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Frailty, clinical outcomes, and cost in patients undergoing trans-catheter aortic valve implantation (TAVI)

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Abstract

The objective of this doctoral was three-fold: 1) to systematically review frailty measures and prognosis of frail patients undergoing TAVI, 2) to examine the performance of frailty indices in predicting clinical outcomes after TAVI, and 3) to examine the performance of frailty indices in predicting one-year costs of TAVI and high-cost TAVI patients.

For the first objective, we systematically reviewed the literature published in 2006 or later. We found that frailty instruments varied across studies, leading to a wide range of frailty prevalence estimates for TAVI recipients and substantial heterogeneity.

For the second objective, we utilized data from the CorHealth Ontario TAVI registry and administrative databases housed at the Institute for Clinical Evaluative Sciences (IC/ES), Canada. Two administrative database frailty indices, the Johns Hopkins Adjusted Clinical Group (ACG) frailty indicator and the Hospital Frailty Risk Score (HFRS), were used to assign frailty status. We found that the agreement between the Johns Hopkins ACG frailty indicator and the HFRS was fair. Both the Johns Hopkins ACG frailty indicator and the HFRS were significantly associated with one-year mortality and rehospitalization following TAVI. We found that both the Johns Hopkins ACG frailty indicator and HFRS improved performance in predicting one-year mortality and rehospitalization.

For the third objective, we analyzed cost data from the same Ontario TAVI cohort. We found that frail patients incurred significantly increased one-year healthcare costs. The HFRS was a significant predictor for high-cost patients. We found that the HFRS improved the performance of the model in predicting high-cost patients.

Keywords

Transcatheter aortic valve implantation, frailty, Johns Hopkins ACG frailty indicator, Hospital Frailty Risk Score, cost analysis

Summary for Lay Audience

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative, less invasive treatment option for patients with severe symptomatic aortic stenosis who are at high or intermediate risk for poor outcomes with surgical aortic valve replacement (SAVR). Frailty is a biological syndrome characterized by an increased vulnerability to illnesses, and has been recognized as a predictor for poor outcomes after TAVI.

In this study, we reviewed and analyzed existing literature that reported outcomes of frail patients undergoing TAVI. We also compared the predictive performance of two frailty indices: 1) the Johns Hopkins Adjusted Clinical Groups (ACG) frailty indicator and 2) the Hospital Frailty Risk Score (HFRS). We analyzed data in 3,866 patients who underwent a TAVI procedure in Ontario, Canada from 2012 to 2018. We found that the prevalence of frailty in patients undergoing TAVI ranged widely across the literature, due to the variety of frailty definitions. Pooling prognosis of frail patients, we found very low or low confidence in the overall estimates due to inconsistency of frailty measures identified in the studies. Drawing on data from the Ontario TAVI registry, we found similar proportions of frail patients diagnosed. We found a fair agreement between the Johns Hopkins ACG frailty indicator and the HFRS, due to key differences amongst the two frailty indices. Both the Johns Hopkins ACG frailty indicator and the HFRS were associated with increased risk of death and rehospitalization at one year following TAVI. Both the Johns Hopkins ACG frailty indicator and the HFRS added incremental predictive value when predicting death and rehospitalization at one year. Analyzing cost data in the cohort, we found that frail patients incurred dramatically increased one-year healthcare costs after TAVI. The HFRS was identified as a powerful predictor for high-cost patients, and added incremental predictive value when predicting high-cost patients undergoing TAVI. Our study suggests that preoperative frailty assessment may add predictive value for outcomes after TAVI.

Co-Authorship Statement

All chapters of this doctoral research dissertation were written by Zhe Li as part of the fulfillment of requirements for her Doctoral of Philosophy from the Department of Epidemiology and Biostatistics. Chapters 3 and 4 were based on a systematic review and meta-analysis. Chapters 5 and 6 were based on administrative data housed at the Institute for Clinical Evaluative Sciences. Zhe Li was responsible for conducting all statistical analyses, conducting literature review and writing this thesis and manuscripts. Zhe Li's supervisory committee (Dr. Ava John-Baptiste, Dr. Davy Cheng, Dr. Rodrigo Bagur, Dr. Janet Martin, and Dr. Bob Kiaii) provided academic supervision and guidance. Supervisory committee members and colleagues (Dr. Ava John-Baptiste, Dr. Davy Cheng, Dr. Rodrigo Bagur, Dr. Janet Martin, Dr. Bob Kiaii, Emily Dawson, Jessica Moodie, Dr. Harindra Wijeysundera, Feng Qiu and Jiming Fang) were listed as co-authors where they assisted in searching, screening and appraising the articles, creating datasets housed at the Institute for Clinical Evaluative Sciences, interpreting the findings, and revising the manuscripts. Co-authors of each chapter are listed below in order.

Chapter 3: Frailty in patients undergoing transcatheter aortic valve implantation: A protocol for a systematic review.

Authors: Zhe Li, Emily Dawson, Jessica Moodie, Janet Martin, Rodrigo Bagur, Davy Cheng, Bob Kiaii and Ava John-Baptiste.

Chapter 4: Measurement and prognosis of frail patients undergoing transcatheter aortic valve implantation: a systematic review and meta-analysis.

Authors: Zhe Li, Emily Dawson, Jessica Moodie, Janet Martin, Rodrigo Bagur, Davy Cheng, Bob Kiaii and Ava John-Baptiste.

Chapter 5: Performance of frailty indices in predicting clinical outcomes of patients undergoing transcatheter aortic valve implantation.

Authors: Zhe Li, Harindra Wijeysundera, Rodrigo Bagur, Davy Cheng, Janet Martin, Bob Kiaii, Feng Qiu, Jiming Fang and Ava John-Baptiste.

Chapter 6: Performance of frailty indices in predicting cost outcomes in patients undergoing transcatheter aortic valve implantation.

Authors: Zhe Li, Harindra Wijeysundera, Rodrigo Bagur, Davy Cheng, Janet Martin, Bob Kiaii, Feng Qiu, Jiming Fang and Ava John-Baptiste.

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List of Abbreviations

A

ACG: adjusted clinical groups

AF: atrial fibrillation

AIC: Akaike information criterion

B

BIC: Bayesian information criterion

C

CABG: coronary artery bypass grafting

CI: confidence interval

COPD: chronic obstructive pulmonary disease

D

DAD: discharge abstract database

E

ED: emergency department

H

HFRS: Hospital Frailty Risk Score

I

ICD: implantable cardiac defibrillator

IC/ES: Institute for Clinical Evaluative Sciences

IDI: integrated discrimination improvement

K

KCCQ: Kansas City Cardiomyopathy Questionnaire

M

MI: myocardial infarction

MOHLTC: Ontario Ministry of Health and Long-Term Care

N

N: sample size

NARCS: national ambulatory care reporting system

NRI: net reclassification index

O

ODB: Ontario drug benefit claims

OHIP: Ontario health insurance plan

OR: odds ratio

P

PCI: percutaneous coronary intervention

PVD: peripheral vascular disease

R

RPDB: registered persons database

RR: rate ratio

S

SAVR: surgical arotic valve replacement

SDS: same day surgery

STS: Society of Thoracic Surgeons

T

TAVI: transcatheter aortic valve implantation

Chapter 1

1 Introduction

1.1 Thesis objectives

The overall objective of this doctoral research work was to explore and advance the knowledge on frailty in patients undergoing TAVI and investigate the tools used to measure frailty, the impacts of frailty on patient outcomes and cost for TAVI patients, and test the performance of recently developed administrative database frailty indices in predicting patient outcomes and costs for patients undergoing TAVI in Ontario. Specifically, this thesis had three main objectives:

Objective 1: To review the literature to identify frailty instruments in use for TAVI recipients and synthesis prognostic data from these studies, in order to inform clinical management of frail patients undergoing TAVI. To this end, we systematically reviewed the literature published in 2006 or later. This objective had two sub-objectives:

1a: To review the operationalization of frailty instruments in use for TAVI recipients.

1b: To determine the prognosis of frail patients undergoing TAVI.

