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Preoperative Frailty Assessment and Outcomes At 6 Months or Later In Older Adults Undergoing Cardiac Surgical Procedures: A Systematic Review

Dae Hyun Kim, MD, MPH, ScD[1,2], **Caroline A. Kim, MD, MS, MPH**[1], **Sebastian Placide, BA**[3], **Lewis A. Lipsitz, MD**[1,4], and **Edward R. Marcantonio, MD, ScM**[1,5]

[1] Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

[2] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[3] Albert Einstein College of Medicine, Bronx, NY

[4] Institute for Aging Research, Hebrew SeniorLife, Harvard Medical School, Boston, MA

[5] Division of General Medicine and Primary Care, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Abstract

Background—Frailty assessment may inform surgical risk and prognosis that are not captured by conventional surgical risk scores.

Corresponding author: Dae Hyun Kim, MD, MPH, ScD, 110 Francis Street 1A, Boston, MA, 02120, Tel: 617-632-8696, Fax: 617-632-8968, dkim2@bidmc.harvard.edu.

Author contributions:

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- Acquisition, analysis, or interpretation of data: All authors
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- Data: See Appendices

Purpose—To evaluate the evidence for various frailty instruments to predict mortality, functional status, or major adverse cardiovascular and cerebrovascular events (MACCE) in older adults undergoing cardiac surgical procedures.

Data Sources—MEDLINE and EMBASE (without language restrictions), from their inception to May 2, 2016.

Study Selection—Cohort studies that evaluated the association of frailty with mortality or functional status at ≥6 months in patients aged ≥60 years undergoing major or minimally invasive cardiac surgical procedures.

Data Extraction—Two reviewers independently extracted study data and assessed study quality.

Data Synthesis—Mobility, disability, and nutrition were frequently assessed domains of frailty in both types of procedures. In patients undergoing major procedures (N=18388, 8 studies), 9 frailty instruments were evaluated. There was moderate-quality evidence to assess mobility or disability and very-low-to-low-quality evidence to use a multi-component instrument to predict mortality or MACCE. No studies examined functional status. In patients undergoing minimally invasive procedures (N=5177, 17 studies), 13 frailty instruments were evaluated. There was moderate-to-high-quality evidence to assess mobility to predict mortality or functional status. Several multi-component instruments predicted mortality, functional status, or MACCE, but the quality of evidence was low to moderate. Multi-component instruments that measure different frailty domains seemed to outperform single-component instruments.

Limitations—Heterogeneity of frailty assessment, limited generalizability of multi-component frailty instruments, few validated frailty instruments, and potential publication bias.

Conclusions—Frailty status, assessed by mobility, disability, and nutritional status, can predict mortality at 6 months or later after major cardiac surgical procedures and functional decline after minimally invasive cardiac surgical procedures.

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INTRODUCTION

Approximately 500,000 cardiac surgical procedures are performed each year in the United States and more than 50% of these are performed in older adults.(1) Due to high burden of cardiovascular disease and evolution of minimally invasive surgical techniques, this number is expected to rise.(2-4) While older patients may benefit from cardiac surgical procedures, some do not survive or experience complications,(5-10) functional decline,(11, 12) and poor quality of life.(13-15) Identifying patients who are most or least likely to benefit from surgical procedures remains a significant challenge.

One of the factors underlying the heterogeneity of health outcomes in older patients is the presence of frailty, which reflects an individual's reduced physiologic reserve, inability to tolerate stressful events (e.g., surgery), and vulnerability to adverse outcomes.(16) Experts have developed several instruments to measure frailty by assessing gait speed, grip strength, or deficit accumulation,(17-23) but there is no consensus on how to best measure this vulnerability.(24, 25) Despite lack of consensus, accumulating evidence suggests that assessment of frailty using any validated measures provides additional information on surgical risk and prognosis not captured by traditional surgical risk assessment.(5-10) However, most surgical risk scores do not include measures of frailty.(26-29) To incorporate frailty screening in the risk assessment before cardiac surgical procedures, it is essential to evaluate the feasibility and validity of frailty instruments in this setting. If preoperative frailty status predicts mortality, functional status, and quality of life, such information will be useful to make informed decision about the procedures.

This review aims to evaluate the evidence on feasibility of frailty instruments and their validity in predicting mortality or functional status in older patients who are undergoing major or minimally invasive cardiac surgical procedures. Since several previous reviews (30-35) have reported short-term mortality and complications, we reviewed up-to-date literature on clinical outcomes at 6 months or later after cardiac surgical procedures.

METHODS

We developed but did not register a protocol for the review (see Data Supplement) and prepared this report according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.(36)

Data Sources and Searches

We searched MEDLINE and EMBASE for original research articles that evaluated any frailty measures in adults undergoing cardiac surgery, without language restriction, from the inception of database to May 2, 2016, using the following keywords and their variations: *"aged"* and *"cardiac surgery"* and "frailty, geriatric assessment, mobility, gait speed, muscle strength, grip strength, physical activity, exhaustion, weight loss, nutrition, cognitive function, functional status, activities of daily living" (see Data Supplement). We also examined reference list of reviews (30-35) and articles meeting inclusion criteria.

