; Janssen 2019; McCaffrey 2016]. Comparatively, frail patients have significantly lower QoL levels. Henry et al. observed that frailty only was associated with a poorer physical QoL, finding that preoperative mental QoL is fair regardless of frailty status [Henry 2019]. Fried frailty is defined through poor physical functioning and may account for this weighting of physical QoL characteristics. Quality of life improvements were more substantial in those that are frail, however, QoL postoperatively remained inferior to pre-surgical QoL in non-frail patients [Henry 2019; Miguelena-Hycka 2019]. Consequently, frail patients should be aware that the physiological decline associated with frailty is not entirely related to cardiac pathology and that surgical intervention may not completely restore their QoL to national averages. Postoperative QoL in robust patients was unchanged, although only generic QoL assessments were used which may not be sensitive enough to identify a relief in cardiac specific symptoms. The interpretation of results must be constrained as the maximum follow up for quality-of-life data was only one year. Previous studies have suggested QoL improvements after cardiac surgery can be sustained for up to 10 years with a gradual decline in functioning related to loss of graft patency and multifactorial age-related decline [Gjeilo 2018]. This may not hold true for frail patients due to the multifactorial nature of frailty and consequently longer-term studies are required to inform surgical decision-making. Overall, contrary to morbidity outcomes, frailty does not appear to be associated with detrimental functional outcomes. Patients and clinicians must reconcile the immediate perioperative morbidity caused by surgery, as well as the double-fold risk of mortality within one year, against possible improvements in QoL.

Identifying frail patients pre-operatively may also provide an avenue to attempt health optimization in anticipation of surgery. Nutritional input, as well as strength and conditioning regimes, have been shown to reduce or limit the progression of patient frailty, so called 'pre-habilitation,' and efforts to characterize patient outcomes in this domain is an ongoing area of investigation [McCann 2019; Travers 2019]. A significant portion of frail patients also do not experience straightforward postoperative courses. Anticipation of postoperative complications with careful surgical planning and efficient postoperative care may improve patient outcomes in this area. Given the high rates of institutional discharge, early preparation for discharge and arrangement of outpatient services may facilitate efficiency during the inpatient episode and allow reduced hospital expenditure as an avenue for cost containment [Montgomery 2021].

**Limitations:** This review has several important limitations to consider. Only a limited meta-analysis could be performed, due to the inclusion of only a small number of studies and several important perioperative outcomes, including 30-day mortality and MACCE, were unable to be assessed.

Existing cardiac risk assessment tools, including EuroSCORE and STS-PROM, also were not stratified in this analysis, and the value of frailty as an additive element or separate assessment remains uncertain. An analysis of quality of life also was unable to be conducted given heterogeneous QoL tools and long-term data would be required to better inform patients of functional outcomes after surgery. Additionally, the concept of an intermediate ‘prefrailty’ stage has been recognized as providing further granularity in predicting patient outcomes. Pre-frail cohorts were reported in only two studies and definite conclusions regarding this subset of patients remains unclear. Further research is required to clarify outcomes in frail patients and better understand the risk-benefit profile essential to surgical decision making, and this review of Fried frailty serves as the first step in substantiating this clinical issue.

## CONCLUSIONS

This focused review on the Fried frailty measures demonstrates that frail patients have double the risk of all-cause mortality within one year of cardiac surgery. Patients also experience considerably worse perioperative outcomes, including ICU length of stay, hospital length of stay, institutional discharge, and postoperative complications. Quality of life improves remarkably following surgery but remains inferior to the general population in frail patients. Resolution of cardiac pathology may not entirely resolve the poorer quality of life in frail patients. Identification of frailty during preoperative assessment may be useful in discussions surrounding surgical suitability and patient expectations.

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