Objective 2: To test the performance of administrative database frailty indices in predicting clinical outcomes for patients undergoing TAVI. To do this, we used linked administrative databases at the Institute for Clinical Evaluative Sciences (IC/ES) to create a cohort of patients who underwent a TAVI procedure from April 1, 2012 to March 31, 2018 in Ontario and applied administrative database frailty algorithms to predict clinical outcomes. Specifically, this objective had two sub-objectives:

2a: To compare frailty prevalence and measure agreement amongst three administrative database frailty indices.

2b: To compare discrimination, classification and reclassification performance amongst the frailty indices when predicting in-hospital mortality, 1-year mortality and readmission.

Objective 3: To test the performance of frailty indices in predicting one-year costs of TAVI and high-cost TAVI patients. To do this, we used linked administrative databases at the Institute for Clinical Evaluative Sciences (IC/ES) to create a cohort of patients who underwent a TAVI procedure from April 1, 2012 to March 31, 2018 in Ontario and applied administrative database frailty algorithms to predict cost outcomes. Specifically, this objective had two sub-objectives:

3a: To determine whether or not frailty is a significant predictor of one-year costs.

3b: To compare discrimination, classification and reclassification performance amongst the frailty indices when predicting high-cost patients.

1.2 Thesis organizations

Chapter 1: This chapter introduces the background and research objectives of this thesis.

Chapter 2: This chapter consists of a comprehensive review of the literature in line with the main objectives of this thesis.

Chapter 3: This chapter consists of a protocol for a systematic review of frailty in patients undergoing TAVI. A version of this chapter has been published in *BMJ Open*.

Chapter 4: This chapter addresses objective 1: identifying frailty instruments in use for TAVI recipients and determining prognosis of frail patients undergoing TAVI.

Chapter 5: This chapter addresses Objective 2: examining the predictive performance of administrative database frailty indices in predicting clinical outcomes for patients undergoing TAVI.

Chapter 6: This chapter addresses Objective 3: examining the predictive performance of administrative database frailty indices in predicting cost outcomes for patients undergoing TAVI.

Chapter 7: This chapter provides an integrated discussion, conclusions and future directions.

Chapter 2

2 Literature review

The literature review begins with the etiology and clinical manifestations of aortic stenosis with therapeutic options, including medical management, surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI). This is followed by theories surrounding frailty and a summary of frailty measurements. The literature review ends with discussions of the usefulness of frailty assessment in clinical practice.

2.1 Aortic valve stenosis

Aortic valve stenosis is a severe heart valve disease characterized by a narrowing of the opening of the aortic valve.[1] Common symptoms of aortic stenosis include difficulty breathing (dyspnea), heart failure, chest pain (angina), and temporary loss of consciousness (syncope).[1] If left untreated, individuals with severe aortic valve stenosis have a poor prognosis.[1,2,3] Treatment of aortic valve stenosis includes pharmaceutical and surgical interventions, but only surgical options are demonstrated to be effective and improve survival.[4,5] The prevalence of aortic valve stenosis is expected to increase due to the ageing of the global population.[3] With significant clinical and economic implications, managing patients with aortic valve stenosis remains a key issue in cardiovascular epidemiology and financial burden in our healthcare system.

2.1.1 Causes

The human heart's main function is to pump blood throughout the body and supply the tissues with oxygen and nutrients.[1] The human heart receives deoxygenated blood via the circulatory system and then provides a pumping force to move the blood to the pulmonary system for oxygenation.[1] The coordinated cardiac contraction, chamber system, and valves, designed to allow only one-way blood passage, ensure a consistent unidirectional flow of the circulation.[1] When aortic stenosis occurs, the narrowing of the opening to the aortic valve obstructs blood flow from the left ventricle out into the aorta, leading to pathophysiological cardiac dysfunction .[1, 2]

Most cases of aortic stenosis result from the calcification of the aortic valve cusps.[1] The normal aortic valve consists of three cusps that ensure a one-way passage of blood from the left ventricle to the aorta.[6] The three layers of cell types in the aortic valve are fibrosis, ventricularis and spongiosa.[1,6] These three layers provide strength, elasticity, and cushion, respectively; they also become the site for possible ossification and stenosis.[6] When cusps of the valve begin to accumulate calcium deposits, the cusps become thicken, narrowing the

aortic valve opening.[6] Several mechanisms can cause this calcification: cellular injury, improperly functioning regulatory cells, cellular transition, and vascularization to the valve.[1,7,8] Because each mechanism requires a long time to develop, most patients are generally asymptomatic.[1,7,8] By the time the calcification and subsequent narrowing of the aortic valves are significant enough to cause symptoms, the patient's cardiac function is already highly compromised.[1,7,8]

2.1.2 Symptoms

Once aortic valve stenosis has become symptomatic, it deteriorates very quickly.[1] The classic symptoms of symptomatic aortic stenosis are angina, syncope, and dyspnea.[9]

Angina, or chest pain, occurs when the myocardial blood supply does not meet the heart's energy demands.[10] Obstructions caused by aortic stenosis lead to the decreased blood outflow; due to the myocardial tissues not receiving enough oxygenated blood, cardiac output decreases, ultimately causing decreased blood to the myocardium and angina.[1, 9] In patients affected by aortic stenosis, approximately 35% present with angina as the initial symptom.[9] The reported incidence of angina among aortic stenosis patients ranges from 35% to 50%.[10,11,12]

Syncope is a temporary loss of consciousness, resulted from the heart's inability to increase stroke volume to the brain when peripheral demand increases.[13,14] The normal response to physical exercise is to have peripheral vasodilation compensated by increased cardiac output. This response will lead to increased blood pressure and increased blood flow to the tissues.[1, 2] In a calcific aortic valve diseased patient, the heart cannot increase its cardiac output to the demands needed; this leads to vasodilation without compensative effects, ultimately causing a drop in blood pressure and syncope.[1,9] Research suggests that syncope represents an underestimated threat to patients with aortic stenosis and carries the highest risk for poor prognosis even after aortic valve replacement.[13,15]

Difficulty in breathing, or dyspnea, is most likely caused by heart failure that often accompanies aortic stenosis.[1,9] Through different mechanisms, both systolic and diastolic dysfunction can lead to dyspnea.[9] In general, dyspnea is caused by a backup of fluid in the pulmonary system.[9] In the case of diastolic dysfunction, the pressure difference between the atrium and the ventricle decreases. [1,16,17] This decreased pressure difference leads to the reduced blood passage from the pulmonary side to the left ventricle, creating a backup of fluid into the pulmonary system and therefore dyspnea.[1,16,17] In the case of systolic dysfunction, the hypertrophied ventricle cannot create a large enough pressure to maintain the cardiac output, leading to an increase in the preload of the cardiac ventricles.[1,18,19] The decreased blood passage from the atrium to the ventricles causes a pulmonary fluid backup, ultimately resulting in dyspnea.[18,19] Research has suggested that in patients with severe stenosis, the number of patients with dyspnea is higher than that of patients with syncope or angina.[20]

Symptoms of aortic stenosis, in the beginning, are usually deceptive, such as decreased exercise tolerance. [13,20] Angina, syncope, and dyspnea are considered late manifestations of aortic stenosis, and the presence of these symptoms indicate a need for intervention.[13,21] Evidence has shown that the patient's expected survival is very short once a patient develops symptoms, and median expected survival can be correlated to the type of symptoms the patient develops.[20] Therefore, it is important to assess the symptoms of patients with aortic stenosis and rule out other possible explanations for symptoms.[22]

2.1.3 Diagnosis and severity

In the past, most patients with aortic stenosis were not diagnosed until the onset of symptoms such as angina, syncope or dyspnea.[23] Since most patients are generally asymptomatic until later in the disease course, aortic valve stenosis is often diagnosed based on clinical manifestation which usually results in a short time interval between diagnosis and intervention.[23,24] With the recent widespread use of echocardiography, patients with aortic

valve stenosis are more commonly diagnosed earlier in the disease course, allowing for early interventions even before severe valve obstruction develops.[23]