Study Selection

Two investigators (C.A.K., S.P.) independently screened titles and abstracts and then texts of full-length articles passing the title and abstract screen. Disagreement was resolved by consensus involving a third investigator (D.H.K.). Original research articles published in any language were eligible if 1) the mean age of study participants was ≥60 years; 2) the surgical procedure was coronary artery bypass grafting (CABG), open valve surgery, or transcatheter valve replacement; 3) the study was a cohort study with ≥6 months of follow-up; and 4) mortality or functional status were reported according to preoperative frailty status. We considered any measures of physical function (mobility, muscle strength, physical activity, exhaustion, nutrition, balance, disability) or any combinations thereof as acceptable screening for frailty. We did not consider comorbidity or cognitive function alone as a measure of frailty if it was not combined with measures of physical function. Although 6-minute walk test (6MWT) is a measure of endurance, we classified it under mobility as it is highly correlated with mobility.(37, 38) Articles were excluded if a study design other than a cohort study was used; sample size was <100; or frailty measures were not assessed before surgery. When ≥2 articles originated from the same population, studies with the larger sample size and/or longer follow-up were included.

Data Extraction

Two investigators (C.A.K., D.H.K.) independently extracted data on patient characteristics, type of procedures (major vs. minimally invasive), frailty assessment domains (see Appendix Table 1), and outcomes (see Data Supplement). Any disagreement was resolved by consensus. We classified CABG and open valve surgery as major surgical procedures and transcatheter aortic valve replacement (TAVR) as a minimally invasive surgical procedure. To assess feasibility of frailty assessment, we extracted administration time for frailty measures or, if not reported, approximated it based on the literature or our own experience (see Data Supplement). The prevalence of frailty was estimated according to the study-specific definition.

Our main outcomes of interest were mortality or poor functional status at ≥6 months after surgery. We considered the following measures of functional status: activities of daily living (ADL), instrumental activities of daily living (IADL), Duke Activity Status Index,(39) Kansas City Cardiomyopathy Questionnaire,(40) or New York Heart Association class. Our secondary outcome was major adverse cardiovascular and cerebrovascular events (MACCE). We extracted the absolute risk and relative risk (RR) of each outcome and 95% confidence interval (CI) according to frailty status, with or without adjustment for traditional surgical risk scores. When RR was not reported, we calculated it from the count data. Metrics to evaluate diagnostic tests or prediction models (e.g., sensitivity, specificity, calibration, and discrimination) were obtained, if reported. Data extracted from individual studies are provided in Appendix Table 2.

Quality Assessment

Two investigators (C.A.K, D.H.K.) independently evaluated each study for the following: 1) representativeness of the study population, 2) use of frailty measures that have been validated in general population of older adults, 3) frailty status determination, 4) loss to follow-up or amount of missing outcome data (mortality and functional status, separately), 5) missing data on frailty measures, and 6) validation of the risk prediction performance (See Data Supplement). Any disagreement was resolved by consensus. We determined the overall quality of evidence for each pair of a frailty instrument and an outcome as high, moderate, low, and very low quality, based on the representativeness of study populations, the risk of bias, consistency in the results across studies, and strength of associations (See Data Supplement).

Data Synthesis

We qualitatively summarized the evidence by type of cardiac surgical procedures (major vs. minimally invasive procedures) and type of frailty instruments (single-component vs. multi-component instruments). One study included both major and minimally invasive procedures without stratified data by procedure type.(41) Since only 15% of patients underwent minimally invasive procedures in this study, it was categorized as the major cardiac surgical procedure. A substantial variation in frailty assessment and patient characteristics across the studies did not allow pooling individual study estimates into a summary result.

Role of the Funding Source

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RESULTS

We identified 25 studies that evaluated the association of frailty with mortality or functional status at ≥6 months in 18388 patients undergoing major cardiac surgical procedures (9 frailty instruments in 8 studies of CABG or open valve surgery)(41-49) and 5177 patients undergoing minimally invasive cardiac surgical procedures (13 instruments in 17 studies of TAVR)(11-15, 50-61) (Appendix Figure 1).

Frailty Assessment in Major Cardiac Surgical Procedures

There were 8 studies evaluating 4 single-component and 5 multi-component frailty instruments in patients undergoing major cardiac surgical procedures (Figure 1 and Table 1). Studies varied widely in terms of sample size (166-11815 patients), mean age (62-79 years), follow-up period (7-65 months), or prevalence of frailty (4-70%). Mobility (5 studies), disability (4 studies), and nutrition (3 studies) were commonly assessed (Figure 1).

Single-component frailty instruments—Except for the 6MWT, single-component instruments could be administered within 5 minutes (Table 1). The 6MWT distance,(43) low albumin,(44) and ADL dependence(45) were statistically significantly associated with a 2.4- to 3.6-fold risk of mortality or MACCE. The study by Robinson et al.(42) was underpowered to detect a clinically significant mortality difference by the Timed-Up-and-Go (TUG) test performance. No studies examined functional status. Only the 6MWT(43) and ADL dependence(45) were evaluated in highly representative samples of routine clinic patients (e.g., a multi-center study of consecutive patients); other measures were evaluated in less-representative, single-center samples (Appendix Figure 2 panel A). None of the single-component instruments have been validated in an independent sample of patients undergoing major cardiac surgical procedures. Accordingly, we judged the overall quality of evidence for predicting mortality moderate for mobility and ADL dependence, and low for serum albumin (Appendix Figure 2 panel B).