In the diagnosis of aortic stenosis, echocardiography is the most commonly used diagnostic test.[24] Current guidelines suggest that the recommended primary hemodynamic parameters used for clinical evaluation of aortic stenosis severity include aortic jet velocity, mean gradient, and aortic valve area.[25] Aortic jet velocity is defined as the highest blood flow velocity when moving through the aortic valve.[25,26] The concept of jet velocity in the evaluation of aortic valve stenosis is that velocity increases as stenosis severity increases. The cut-off for severe aortic stenosis, measured using Continuous-wave Doppler ultrasound, is a peak aortic jet velocity of 4.0 m/s.[25,27,28,29] Transaortic pressure gradient is the difference in pressure between the left ventricle and aorta during systole, and the mean gradient is defined as the average gradient of instantaneous gradients over the ejection period.[25,27,28] The mean gradient can also be measured using Doppler ultrasound.[25,30] The normal aortic valve area in adults is 3.0-4.0 cm^2.[25] When a patient's valve area is reduced to approximately 25% of the normal size (1.0 cm^2) the stenosis is defined as severe.[25]

Doppler echocardiography is a non-invasive technique, and has become the standard technique for the evaluation of aortic stenosis severity.[25,26,31] In addition to echocardiography, other tests such as cardiac catheterization, 12-lead electrocardiography and chest radiography are also used to evaluate different aspects of associated symptoms, risk factors or clinical outcomes of aortic stenosis.[32,33,34]

Threshold values for aortic jet velocity, mean gradient, and aortic valve area are used to categorize the severity of aortic stenosis.[35,36,37] The American College of Cardiology (ACC)/ American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines categorize aortic stenosis severity as mild, moderate, or severe.[35,36,37] Classification of aortic stenosis is shown in **Table 2.1**. In addition to aortic jet velocity, mean gradient, and aortic valve area, indexed aortic valve area and velocity ratio are also essential indexes used for clinical decision-making. Indexed aortic area and velocity size are particularly helpful for

clinical decision-making in younger adults and children, whose valve area may seem severely narrowed while stenosis is classified moderate.[25] The indexed aortic valve area adjusts to body surface area, and an indexed aortic valve area of <0.6 cm^2/m^2 is considered severe aortic stenosis.[25,38] The velocity ratio is the ratio of left ventricular outflow tract velocity to aortic valve velocity.[25,39] The velocity ratio reflects the ratio of the actual valve area to the expected valve area.[25,39]

Table 2.1. Recommendations for the classification of aortic stenosis severity

	Mild	Moderate	Severe
Aortic jet velocity (m/s)	2.6-2.9	3.0-4.0	>4.0
Mean gradient (mmHg)	<20 (<30[a])	20-40[b] (30-50[a])	>40[b] (>50[a])
Aortic valve area (cm^2)	>1.5	1.0-1.5	<1.0
Indexed aortic valve area (cm^2/m^2)	>0.85	0.60-0.85	<0.6
Velocity ratio	>0.50	0.25-0.50	<0.25

[a:] ESC Guidelines[25]

[b:] ACC/AHA Guidelines[25]

2.1.4 Therapies

For patients with symptomatic aortic stenosis, if untreated, the rate of death is more than 50% at two years.[15] Therapies for aortic stenosis to date include both pharmaceutical and surgical options. Based on the severity and stage of the disease, options to treat aortic stenosis vary. Pharmaceutical therapy has been tried to slow the progression of aortic stenosis for patients in the early stages of the disease. For example, medications such as lipid-lowering drugs,

antihypertensive drugs and bisphosphonates have been investigated.[6, 40] Unfortunately, there remains no definitive evidence from clinical trials that these drugs can slow the progression of aortic stenosis or meaningfully reduce adverse clinical outcomes.[40, 41] Without a reliable pharmaceutical intervention, surgical intervention to correct the aortic valve dysfunction become the definitive management and the only viable option for patients with severe symptomatic aortic stenosis.[1,41]

Currently, there are three surgical interventions for patients who require surgery: surgical aortic valve replacement (SAVR), balloon valvuloplasty, and transcatheter aortic valve implantation (TAVI).[33,37] Each surgical intervention has its indications.[1,33] Balloon valvuloplasty will not be discussed here because it is solely a temporary approach to sustain a patient until SAVR or TAVI is performed.[1, 42, 43]

In 1952, the first mechanical valve was implanted in the descending thoracic aorta to treat severe aortic regurgitation.[44] Further developments of this technique allowed for cardiac surgical intervention to treat aortic stenosis.[1] In 1960, the first mechanical valve was placed in the anatomical location of the natural aortic valve.[45] Since that time, SAVR has become the standard of care for severe symptomatic aortic stenosis.[45] In the absence of serious coexisting conditions, SAVR can reduce symptoms of patients with severe aortic stenosis and improve survival.[42,46,47] Due to advanced age, left ventricular dysfunction or the presence of comorbidities, typically 30% of patients with severe aortic stenosis are considered contraindicated for conventional SAVR.[47]

TAVI provides an option for patients with severe symptomatic aortic stenosis who are not candidates for SAVR. In 2011, the Food and Drug Administration (FDA) approved TAVI as a treatment for patients who cannot undergo surgery or those at high risk for SAVR.[1] First developed in 2002, TAVI is a minimally invasive approach to valve replacement.[48] It is a form of surgery that replaces the aortic valve through a catheter rather than open-heart surgery.[47,48,49] The valve is implanted within the diseased aortic valve through standard

catheterization techniques, without requiring patients to undergo cardiopulmonary bypass or sternotomy.[1,49]

Since sheaths and catheters are associated with a risk of vascular complications, it is essential to perform a TAVI procedure via an appropriate approach.[50] Choice of access site should take into account the vascular features and valve size.[50] Currently, the transfemoral approach, in which the catheter is inserted through the femoral artery, remains the preferred approach in TAVI procedures because it allows for a fully percutaneous TAVI least invasively and possibly performed under local anesthesia.[50,51] In patients who are not suitable to receive a transfemoral TAVI, such as those who have serious femoral atherosclerosis and calcifications, alternate approach should be considered such as the transapical approach.[50,51] Transapical TAVI requires general anesthesia and is commonly recommended in patients with high risk of stroke or embolic events.[50,51,52,53]

Findings of research comparing outcomes after transapical and transfemoral TAVI are inconsistent. Some observational studies found that mortality was lower in patients with transfemoral TAVI. For example, Blackman et al.[54] conducted a prospective observational study. They utilized data on 1,620 patients undergoing TAVI in the UK.[54] They compared outcomes of patients undergoing transfemoral TAVI with those undergoing transapical TAVI.[54] The study demonstrated that mortality was lower in patients undergoing transfemoral TAVI at 30 days (11.2% vs. 4.4%, $p<0.01$), 1 year (28.7% vs. 18.1%, $p=0.01$), and 2 years (56.0% vs. 43.5%, $p=0.01$).[54] An observational study by Di Mario et al.[55] analyzed data on 4,571 patients undergoing TAVI in 10 European countries. The study showed that in-hospital mortality was significantly lower in patients undergoing transfemoral TAVI (5.9%) than that in those undergoing transapical (12.8%).[55] Van der Boon et al.[56] collected data on a total of 882 patients undergoing TAVI. They found transapical TAVI was associated with an increased risk of all-cause mortality at 30 days (odds ratio [OR], 3.12, 95% confidence interval [CI], 1.43 to 6.82; $p=0.004$). They also found that transapical TAVI was associated with an increased risk of 1-year all-cause mortality (hazard ratio, 1.88, 95% CI, 1.23 to 2.87; $p=0.004$).[56] Although these observational studies found lower mortality in

patients undergoing transfemoral TAVI, the two group are different.[57] Patients undergoing transapical TAVI had a higher estimated risk of mortality and had more co-morbidities. [56,57] Some studies suggested no significant difference in either the transapical or the transfemoral group. For example, a study by Bleiziffer et al.[58] compared 30-day survival between patients undergoing transfemoral TAVI and patients undergoing transapical TAVI. Patients underwent a transapical TAVI due to contradictions for transfemoral TAVI.[58] The study did not find a significant difference in 30-day survival (88.8% vs. 91.7%, p=0.918).[58] A study by Ewe et al.[59] compared the clinical outcomes of patients undergoing transfemoral versus transapical TAVI. The study found comparable baseline characteristics between the two groups.[59] The study showed that mortality at 30 days, six months, and 1 year was comparable between transfemoral and transapical.[59]