Multi-component frailty instrument—There were 5 multi-component frailty instruments that required information from self-report or medical records alone(46, 47) (administration time <5 minutes) or administration of performance tests(41, 48, 49) (up to 20 minutes). Frequently included components were mobility (4 instruments) and disability (4 instruments). Lee et al.(46) and Sundermann et al.(41, 48) found a statistically significant, 1.5- to 4.5-fold risk of mortality for frail patients. Such association was not found for the

Cervera index and frailty phenotype due to simultaneous adjustment for other frailty markers(47) or insufficient power.(49) None of the studies examined functional status. All 4 studies of multi-component instruments were conducted in single-center samples (Appendix Figure 2 panel A) and only Lee et al. evaluated the model performance after accounting for overfitting.(46) Some studies did not employ validated measures of frailty(46, 47) or determined the frailty status according to a previously validated definition or clinical cutpoints.(41, 46-48) The overall quality of evidence for multi-component instruments for mortality was low or very low (Appendix Figure 2 panel B).

Frailty Assessment in Minimally Invasive Cardiac Surgical Procedures

There were 17 studies evaluating 8 single-component and 5 multi-component frailty instruments in patients undergoing TAVR (Figure 1 and Table 2). The mean age of TAVR patients was older (79-86 years) than that of patients undergoing major cardiac surgical procedures. Sample size (100-2137 patients), follow-up period (6-42 months), and prevalence of frailty (5-85%) were highly variable across studies. Mobility (13 studies), nutrition (7 studies), disability (7 studies), and subjective assessment (6 studies) were frequently assessed domains (Figure).

Single-component frailty instrument—A simple assessment of mobility (administration time <1 minute), such as impaired mobility due to musculoskeletal or neurologic disorder(56) or use of assistive devices(50), and 6MWT (10 minutes) distance below various thresholds(12, 51-53) were statistically significantly associated with a 1.2- to 3.2-fold increase in mortality (Table 2). ADL dependence (5 minutes) was statistically significantly associated with mortality in 2 of the 3 studies.(54, 55) The Clinical Frailty Scale (3 minutes), a global assessment based on medical problems, activity level, and disability, predicted mortality,(50, 60) whereas subjective assessment without such a scale did not.(12, 56, 57) A majority of studies of single-component instruments were conducted in highly representative samples, but the risk of bias was high due to determination of frailty status without using previously validated or clinical cutpoints and lack of validation (Appendix Figure 2 panel A). The overall quality of evidence was moderate for mobility, Clinical Frailty Scale, and subjective assessment, and low for disability in mortality prediction (Appendix Figure 2 panel B). There were 3 studies that examined a composite outcome of mortality and poor functional status (Table 2). Wheelchair-bound status(15) and 6MWT distance <170m (among COPD patients)(12) were statistically significantly associated with a 2.6- to 2.8-fold risk of the composite outcome. Serum albumin was not associated with the outcome after adjusting for mobility impairment.(15) Subjective assessment did not predict the outcome in COPD patients.(12) All 3 studies were conducted in highly representative samples, but the risk of bias was moderate due to missing outcomes and lack of validation (Appendix Figure 2 panel A). The quality of evidence was high for mobility and low for nutrition and subjective assessment (Appendix Figure 2 panel B).

Multi-component frailty instrument—There were 5 different multi-component frailty instruments that would require 10 minutes (Green index)(14) to 25 minutes (Stortecky index)(11, 58) for administration (Table 2). Multi-component instruments frequently included an objective measure of mobility (5 instruments), nutrition (4 instruments), and disability (3 instruments). Ewe et al.(59) found that frailty phenotype was statistically significantly associated with a 4.2-fold risk in mortality or MACCE, whereas Munoz-Garcia et al.(51) did not find such association, likely due to overadjustment for post-procedure ADL dependence. Frailty defined by all other instruments (11, 14, 58, 61) was statistically significantly associated with a 1.9- to 5.6-fold risk in mortality. Only the Green index(14) was developed in a highly representative sample (Appendix Figure 2 panel A). Except for frailty phenotype, frailty status was defined according to the study population distribution. Validation was not performed. In mortality prediction, the overall quality of evidence was moderate for Stortecky index(11, 58) and very low or low for other instruments (Appendix Figure 2 panel B). Multi-component instruments by Green,(14) Arnold(13), and Stortecky(11) examined a composite outcome of mortality and poor functional status (Table 2). Frailty determined by these indices was statistically significantly associated with a 2.2- to 4.2-fold increase in the risk of composite outcome at 6 or 12 months. The Green index(14) and Arnold index(13) have been developed in highly representative samples (Appendix Figure 2 panel A). However, study-specific definitions of frailty have not been tested in an independent sample, and only the Arnold index(13) was internally validated using split-sample validation. The quality of evidence was moderate for the Arnold index(13) and low for the other indices(11, 14) (Appendix Figure 2 panel B).

Comparison of Different Frailty Instruments

There were 8 studies that directly compared different frailty instruments (Appendix Table 3). Objective measures of lower extremity performance (mobility and leg muscle strength), such as TUG,(11, 58), 6MWT(12), and chair rise,(48) seemed to have higher C statistics or RRs than cognitive tests,(11, 58) self-reported mobility impairment,(11, 48, 58) disability,(11, 58) or subjective assessment.(12, 48) Among the non-performance-based measures, self-reported mobility impairment, such as stair climbing,(48) preclinical mobility disability,(11, 58) mobility impairment due to musculoskeletal or neurological disorder,(50) and wheelchair use(15), was more predictive than disability,(11, 50, 58) serum albumin,(15) and subjective assessment.(48, 50) In comparing single-component and multi-component frailty instruments, multi-component instruments seemed to provide better prediction as shown by Green et al.(14) and Sundermann et al.(48) Similarly, the Mini-Nutritional Assessment(62) that considered several risk factors of malnutrition in multiple domains showed higher RR than disability or cognition alone.(11, 58) However, a multi-component instrument that was composed of several measures assessing the same domain showed lower C statistic than its abbreviated version.(48)

DISCUSSION

In this review, we critically appraised heterogeneous literature on the role of frailty assessment in predicting mortality and functional status at ≥6 months after cardiac surgical procedures. There were 9 frailty instruments evaluated in major surgical procedures and 13 instruments in minimally invasive surgical procedures. Despite various ways of measuring frailty, we found strong evidence that frailty predicted mortality at ≥6 months after major or minimally invasive procedures. Some evidence indicated that frailty can predict functional decline, poor quality of life, or no symptomatic benefit after minimally invasive procedures.

Current Evidence for Frailty Assessment in Cardiac Surgical Procedures

Current evidence best supports mobility assessment as a single-component frailty instrument before cardiac surgical procedures. In the general population, gait speed is a highly sensitive marker of frailty(63, 64) and a strong predictor of institutionalization, disability, and mortality.(65) Gait speed predicts short-term mortality and complications after cardiac surgery or TAVR.(6-8) We found a large body of evidence to support use of mobility assessment to predict mortality at ≥6 months after major or minimally invasive procedures and functional status after minimally invasive procedures. Although 6MWT was most frequently evaluated, a simple gait speed or TUG test might be as useful, given its high correlation with 6MWT performance (0.70-0.73).(37, 38) When an objective assessment is not feasible, asking about one's ability to climb stairs, difficulty walking due to musculoskeletal or neurologic disorders, or wheelchair use can be an alternative screening. Disability, nutritional status, and the Clinical Frailty Scale can be useful, but the evidence is not as robust as mobility assessment. There is sufficient evidence that a clinician's subjective assessment does not predict outcomes.(12, 56, 57) Such an assessment without standardized criteria is prone to personal bias and low reproducibility.(66)

Several multi-component frailty instruments predicted mortality at ≥6 months after major or minimally invasive cardiac surgical procedures and functional status after minimally invasive procedures. These instruments included assessments of mobility (based on a performance test), disability, and nutrition. Although widely validated frailty phenotype(17) predicted mortality and MACCE after TAVR,(59) this finding was not consistent in other studies.(49, 54) The deficit accumulation frailty index is another validated frailty instrument,(18, 67) but its association with clinical outcomes has not been tested in patients undergoing cardiac surgical procedures.

Some evidence suggests that multi-component frailty instruments may offer better risk discrimination than single-component instruments in major or minimally invasive cardiac surgical procedures. Green et al.(14) and Sundermann et al.(48) showed that combining measures in different frailty domains might improve risk prediction. Stortecky et al.(58) and Schoenenberger et al.(11) found that the Mini-Nutritional Assessment(62), a multi-component screening tool for malnutrition, was more strongly associated with mortality and functional decline than disability or cognitive function alone. Moreover, information from multi-component frailty instruments may inform clinicians of each patient's need and vulnerability for perioperative management.

Other Relevant Reviews on Frailty Assessment Before Cardiac Surgical Procedures

We searched MEDLINE using the keywords "*cardiovascular surgical procedures*" and "*frailty*" on June 1, 2016 and identified 6 reviews.(30-35) These reviews highlighted high prevalence of frailty and its prognostic power in predicting short-term and long-term clinical outcomes after cardiac surgical procedures. The authors of the reviews called for development and validation of a standardized frailty instrument for preoperative risk assessment. Our review adds to the previous reviews by summarizing up-to-date literature and evaluating the strength of evidence by types of frailty instruments and by cardiac surgical procedures. The definition and feasibility of frailty instruments were summarized, with the absolute and relative risk of mortality and poor functional status by frailty status. We focused on the outcomes at ≥6 months after cardiac surgical procedures, because mortality and functional status beyond early postoperative period would be better aligned with the patient's value than surviving first 30 days after procedure.(68) Our review may facilitate adoption of evidence-based frailty assessment, objective assessment of prognosis, and transparent decision-making regarding cardiac surgical procedures.