With advancements in TAVI technology, several novel implantation approaches are used as alternative access options in selected patients.[60,61,62,63,64,65,66] For example, the transaxillary approach, in which the catheter is inserted through the subclavian artery, has been performed safely in patients who are not suitable for transfemoral and transapical TAVI.[50] Transaortic approach is also an alternative to transfemoral or transapical TAVI. Transaortic TAVI can decrease the risk of complications because of the direct insertion in the aorta.[50,61] Transcarotid approach represents another alternative TAVI access site.[50] Transcarotid TAVI can be performed under local anesthesia and has been shown to improve accuracy of valve positioning.[50]

In terms of prosthetic valves, there are two valve systems that have been widely used in clinical settings: the Edwards valve system and Medtronic CoreValve System.[47,67,68] The Edwards valves are balloon-expandable, comprising a tri-leaflet bovine pericardial valve mounted in a stainless-steel stent.[43,47] The Medtronic CoreValve System is self-expandable, consisting of a self-expanding nitinol frame with three porcine pericardial leaflets. [67,69,70] Over the last decade, transcatheter valve technology has seen great improvements. For example, compared with previous generations of Edwards valve (Cribier Edwards, SAPIEN, and SAPIEN XT), the SAPIEN 3 and ultra valves can be used in a broader range of patients with

the potential for more accurate positioning and associated with less paravalvular regurgitation.[71,72,73] Compared with traditional Medtronic CoreValve, the newer generation Evolut PRO has a new design of the nitinol frame with a lower height and an extended sealing skirt, allowing the valve to be recaptured and repositioned during deployment.[74,75,76] Recent research comparing the newer generation of the balloon-expandable valve and self-expandable valve demonstrated equivalent efficacy and suggested the safe application of newer generations valves in patients undergoing TAVI.[77,78,79,80]

2.1.5 Disease burden

Aortic stenosis is the most prevalent valvular heart disease in developed countries.[4] The prevalence of aortic stenosis consistently increases with age, ranging from <1% in the 50-59-year cohort to nearly 10% in the 80-89-year cohort.[81,82] Because aortic stenosis takes a long time to develop, up to twenty-five years, the elderly are associated with a higher risk of disease.[1, 83, 84, 85, 86] Traditional cardiovascular risk factors such as hypertension, diabetes and dyslipidemia are demonstrated to be associated with increased risk of developing aortic stenosis.[82,87,88] Other clinical factors, such as male sex, elevated serum lipoprotein and low-density lipoprotein levels, and smoking, have also been shown to increase the risk of aortic stenosis.[7,89,90]

With increased life expectancy and ageing, the disease burden of aortic stenosis is increasing in Canada.[91,92] In Ontario, Canada, between 2004 and 2013, the number of aortic stenosis hospitalizations increased by 43%, from 3,228 in 2004 to 4,626 in 2013. [92] The overall age- and sex-standardized rate of aortic stenosis increased from 36 per 100,000 in 2004 to 39 per 100,000 in 2013, while in patients ≥85 years, the observed rate increased from 400 per 100,000 to 516 per 100,000. [92] The increasing disease burden is compounded by the fact that no pharmaceutical intervention can prevent the progression of the disease, leading to a substantial increase in the utilization of TAVI/SAVR.[92] Between 2004 and 2013, the overall proportion of patients who underwent an aortic valve intervention within one year of aortic stenosis hospitalization increased from 38.9% to 44.4% in Ontario, Canada.[92] Effective

interventions are needed to provide care for those affected by severe symptomatic aortic stenosis given the increased prevalence of aortic stenosis and an ageing population.

2.2 Transcatheter aortic valve implantation

Assessment of patients with aortic stenosis and treatment decisions should consider patient symptoms, the severity of valve obstruction, and the left ventricular responses to pressure overload.[15] Since the first TAVI procedure was performed in 2002, many studies have been conducted to evaluate the safety, efficacy, and cost-effectiveness of TAVI. Over the last decade, improvements in TAVI technology and the accumulation of clinical experience have led to a significant reduction in complication rates.[93] These advances have allowed indications for TAVI to expand in patients with a lower surgical risk profile.[93] With the increased uptake of TAVI, patient selection has become essential to avoid expensive, high-risk, and ultimately futile procedures in patients who will derive little benefit or improvement in health outcome.[93]

2.2.1 Risk stratification

Quality of patient care needs to be evaluated based on expected improvements in patient outcomes and anticipated risks given the patient's severity of illness, presence of comorbidities, and the medical services received.[94,95] To ensure safety and efficacy, the risk of the procedure and predicted mortality should be weighed against the benefits of the procedure.[96] Risk assessment and stratification are an essential step in deciding the optimal treatment for valvular heart disease. In clinical settings, the surgical risk can be estimated using scoring systems. The Society of Thoracic Surgeons (STS) predicted risk of mortality and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) are the most commonly used risk scores.[97,98] Based on the surgical risk score and coexisting conditions, patients with aortic stenosis are generally categorized into inoperable, high risk, intermediate risk and low risk.

The STS score is a validated tool for estimating 30-day mortality that has been widely used for patients undergoing cardiac surgeries.[99] The earliest version of the STS risk model was developed in 1986.[100] Because the original STS risk model was developed for coronary artery bypass graft (CABG) surgery, predictor variables were risk factors for CABG, including demographics (i.e. age, sex and race), anthropometric (i.e. weight and height), status (i.e. procedure status, shock and resuscitation) , cardiac variables (i.e. angina, New York Heart Association [NYHA] functional class, arrythmia and myocardial infarction), hemodynamics (i.e. ejection fraction, number of diseased vessels, left main disease, pulmonary artery mean pressure, mitral stenosis, aortic stenosis, tricuspid stenosis, pulmonic stenosis, mitral insufficiency, aortic insufficiency, tricuspid insufficiency and pulmonic insufficiency), comorbidities (i.e. serum creatinine, dialysis, renal failure, endocarditis, diabetes, chronic lung disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hypercholesterolemia, dyslipidemia, hypertension and smoking), preoperative interventions (i.e. preoperative intra-aortic balloon pump, preoperative inotropes, immunosuppressive treatment and percutaneous coronary intervention) and previous interventions (i.e. previous CABG, previous valve surgery, previous cardiac surgery and number of previous cardiovascular surgeries).[100] To take into account different patient characteristics, STS risk models have undergone several revisions and adjustments.[100]

While there have been several STS risk models for patients undergoing valve surgeries, the first STS risk model for the TAVI population (STS/ACC TAVR Risk score) was developed, validated and published in 2016.[101] This model was developed using data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) Registry.[101] The model's covariates included age, glomerular filtration rate per 5-U increments, hemodialysis, NYHA class IV, severe chronic lung disease, nonfemoral access site and procedural acuity, demonstrating better discrimination and calibration than other models.[101] This model has been incorporated into the TVT registry for patient selection decision-making for TAVI.[101] The STS/ACC TAVR Risk score is a calculated probability, ranging from 0% to 100%.[99] Patients are considered inoperable if they have coexisting

conditions that would be associated with a predicted probability of ≥50% of either death within 30 days after surgery or irreversible severe conditions.[47,94] If a patient's STS/ACC TAVR Risk score is >10% or the patient has coexisting conditions associated with a predicted probability of ≥15% of death within 30 days, the patient is considered at high surgical risk.[47] Patients are considered at intermediate risk if the STS/ACC TAVR Risk score is 4%-8% [102] and at low risk if the score is <4%.[103] Generally, TAVI is recommended when STS/ACC TAVR Risk score is ≥10%.[104]

The EuroSCORE is a simple and objective scoring system for the prediction of early mortality in cardiac surgical patients.[105] The EuroSCORE was developed and validated based on one of the largest, most complete and accurate databases in European cardiac surgical history.[105,106] The EuroSCORE risk model was published in 1999, based on a set of risk factors for patients undergoing cardiac surgeries.[106] Predictor variables in the EuroSCORE included patient-related factors (i.e. age, sex, chronic pulmonary disease, extracardiac arteriopathy, neurological dysfunction, previous cardiac surgery, serum creatinine, active endocarditis and critical preoperative state), cardiac-related factors (i.e. unstable angina, left ventricular dysfunction, recent myocardial infarct and pulmonary hypertension) and operation-related factors (i.e., emergency, major cardiac procedure other than CABG, surgery on the thoracic aorta and postinfarct septal rupture).[105] The EuroSCORE risk model has two versions: additive and logistic. Addictive EuroSCORE is an additive risk score, and logistic EuroSCORE is a calculated predicted probability based on the logistic regression model.[105,107] Although both versions demonstrated robust discrimination, logistic EuroSCORE is utilized more commonly because it is more accurate in very high-risk patients.[108]

EuroSCORE II is an updated version of the risk model, which was developed based on more current patient data and was better calibrated.[108] However, although validation studies demonstrate the better predictive performance of EuroSCORE II over the original EuroSCORE, the improved performance was mainly for patients undergoing combined AVR and CABG, not in those undergoing isolated AVR procedure.[108,109] When the Logistic Euro

SCORE is ≥20%, TAVI is recommended.[52] The EuroSCORE II is an updated version of the Logistic EuroSCORE and is considered to provide a better risk assessment of patients undergoing cardiac surgery. [109,110] When the EuroSCORE II is ≥7%, TAVI is recommended.[104]

2.2.2 Current indications for TAVI

TAVI has been considered an effective treatment option for severe aortic stenosis in patients who have a prohibitive surgical risk and a reasonable alternative to SAVR in patients who are at high risk but are suitable candidates for surgery.[15]

Current guidelines [96] suggest: 1) in patients who meet indications for SAVR with low or intermediate surgical risk, SAVR is recommended;[111,112] 2) in patients who meet indications for SAVR with a prohibitive surgical risk and a predicted post-TAVI survival >12 months, TAVI is recommended;[47,113] 3) in patients who meet indications for SAVR but have high surgical risk, TAVI is a reasonable alternative to SAVR and choice of intervention should be based on a collaborative heart team;[49,114] 4) in patients who have existing co-morbidities that would preclude the expected benefit, TAVI is not recommended.[115] The benefits of TAVI are mostly observed in selected patients.[96] Patients living with conditions that are associated with poor outcomes may be less likely to benefit from TAVI. These conditions include advanced age, frailty, smoking, chronic lung diseases, pulmonary hypertension, liver disease, stroke, anemia and other systemic conditions.[96] Clinical guidelines [96] suggest TAVI is not recommended if a patient's life expectancy is less than one year even with a successful procedure, or the chance of 2-year survival is less than 25%.

The STS/ACC TAVR Risk score and the EuroSCORE provide clinicians and hospitals with a tool to predict estimated risk of patient outcomes and to guide treatment options. However, an important limitation to these scores is that medical diagnoses and comorbidities are the main variables included for risk stratification, and the 'biological status' of the patient is not truly represented.[97,116] To improve risk stratification and better support decisions related to

treatments of aortic stenosis, it is crucial to integrate factors that describe the patient's biological status.[97,116] Current guidelines suggest the choice of proceeding with SAVR versus TAVI should consider factors in addition to surgical risk, including frailty, comorbidities, and patient values.[117,118]

2.2.3 Safety and efficacy of TAVI

The Placement of Aortic Transcatheter Valves (PARTNER) trial was a landmark randomized control trial (RCT) evaluating the safety and effectiveness of TAVI. The PARTNER trial was a prospective, multi-centred, randomized, and controlled trial. [47, 119] All patients enrolled had severe symptomatic aortic stenosis. There were two arms of this trial: Cohort A –consisted of high-risk patients[119] and Cohort B- consisted of inoperable patients.[47]

Cohort B of the PARTNER trial comprised 358 patients who were considered ineligible for surgery.[47] Patients were randomized 1:1 to transfemoral TAVI or standard medical therapy.[47] The follow-up was at least one year for all patients. There were two primary endpoints: 1) death from any cause over the study duration, and 2) a composite outcome of the time to death from any cause or the time to the first rehospitalization.[47] At one year, the all-cause mortality was 30.7% in those treated with TAVI, as compared with 50.7% in those treated with standard therapy.[47] The rate of the composite endpoint of death from any cause or rehospitalization was 42.5% in those treated with TAVI, as compared with 71.6% in those treated with standard therapy.[47] Among survivors at one year, the proportion of NYHA class III or IV occurred in 25.2% among those undergoing TAVI, as compared with 58.0% in those treated with standard therapy.[47]

Cohort A of the PARTNER trial comprised 699 high-risk patients with severe aortic stenosis.[119] Patients were randomly assigned to undergo either TAVI (either a transfemoral or a transapical approach) or SAVR.[119] In Cohort A of the PARTNER trial, TAVI was not demonstrated to be inferior to SAVR.[119] Neither intervention showed better outcomes overall than the other by one year. At one year, the all-cause mortality was 24.2% in the TAVI group

and 26.8% in the SAVR group;[119] the rate of major stroke was 5.1% in the TAVI group and 2.4% in the SAVR group.[119] Two-year clinical outcomes in Cohort A of the PARTNER trial were also comparable between high-risk patients who underwent TAVI versus SAVR.[113] The rate of death from any cause at two years was 33.9% in the TAVI group and 35.0% in the SAVR group;[113] the frequency of all strokes did not differ significantly. The decision to choose TAVI or SAVR as a therapeutic option presents a tradeoff.[113] With SAVR, patients undergo sternotomy and cardiopulmonary bypass, leading to a longer post-operative recovery. TAVI is associated with a higher risk of stroke and vascular injury, with implications for long-term morbidity.[69]

Apart from RCTs, several registries, which reflect real-world data, also investigated the uptake of TAVI. [57,120,121,122,123,124,125,126,127] For example, Moat et al [120] reported outcomes on 870 patients who underwent TAVI. Data were collected prospectively up until December 31, 2009, by the United Kingdom TAVI registry.[120] The study reported survival after TAVI was 92.9% at 30 days, 78.6% at one year, and 73.7% at two years.[120] Eltchaninoff et al[123] reported outcomes on 244 high-risk patients included in the FRANCE (FRench Aortic National CoreValve and Edwards) registry, a multicentre registry administered by the French Ministry of Health. Data were collected from February 2009 to June 2009. The study showed that at one month after TAVI, mortality was 12.7%, and the rates of stroke and other complications were 3.6% and 7.3%, respectively.[123] The Society of Thoracic Surgeon /American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) registry is a national TAVI registry that includes the participation of more than 250 clinical sites.[126] Mack et al [126] reported outcomes on 7710 patients undergoing TAVI between November 1, 2011, and May 31, 2013, including 6151 high-risk patients and 1559 inoperable patients. The study showed that overall, the in-hospital mortality was 5.5%, major in-hospital complications included stroke (2.0%), major vascular injury (6.4%), and acute renal insufficiency (5.5%), and major bleeding (3.5%).[126] Among the 3133 patients with available 30-day outcome data, the incidence of death was 7.6%.[126] Rodes-Cabau et al [127] reported outcomes on 339 patients who underwent a TAVI procedure between January 2005 and June 2009 in 6 Canadian centers.