Limitations of the Systematic Review

Our evidence synthesis is limited by heterogeneity of frailty instruments and low-to-moderate quality of included studies. The majority of multi-component frailty instruments were evaluated in single-center samples. Population-specific cutpoints were commonly used to define frailty status, and procedures to minimize model overfitting were rarely employed. These limitations make it difficult to generalize predicted risks derived from one instrument (particularly, multi-component frailty instruments) to typical clinic patients. We found only 5 studies on functional status(11-15); even if they were measured, the measurement interval was not adequate to capture fluctuation of functional status in frail older patients. Our screening could have missed relevant studies in which the frailty-outcome association was not the main focus of analysis (i.e., frailty as a covariate), and publication bias due to selective reporting is possible.

Remaining Questions for Future Research

Several key questions need to be answered for adoption of frailty assessment in preoperative assessment and decision-making. First, when a multi-component frailty instrument is preferred to a single-component instrument and which domains should be measured should be established. Instead of developing a new instrument, we believe that risk prediction based on a common set of frailty domains that can inform clinical care (e.g., mobility, nutrition, disability, and cognition) may streamline the assessment and interventions. Such standardization may also facilitate validation in different populations. Second, frailty may be reversed with cardiac surgical procedures in some patients, but none of the studies assessed change in frailty after the procedure. Third, while most studies on frailty assessment aimed to improve surgical risk stratification, more research is needed for patient-centered outcomes, such as functional status and quality of life. Fourth, making decisions about cardiac surgical procedures is challenging without knowing the expected outcome under alternative treatment options (e.g., TAVR vs. surgical aortic valve replacement or TAVR vs. palliative care). Secondary analyses of clinical trial data can be useful to address this key question. A core set of frailty measures should be obtained in future clinical trials in older adults. Finally, when reporting the results of analysis, the investigators should include absolute risks in addition to RRs. When the background risk is low, RRs can be misleading.(69) Metrics of prognostic models, such as sensitivity, specificity, calibration, and discrimination, should be also reported.

Recommendations for Clinical Practice

Clinicians should attempt to classify patients into the 3 groups: 1) extreme-risk patients whose predicted health status after the procedure is unlikely to be meaningfully better than the status without the procedure; 2) high-risk patients in whom predicted health status after the procedure is likely to be better than the status without the procedure, but there is a high yet not prohibitive risk of harms; and 3) low-risk patients who are likely to benefit from the procedure with a low risk of harms. The health status should not be confined to the risk of short-term complications or mortality; functional status may be as important, depending on the patient's value.

An ideal screening test should be practical, sensitive, and validated in a broad spectrum of patients. Gait speed or TUG test is a reasonable screening test, since it is highly correlated with 6MWT and highly sensitive for frailty (sensitivity: 0.99 if gait speed <0.8 meter/second(63) and 0.93 if TUG >10 seconds(64)). When an objective assessment of mobility is not feasible, self-reported mobility, disability, nutritional status, or the Clinical Frailty Scale can be used. The American Heart Association and American College of Cardiology recommend assessments of mobility and ADL disability.(70) Patients who screen positive should undergo a comprehensive geriatric assessment that is a gold standard in evaluating and managing frail older adults.(71) The purpose of comprehensive assessment is to refine surgical risk stratification and to deliver an individualized care to prevent complications and promote recovery and independence after cardiac surgical procedures.

Case Example

An 87-year-old patient with severe aortic stenosis is evaluated for TAVR after a recent heart failure exacerbation. His medical history includes systolic heart failure, coronary artery disease, chronic lung disease, chronic kidney disease, and spinal stenosis. He has been using a walker at home and a wheelchair outside for the past 5 years. His aide helps him with bathing and dressing, and family members provide assistance with all IADLs. It took 30 seconds for him to complete TUG test. A comprehensive assessment revealed moderate-to-severe impairments in mobility (gait speed: 0.3 meter/second), nutrition (at risk of malnutrition), and cognition (Mini-Mental State Examination: 17/30 points). His risk of in-hospital mortality after TAVR is 8% (vs. national average 4%).(29) This risk is probably underestimated because frailty is not included in the risk calculator. Given his severe mobility impairment, frailty, and chronic lung disease, his risk of mortality or functional decline after TAVR is greater than 40-50% at 6 months.(11, 12, 58) These risks should be presented to the patient against the potential benefits of TAVR in an unbiased fashion. When the likelihood for benefit is unclear and the risk of harms is high, the decision should be guided by his personal values and preferences.