The study suggested that at a mean follow-up of 42 ± 15 months, 188 patients (55.5%) had died, and 36 patients (10.4%) had died within 30 days.[127]

Over the last decade, the evolution of TAVI saw a trend towards its usage in lower-risk patients. Recently, observational studies and trials have demonstrated acceptable outcomes in lower surgical risk patients.[128,129,130,131,132,133,134] For example, between December 2011 and November 2013, the PARTNER II trial enrolled 2,032 patients who were considered intermediate risk.[132] All patients enrolled had an STS score of 4%-8% and were randomly assigned to undergo either TAVI or SAVR.[132] In the PARTNER II trial, the rate of death from any cause or disabling stroke was 19.3% in the TAVI group and 21.1% in the SAVR group.[132] TAVI was found to be similar to SAVR with respect to the primary endpoint of death or disabling stroke in intermediate-risk patients. Further to this, the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial compared the safety and efficacy of TAVI with SAVR in intermediate-risk patients.[135] The SURTAVI trial enrolled 1,746 patients at 87 centers.[135] Patients were randomized to undergo either SAVR or TAVI with a self-expanding prosthesis valve. The primary outcome was a composite of death from any cause or disabling stroke at 2 years. The SURTAVI trial did not find a significant difference in the primary outcome (12.6% in the TAVR group vs. 14.0% in the SAVR group).[135] The SURTAVI trial found that patients undergoing SAVR had higher acute kidney injury rates, atrial fibrillation, and transfusion.[135] In comparison, patients undergoing TAVI were associated with higher rates of residual aortic regurgitation and pacemaker implantation.[135] Recently, the PARTNER III trial enrolled 1,000 low-risk patients.[103] All patients enrolled had STS score of less than 4% and were randomly assigned to undergo either TAVI or SAVR.[103] At one year, the rate of the composite of death, stroke, or rehospitalization was significantly lower in the TAVI group than that in the SAVR group (8.5% versus 15.1%).[103] The Evolut trial in low risk patients compared the safety and efficacy of TAVI with a self-expanding bioprosthesis with SAVR.[136] The Evolut trial randomized 1,468 patients to undergo either TAVI or SAVR. The primary outcome was a composite of death or disabling stroke at 2 years. The Evolut trial found that in patients who were

considered at low preoperative risk, TAVI was noninferior to SAVR with respect to the primary outcome (5.3% in the TAVI group vs. 6.7% in the SAVR group).[136]

2.2.4 Complications of TAVI

TAVI is a minimally invasive procedure as compared with SAVR because patients undergoing TAVI do not typically undergo sternotomy and cardiopulmonary bypass.[1,49] When evaluating the safety and efficacy of TAVI, a unique set of complications need to be considered, including stroke, vascular complications, conduction disturbances, and acute kidney injury.[137] The Valve Academic Research Consortium (VASC) 1 and 2 consensus documents have documented standardized clinical endpoints after TAVI.[138,139]

Stroke is a critical periprocedural complication after TAVI.[139,140] It is a medical condition characterized by an acute focal or global neurological dysfunction, caused by the brain, spinal cord, or retinal vascular injury due to hemorrhage or ischemic infarction.[139] Ischemic stroke is caused by infarction of central nervous system issue.[139] Hemorrhagic stroke is caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.[139] Defined as a transient episode of focal neurological dysfunction caused by the brain, spinal cord, or retinal ischemia, without acute infarction, transient ischemic attack (TIA) is closely related to an ischemic stroke.[139] In Cohort A of the PARTNER trial, the rates of stroke or TIA were 5.5% in the TAVI group and 2.4% in the SAVR group at 30 days and 8.3% and 4.3%, respectively, at one year.[49] In Cohort B of the PARTNER trial, the rates of stroke or TIA were 6.7% in the TAVI group and 1.7% in the standard therapy group at 30 days and 10.6% and 4.5%, respectively, at one year.[47] Regardless of therapy, TAVI increased the risk of stroke within the first 30 days and one year in the PARTNER trial. With clinical experience, advancements in valve technology, and improvement in patient selection, the risk of stroke has declined.[140] A meta-analysis conducted in 2014 found there was no difference in stroke between the transfemoral and transapical approach or the type of valve used for TAVI; this study also demonstrated a decline in stroke over time, reflecting on continually improving outcomes after TAVI. [140]

Vascular complications are the most common and severe complications of TAVI and are most frequently seen with the transfemoral approach, due to the large diameter of the sheaths required to deliver the valve, balloon inflation of the valve, and guide-wire rupture of vessels.[69,141,142,143,144] In Cohort A of the PARTNER trial, the rates of vascular complications were 17.0% in the TAVI group and 3.8% in the SAVR group at 30 days and 18.0% and 4.8%, respectively, at one year.[49] In Cohort B of the PARTNER trial, the rates were 30.7% in the TAVI group and 5.0% in the standard therapy group at 30 days and 32.4% and 7.3%, respectively, at one year.[47] Vascular complications are often categorized into major and minor. Definitions developed by the VARC are shown in **Table 2.2**. Vascular complications are associated with bleeding events, transfusions, and increased mortality, but the impact may decrease in lower-risk populations.[143]

Table 2.2. Major and minor vascular complications defined by the VARC.

Major vascular complications[145]	**Minor vascular complications**[145]
1) any thoracic aortic stenosis; 2) access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to either death, significant blood transfusion (≥4 U), unplanned percutaneous or surgical intervention, or irreversible end-organ damage; or 3) distal embolization that requires surgery or results in amputation or irreversible end-organ damage.	1) access site or access-related vascular injury not requiring unplanned percutaneous or surgical intervention and not leading to irreversible end-organ damage; 2) distal embolization not resulting in amputation or irreversible end-organ damage; or 3) failure of percutaneous access site closure resulting in interventional or surgical correction and not associated with death, significant blood transfusions, or irreversible end-organ damage.

Conduction disturbances, mainly new-onset left bundle branch block and advanced atrioventricular block requiring permanent pacemaker implantation, are common in patients undergoing TAVI.[146] The occurrence of conduction disturbances is attributed mainly to the

close proximity between the aortic valve and the conduction system.[146,147,148,149] The location of the atrioventricular node in relation to the aortic valve makes it vulnerable to encroachment during TAVI; this puts patients undergoing TAVI at risk for developing left bundle branch block and complete heart block.[146,147,148,149] Overall, the occurrence of new-onset left bundle branch block is more frequent when the self-expandable CoreValve system is used, with rates ranging from 18% to 65%, as compared with 4% to 30% when the balloon-expandable SAPIEN valve is used.[146,147] Similarly, the occurrence of permanent pacemaker implantation was more frequent when the self-expandable CoreValve system is used, with rates of 25% -28%, as compared with 5%-7% when the balloon-expandable SAPIEN valve is used.[146,150,151,152] Improvements in TAVI technology have led to a significant reduction in periprocedural complications.[153,154] However, the incidence of conduction disturbances remains high, and use of newer generation transcatheter valves failed to reduce the rates.[72,146,155,156,157, 158,159]

Acute kidney injury is a well-known complication following cardiac surgery.[139,160] Acute kidney injury is common in patients undergoing TAVI because TAVI is typically performed in elderly and high-risk patients associated with a high prevalence of chronic kidney disease.[160] On the other hand, in patients undergoing TAVI, the use of contrast dye may increase the risk of contrast-induced nephropathy, and the manipulation of large catheters in the aorta of patients with diffuse atherosclerosis may cause distal embolization of atherosclerotic debris to the renal vascular bed.[160] In patients undergoing TAVI, the reported incidence of acute kidney injury ranges from 12% to 21%.[137] Acute kidney injury is associated with enhanced 30-day and 1-year mortality, and Stage III may lead to a reduced 1-year survival.[137,160,161,162,163]

2.2.5 Economic considerations for TAVI

TAVI is generally associated with a high cost of the device. In addition to the device, patient factors and procedure-related factors can also increase the healthcare cost associated with TAVI. For patient-level factors, age over 75 years and lung disease were found to be

associated with an increased cost for the index hospitalization.[164,165] For procedure factors, a non-transfemoral approach and a long hospital stay were found to be strong drivers of increased cost.[164,165]

New technologies are often associated with increased healthcare costs.[166] The rapid evolution of new health technologies confronts the health care system with difficult decisions regarding the appropriate allocation of scarce health care resources.[167] Given the high cost associated with TAVI and the growing number of potential patient candidates, the economic evaluation of TAVI becomes of equal importance to the evaluation of clinical outcomes.[168] Economic evaluation is a systematic process of identification, measurement and valuation of the inputs and outcomes of two alternative interventions and the subsequent comparisons of these.[169] Economic evaluation can take a number of forms, including cost analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis.[170] The identification of costs and their subsequent measurement in monetary units is similar, but the nature of the consequences stemming from the interventions being examined is different.[170]

In economic evaluation, the quality-adjusted life-year (QALY) is the most commonly used measure of health outcome value.[170,171] The QALY incorporates both the quality and quantity of life lived.[171,172] The incremental cost-effectiveness ratio (ICER) is a key metric used in economic evaluation to reflect on the cost-effectiveness of a health care intervention.[170,173] It is defined by the difference in cost between two interventions, divided by the difference in consequences (or effect).[170,173] The ICER represents the average incremental cost given one additional unit of the effect.[170,173] The formula is given as: $ICER = (Cost_1 - Cost_0) / (Effect_1 - Effect_0)$.[170,173] $Cost_1$ and $Effect_1$ are the cost and effects associated with the new intervention. $Cost_0$ and $Effect_0$ are the cost and effect associated with the comparator or the reference intervention.[170,173] The ICER is used as a decision rule in policy-making: if the ICER lies below the willingness-to-pay threshold, the maximum amount of money that a decision-maker is willing to sacrifice to implement a new intervention, the intervention is considered cost-effective; if the ICER is above the threshold the intervention will be considered too expensive and thus should not be funded.[170,174,175]

There are two approaches to economic evaluation: clinical trial-based analysis and decision-analytic modelling. Clinical trial-based economic evaluation has a long history. Using clinical trial-based economic evaluation, parameters (i.e. costs and patient outcomes) are obtained from a single clinical study, which provides all sources of data and evaluation framework.[176] Although clinical trials remain a gold standard to provide treatment effect in a clinical context, the use of clinical trial-based economic evaluation has unique limitations, including a failure to compare all relevant options, a limited time horizon, irrelevance to the decision context and failure to incorporate all available evidence and quantify uncertainty.[176] Decision-analytic modelling is an alternative approach for economic evaluation. Different to clinical trial-based analysis, a decision-analytic model utilizes evidence from a wide range of sources, including clinical trials, cohort studies, surveys and published reports.[176] Decision-analytic modelling enables decision-makers to incorporate different sources of evidence, quantify decision uncertainty and consider a non-truncated time horizon.[176]

Along with the emergence of studies evaluating the safety and efficacy of TAVI, studies determining the cost-effectiveness of TAVI provided valuable evidence for decision-making related to TAVI. In studies evaluating the cost-effectiveness of TAVI compared with medical therapy, most studies were in favour of TAVI. [166,168,177,178,179,180,181 ,182,183,184] Specifically, the estimated costs of TAVI, regardless of access approaches, were consistently higher than those of medical therapy, and the cost of the valve is one of the most important cost drivers. [178,181] However, the incremental cost of TAVI was offset by the higher QALY gain. Therefore, ICERs reported in most studies were close to or below maximum acceptable thresholds.[168]

Studies evaluating the cost-effectiveness of TAVI compared with SAVR in high-risk patients did not reach consistent and conclusive results, given a broad range of health care systems, modelling techniques, and willingness-to-pay thresholds.[168,181, 183, 184,185,186,187,188,189,190] The access approaches (transfemoral or transapical) have an impact on TAVI's cost-effectiveness.[168] Specifically, compared with SAVR, transfemoral TAVI is cost-effective, while transapical TAVI is dominated by SAVR. Due to the high cost of valves, both transfemoral and transapical TAVI are associated with higher procedural costs than SAVR.[168]

However, overall costs with transfemoral TAVI can be offset by reduced length of hospital stay and thus result in a better ICER.[168]

Studies concerning the cost-effectiveness of TAVI in lower-risk patients are limited. A study by Tam et al [191] examined the cost-effectiveness of TAVI compared with SAVR in the intermediate-risk patients and found TAVI was cost-effective from the Canadian health care system payer's perspective. However, in a Spanish study, Ribera et al [190] suggested that due to the high cost, TAVI is not likely to be cost-effective in patients with intermediate-risk for surgery.

2.2.6 Trends in TAVI utilization

Over the past decade, the number of TAVI procedures performed across countries has increased rapidly. In Germany, there has been a 20-fold increase in the number of TAVI procedures since 2008, from 637 to 13,264 in 2014.[192] In the United Kingdom, the annual number of TAVI procedures increased nearly linearly from 360 in 2007 and 2008 to 1,271 in 2012.[193] TAVI was first introduced in Ontario, Canada in 2006.[92] Since then, a steady rise in procedural volume was seen from 7 patients in 2006 to 344 in 2013.[92] As TAVI volumes began to increase in Ontario, an associated decline in SAVR volumes were observed.[92]

Recent data suggest a trend towards better outcomes in TAVI procedure. In-hospital and 30-day mortality reported are significantly lower, vascular complications have decreased, long-term outcomes have improved, and patients have been discharged earlier. [192,193, 194] The improved outcomes might be attributable to improvements in TAVI technology, increased surgical team's experience and the growing number of patients with lower preoperative risk.[195] Improved patient outcomes after TAVI such as shorter hospital stay, decreased rates of complications and improved overall survival will likely improve the cost-effectiveness of TAVI in the future.[195,196,197,198]

Over time indications for TAVI have expanded to lower risk, younger and asymptomatic patients.[93] A primary concern associated with the expansion of TAVI is the uncertainty

surrounding durability of the valve.[93] The risk of structural valve deterioration, which is defined as degeneration and dysfunction caused by permanent intrinsic changes of the valve, is not clearly documented yet, although it is believed to be affected heavily by valve design and patient age at the time of implantation.[93,199]

Research on TAVI performance is ongoing. However, there has been an increasing recognition that some patients fail to benefit from TAVI.[200] Some patient factors and comorbidities have been associated with poor outcomes after TAVI, including severe chronic lung disease, chronic kidney disease, frailty and pulmonary hypertension.[193,200,201,202,203,204,205,206,207] With the growing use of this procedure and important economic implications of TAVI, accurately identifying patients who are likely to benefit from TAVI remains a priority.[200]

2.3 Frailty

2.3.1 Definitions

The definition of frailty has been discussed for many years. Theoretically, frailty is defined as a clinically recognizable biological syndrome characterized by impaired physiological reserve and increased vulnerability to stressors.[208,209,210] When exposed to stressors, such as chronic disease and surgery, frail people are more prone to poor outcomes.[208,209,210] Weight loss, low physical activity, slowness, weakness and exhaustion are considered the preclinical manifestations of frailty.[211] Previous research hypothesized that any early manifestations could lead to the initiation of the frailty cycle, and the syndrome could be aggregated with manifestations culminating (**figure 2.3.1**).[211] Evidence suggested a hierarchical order in the development of frailty manifestations: weakness was the first sign of increasing vulnerability in the onset of frailty, and weight loss and exhaustion were predictors of rapid adverse progression in women.[211]

Frailty is highly prevalent in older adults.[208] As population ageing accelerates rapidly, with individuals living longer, frailty is an increasing problem amongst older adults.[212] Reported

prevalence of frailty in older adults varies greatly, given a wide range of frailty measures. A systematic review by Collard et al found the prevalence of frailty in community-dwelling adults aged 65 and older ranged from 4.0% to 59.1%.[213] Frailty was found to increase with age and was more prevalent in females.[213] Frailty is associated with a higher risk of adverse health outcomes, and hence, it has been recommended that frailty measurement should be incorporated into routine care for older adults.[208,212,214,215]