Conclusions

Frailty status, assessed in mobility, disability, and nutritional status, can predict the risk of mortality at 6 months or later in older patients after major cardiac surgical procedures and the risk of mortality and functional decline after minimally invasive cardiac surgical procedures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Author (Year)	Study Population: Surgery	N	Age mean	STS mean	FU m	Frailty %	Frailty Assessment: Type	Mobility	Strength	Activity	Exhaustion	Nutrition	Cognition	Disability	Balance	Medical	Subjective
Major Cardiac Surgical Procedures (8 Studies)																	
Gardner (2001)	CABG	11815	64	NR	7	16	Single-component							○			
Rapp-Kesek (2004)	CABG, AVR	886	67	NR	22	7	Single-component					○					
de Arenaza (2010)	AVR	208	70	NR	12	51	Single-component	●									
Lee (2010)	CABG, AVR	3254	66	NR	22	4	Multi-component	○					○	○			
Cervera (2012)	CABG	1503	62	NR	65	21	Multi-component							○		○	
Robinson (2013)	CABG, AVR	174	73	NR	12	70	Single-component	●									
Sundermann (2014)	CABG, AVR	450	79	4	12	49	Multi-component	●	●	○	○	○		○	●	○	○
	(TAVR 15%)					63	Multi-component	○	●		○			○		○	○
Ad (2016)	CABG, AVR	166	74	2	12	23	Multi-component	●	●	○	○	○					
Number of Studies								**5**	**2**	**2**	**2**	**3**	**1**	**4**	**1**	**2**	**1**
Minimally Invasive Cardiac Surgical Procedures (17 Studies)																	
Ewe (2010)	TAVR	147	80	NR	9	33	Multi-component	●	●	○	○	○					
Rodes-Cabau (2010)	TAVR	339	81	10	8	25	Single-component										○
Rodes-Cabau (2012)	TAVR	339	81	10	42	25	Single-component										○
Munoz-Garcia (2012)	TAVR	133	79	7	11	85	Single-component							○			
						14	Multi-component	●	●	○	○	○					
Stortecky (2012)	TAVR	100	84	6	12	49	Multi-component	●				○	●	○			
Green (2013)	TAVR	484	85	11	24	73	Single-component	●									
Mok (2013a)	TAVR	260	79	7	12	55	Single-component	●									
Mok (2013b)	TAVR	319	80	6	12	NR	Single-component	●									
							Single-component										○
Schoenenberger (2013)	TAVR	119	83	6	6	49	Multi-component	●				○	●	○			
Arnold (2014)	TAVR	2137	84	12	12	71	Multi-component	●					●			○	
Dvir (2014)	TAVR	1108	83	12	12	NR	Single-component	●									
Puls (2014)	TAVR	300	82	7	18	48	Single-component							○			
Seiffert (2014)	TAVR	845	81	6	12	5	Single-component										○
Cockburn (2015)	TAVR	312	81	5	26	NR	Single-component	○						○			
							Single-component										
							Single-component										○
Codner (2015)	TAVR	360	82	8	23	NR	Multi-component	●				○	●	○		○	○
Green (2015)	TAVR	244	86	11	12	55	Multi-component	●	●			○		○			
Osnabrugge (2015)	TAVR	436	84	10	6	16	Single-component	○									
							Single-component					○					
Number of Studies								**13**	**3**	**2**	**2**	**7**	**4**	**7**	**0**	**2**	**6**

Figure 1. Frailty Assessment in Cardiac Surgical Procedures*

Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass grafting; FU, follow-up; m, month; NA, not applicable; NR, not reported; STS, Society of Thoracic Surgeons predicted risk of mortality; TAVR, transcatheter aortic valve replacement

* Open circle indicates information obtained from self-report or medical records; solid circle indicates information obtained from performance tests. Prevalence of frailty was determined according to the study-specific definition.

† Administration time was reported by the authors.

‡ Administration time includes explaining the test, performing the test, and allowing the patient to recover according to a clinical trial protocol.

Table 1

Frailty Assessment and Outcomes At 6 Months or Later After Major Cardiac Surgical Procedures in Older Adults

Frailty Assessment (References)	Time min	Outcome	Frailty Category		Absolute Risk %	Relative Risk (95% CI)	C Statistic
			Single-Component Frailty Assessment				
Timed-Up-and-Go test (Robinson, 2013)(42)	<1 [*]	1-y mortality	• Fast • Intermediate • Slow	≤10 s 11-14 s ≥15 s	2 3 12	Reference 1.8 (0.2-17.0) 6.4 (0.8-55.0)	NR
6MWT (de Arenaza, 2010)(43)	30 [*†]	1-y mortality 1-y mortality or MACCE	• Good mobility • Poor mobility • Good mobility • Poor mobility	≥300 m <300 m	3 8 4 14	Reference 2.6 (0.7-9.4) Reference 3.6 (1.2-11.1)	NR NR
Serum albumin (Rapp-Kesek, 2004)(44)	NA	1.8-y mortality	• Normal nutrition • Malnutrition	>3.7 g/dL ≤3.7 g/dL	6 14	Reference 2.5 (1.3-4.9)	NR
Katz index of ADL (Gardner, 2001)(45)	5	7-m mortality	• Independent • Partially dependent • Totally dependent	6 1-5 0	NR	Reference 1.5 (1.1-1.9) [‡] 2.4 (1.6-3.7) [‡]	NR
			Multi-Component Frailty Assessment				
Lee index (Lee, 2010)(46) • ADL dependence • Dependence in ambulation • History of dementia	<5	1.8-y mortality	• Non-frail • Frail	0 1-3	11 30	Reference 1.5 (1.1-2.2) [‡]	NR
Cervera index (Cervera, 2012)(47) • ADL dependence • Nursing home residence • Dialysis or oxygen therapy	<5	5.4-y mortality	• Non-frail • Frail	0 1-3	NR	Reference 1.0 (0.7-1.4) [‡§]	NR
FORECAST (Sundermann, 2014)(41, 48) • Chair rise • Self-reported exhaustion • Self-reported stair climbing • Clinical Frailty Scale • Serum creatinine	5 [*]	1-y mortality	• Non-frail • Moderately frail • Severely frail • Per 1 point increase (range: 1-13)	1-4 5-7 8-13	5 17 21	Reference 3.2(1.6-6.7) 3.9 (1.9-8.0) 1.3(1.1-1.4) [‡]	NR 0.76
Frailty phenotype (Ad, 2016)(49) • 15-ft gait speed • Grip strength • Weight loss • Self-reported exhaustion • Low activity	15	1-y mortality	• Non-frail • Frail	0-2 3-5	3 6	Reference 2.3 (0.3-17.4) [‡]	NR
CAF (Sundermann, 2014)(41, 48) • 4-m gait speed	20 [*]	1-y mortality	• Non-frail • Moderately frail • Severely frail	1-10 11-25 26-35	8 17 36	Reference 2.1 (1.2-3.6) 4.5 (2.4-8.7)	NR 0.70

Frailty Assessment (References)	Time min	Outcome	Frailty Category	Absolute Risk %	Relative Risk (95% CI)	C Statistic
• Grip strength • Self-reported exhaustion • Physical activity from IADL • Standing balance • Chair rise • Put on and remove jacket • Pick up a pen from floor • Turn 360 degrees • Serum albumin • Serum creatinine • Serum brain natriuretic peptide • Forced expiratory volume in 1 s • Clinical Frailty Scale			• Per 1 point increase (range: 1-35)		1.1 (1.0-1.1)[‡]	

Abbreviations: 6MWT, 6-minute walk test; ADL, activities of daily living; CAF, Comprehensive Assessment of Frailty; CI, confidence interval; FORECAST, Frailty predicts death One year after Elective Cardiac Surgery Test; IADL, instrumental activities of daily living; m, month; MACCE, major adverse cardiovascular and cerebrovascular event; NA, not applicable; NR, not reported; s, second; y, year.

[*]Administration time was reported by the authors.

[†]Administration time includes explaining the test, performing the test, and allowing the patient to recover according to a clinical trial protocol.

[‡]Relative risk estimates were adjusted for clinical covariates.

[§]The regression model simultaneously adjusted for other markers of frailty.

Table 2

Frailty Assessment and Outcomes At 6 Months or Later After Minimally Invasive Cardiac Surgical Procedures in Older Adults

Frailty Assessment (References)	Time* min	Outcome	Frailty Category		Absolute Risk %	Relative Risk (95% CI)	C Statistic
			Single-Component Frailty Assessment				
Wheelchair-bound status (Osnabrugge, 2015)(15)	<1	6-m mortality or poor QoL	• Not wheelchair-bound • Wheelchair-bound		NR	Reference 2.6 (1.3-5.2)†‡	0.72
Mobility impairment due to musculoskeletal or neurologic disorder (Cockburn, 2015)(50)	<1	2.2-y mortality	• No severe impairment • Severe impairment		NR	Reference 2.2 (1.3-2.5)	NR
Brighton Mobility Index (Cockburn, 2015)(50)	<1	2.2-y mortality	• Per 1 category worsening (range: 0-6)		NR	1.2 (1.0-1.5)	NR
6MWT (Green, 2013)(52)	10	2-y mortality	• Fast walker • Slow walker • Unable to walk	>128.5 m ≤128.5 m 0 m	29 31 43	Reference 1.2 (0.8-2.0)† 1.8 (1.2-2.7)†	NR
6MWT (Mok, 2013a)(53)	10	1-y mortality	• Good mobility • Poor mobility • Per 10 m decrease	≥182 m <182 m	9 25	Reference 2.8 (NR) 1.1 (1.0-1.1)†	NR NR
6MWT (COPD patients) (Mok, 2013b)(12)	10	6-m mortality or no symptom benefit 1-y mortality	• Good mobility • Poor mobility • Per 20 m decrease • Good mobility • Poor mobility • Per 20 m decrease	≥170 m <170 m ≥150 m <150 m	29 59 24 75	Reference 2.8 (NR) 1.2 (1.0-1.2)†‡ Reference 3.2 (NR) 1.2 (1.1-1.3)†	NR 0.67 NR 0.74
6MWT (COPD patients) (Dvir, 2014)(51)	10	1-y mortality	• Good mobility • Poor mobility	≥50 m <50 m	NR	Reference 1.7 (1.2-2.2)†	NR
Serum albumin (Osnabrugge, 2015)(15)	NA	6-m mortality or poor QoL	• Normal nutrition • Malnutrition	≥3.3 g/dL <3.3 g/dL	NR	Reference 1.8 (0.9-3.5)†‡	0.72
Barthel index of ADL (Munoz-Garcia, 2012)(54)	5	11-m mortality	• Per 1 point improvement (range: 0-100)		NR	1.0 (1.0-1.1)†	NR
Katz index of ADL (Puls, 2014)(55)	5	1.5-y mortality	• Independent • Dependent	6 0-5	24 56	Reference 2.7 (1.8-3.9)†	NR
Katz index of ADL (Cockburn, 2015)(50)	5	2.2-y mortality	• Per 1 point improvement (range: 0-6)		NR	0.9 (0.7-1.1)	NR
Subjective assessment (Rodes-Cabau, 2010(56); Rodes-Cabau, 2012(57))	NA	1-y mortality 3.5-y mortality	• Non-frail • Frail • Non-frail • Frail		23 30 NR	Reference 1.4 (0.8-2.3) Reference 1.4 (1.0-2.2)†	NR NR

Frailty Assessment (References)	Time* min	Outcome	Frailty Category		Absolute Risk %	Relative Risk (95% CI)	C Statistic
Subjective assessment (Mok, 2013b)(12)	NA	6-m mortality or no symptom benefit 1-y mortality	• Non-frail • Frail • Non-frail • Frail		42 45 NR	Reference 1.1 (0.3-4.1)†‡ Reference 0.6 (0.1-2.4)	NR NR
Clinical Frailty Scale (Seiffert, 2014)(60)	3	1-y mortality	• Non-frail • Frail	1-5 6-7	24 63	Reference 3.6 (1.8-7.1)†	0.71
Clinical Frailty Scale (Cockburn, 2015)(50)	3	2.2-y mortality	• Per 1 category worsening (range: 1-7)		NR	1.3 (1.1-1.6)	NR
			Multi-Component Frailty Assessment				
Green index (Green, 2015)(14) • 15-ft gait speed • Grip strength • Serum albumin • ADL dependence	10	6-m mortality or poor QoL 1-y mortality or poor QoL 1-y mortality	• Non-frail • Frail • Non-frail • Frail • Non-frail • Frail	0-5 6-12	28 42 32 50 16 33	Reference 2.2 (1.1-4.5)† Reference 2.4 (1.1-5.1)† Reference 2.5 (1.4-4.4)†	NR NR NR
Frailty phenotype (Ewe, 2010)(59) • 15-ft gait speed • Grip strength • Weight loss • Self-reported exhaustion • Low activty	15	9-m mortality or MACCE	• Non-frail • Frail	0-2 3-5	NR	Reference 4.2 (2.0-8.8)†	NR
Frailty phenotype (Munoz-Garcia, 2012)(54) • 15-ft gait speed • Grip strength • Weight loss • Self-reported exhaustion • Low activity	15	11-m mortality	• Non-frail • Frail	0-2 3-5	7 25	Reference 1.0 (0.2-4.9)†‡	NR
Codner index (Codner, 2015)(61) • Gait speed • ADL dependence • Serum albumin • Oxygen therapy • Cognitive function • General appearance • Subjective assessment	15	2.2-y mortality	• Non-frail • Frail	NR	NR	Reference 1.9 (1.1-3.2)†	NR
Arnold index (Arnold, 2014)(13) • Diabetes • Major arrhythmia • Serum creatinine • Mean arterial pressure • Body mass index	20	6-m mortality or poor QoL 1-y mortality or poor QoL	• Low • Intermediate • High • Low • Intermediate • High • Extremely high	NR NR	18 37 55 29 40 59 73	Reference 2.1 (1.7-2.5) 3.1 (2.5-3.8) Reference 1.4(0.9-2.0) 2.0 (1.4-2.9) 2.5(1.7-3.7)	0.64-0.66 0.62-0.66

Frailty Assessment (References)	Time* min	Outcome	Frailty Category		Absolute Risk %	Relative Risk (95% CI)	C Statistic
• Oxygen-dependent lung disease • Mean aortic valve gradient • Mini-Mental State Examination • 6MWT							
Stortecky index (Stortecky 2012(58); Schoenenberger 2013(11)) • Timed-Up-and-Go test • Mini-Mental State Examination • ADL dependence • IADL dependence • Preclinical mobility disability • Mini-Nutritional Assessment	25	6-m mortality or ADL decline 6-m mortality 1-y mortality 1-y mortality or MACCE	• Non-frail • Frail • Non-frail • Frail • Non-frail	0-2 3-7	15 44 3 19 NR NR	Reference 4.2 (1.7-10.3)† Reference 5.6 (1.3-24.2) Reference 2.9 (0.9-9.2)† Reference 4.2 (1.4-12.7)†	NR

Abbreviations: 6MWT, 6-minute walk test; ADL, activities of daily living; COPD, chronic obstructive pulmonary disease; IADL, instrumental activities of daily living; m, month; MACCE, major adverse cardiovascular and cerebrovascular event; NA, not applicable; NR, not reported; QoL, quality of life; s, second; y, year.

* Administration time was estimated from the literature or our experience.

† Relative risk estimates were adjusted for clinical covariates.

‡ The regression model simultaneously adjusted for other markers of frailty.