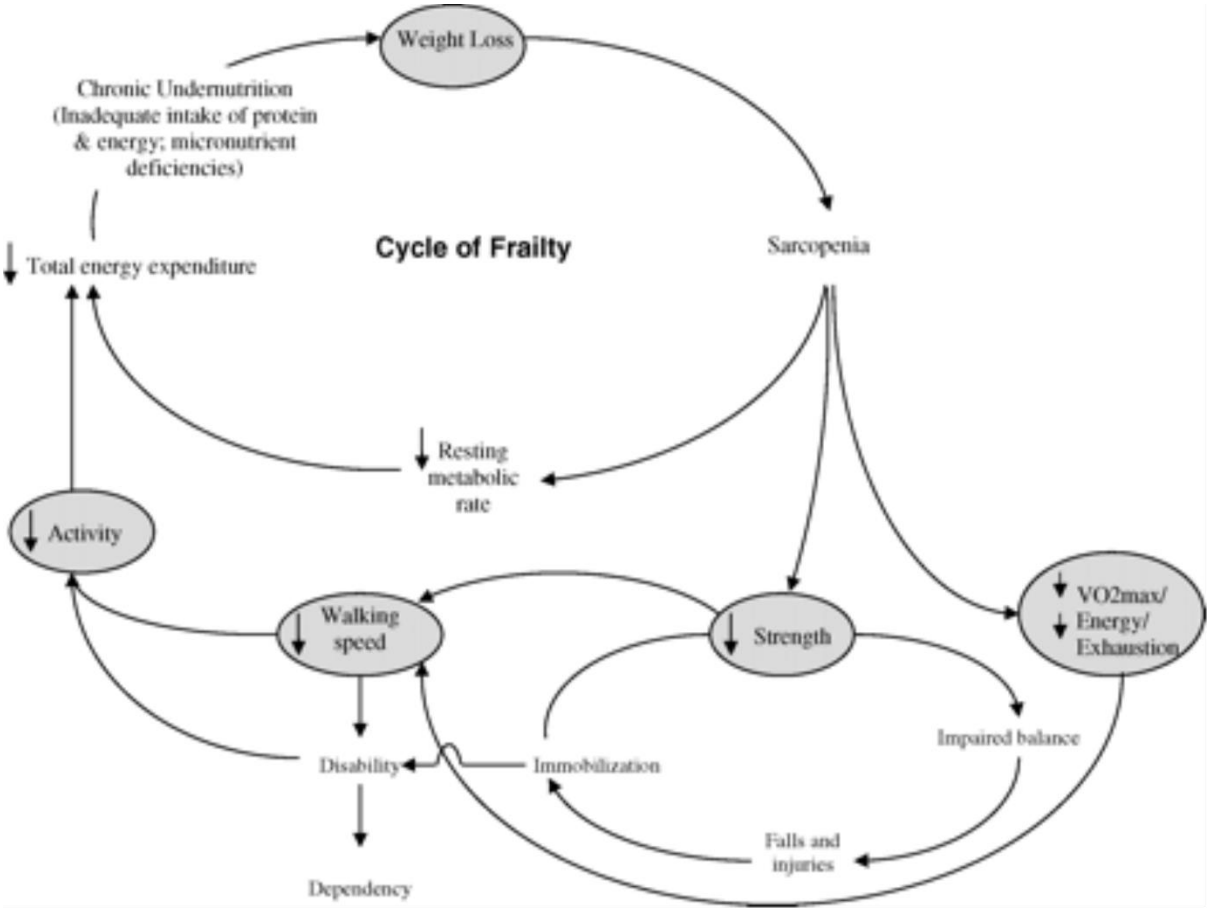

Figure 2.3.1 Cycle of frailty.

The figure describes the cycle of frailty.[211]

2.3.2 Frailty measurement

A number of frailty measures have been proposed. However, there is no gold standard measurement for frailty.[209,216] Currently, frailty measures can be categorized into the

following types: frailty phenotype, multi-dimensional frailty index, accumulated deficits frailty measures, single item frailty measures, serum/biological markers, disability-based frailty measures and clinical judgment.[209,216,217]

2.3.2.1 Frailty phenotype

The frailty phenotype, proposed by Fried et al, defines frailty as a clinical syndrome meeting three or more of five phenotypic criteria (**Table 2.3**): weakness as measured by low grip strength, slowness defined by slowed walking speed, low level of physical activity, self-reported exhaustion, and unintentional weight loss.[208] The frailty phenotype defines the 'pre-frail' state as an intermediate stage if one or more criteria are present.[208] Though less vulnerable than frail people, those identified as pre-frail are at high risk of progressing to frailty.[214] The Fried frailty phenotype recognizes frailty as a different condition from disability and comorbidity, two conditions that are also prevalent in older adults.[208,218,219] Disability is defined as difficulty or dependency in carrying out activities of daily living and is measured by impairment in activities of daily living.[219,220] Comorbidity is defined as the presence of two or more diseases.[218,219] Frailty, disability and comorbidity are different conditions but were found to be interrelated: both frailty and comorbidity can predict subsequent disability, disability may lead to frailty and worsen comorbidity, and frailty may contribute to the progression of comorbidity.[218,219,220] Frailty measures stemming from the Fried phenotype include Physical Frailty Index, Phenotype of Frailty, Modified Phenotype of frailty and Short Physical Performance Battery, amongst others.[217]

Table 2.3The Fried frailty phenotype

Criteria [208]	**Measurement** [208]
Weakness	Grip strength: lowest 20% (by sex, body mass index)
Slowness	Walking time/ 15 feet: slowest 20%

	(by sex, height)
Low level of physical activity	Kcal/ week: lowest 20% Males: 383 Kcal/ week Females: 270 Kcal/ week
Exhaustion	Self-reported exhaustion
Weight loss	>10 lb lost unintentionally in prior year

2.3.2.2 Multi-dimensional frailty index

Multi-component frailty measures assess a wide range of domains, to signify the level of frailty. Frailty is determined by the number of domains that have been affected. Multi-component measures may count the number of domains affected or generate an index score. Domains addressed in multi-component measures may include mobility, muscle strength, physical activity, nutrition, cognition, disability, etc. Multi-component frailty measures include the Edmonton Frailty Scale, Comprehensive Geriatric Assessment Frailty Index and Essential Frailty Toolset, amongst others.[221,222,223,224]

2.3.2.3 Accumulated deficits

Accumulated deficits frailty measures stem from the Rockwood frailty index, a frailty index calculated by counting the number of deficits identified in a comprehensive geriatric assessment, including diseases, physical and cognitive diagnoses, psychosocial risk factors, and other common geriatric syndromes.[219,225,226] The principle of accumulated deficits is to count deficits in health, with the idea that the more deficits a patient has, the more likely the patient is to be frail.[219,225,226] Deficits considered in the calculation of the frailty index are demonstrated to associate with poor outcomes and all deficits are assigned a weight in calculating the frailty score.[219,225,226] Compared to the Fried frailty phenotype, the frailty index definition considers psychological factors.[218,227] As the frailty index has a more finely

graded risk scale, it appears to be a sensitive predictor of adverse outcomes and adds clinical utility in risk assessment and stratification.[218,227] However, the frailty index does not consider frailty as a different concept from disability or comorbidity.[218,227] Accumulated deficits frailty measures commonly used include 40-item frailty index, 70-item frailty index, and comprehensive geriatric assessment frailty index.[217,228,229,230] The idea and approach to calculating the frailty index are simple but selecting candidate variables for the frailty index model and determining cut-points are important issues.[216]

2.3.2.4 Single item frailty measures

Single component measures assess one domain underlying frailty, thus by definition use a single component measure suggests frailty can be sufficiently measured in one dimension. Commonly used single component measures include gait speed, Timed Up-and-Go test, Katz Index of Activities of Daily Living and Body Mass Index, amongst others.[208,231,232,233,234] There has been an increased use of single-component frailty measures as they are simple and convenient to use.[216,231] However, it is unclear whether or not a single measure can reflect a complex biological phenomenon such as frailty.

2.3.2.5 Serum/biological markers for frailty

Due to the complex underlying pathophysiology of frailty, the initiation of frailty involves a range of biological changes, such as inflammation, hormonal change and metabolic dysregulation.[235] Emerging research has used biological markers for inflammation, hormonal change and metallic dysregulation to define frailty. For example, implicated in the pathobiology of frailty, hypoalbuminemia is a biomarker for malnutrition and chronic inflammation.[236,237] Serum albumin level has been considered a simple surrogate marker for frailty.[236,237] Other markers, such as psoas muscle area and body composition (fat mass and skeletal muscle mass), though less commonly cited, are also used to measure frailty.[238,239]

2.3.2.6 Disability based measures

Although frailty is considered to be separate from disability, some frailty scores are operationalized mainly based on the presence of disability, such as the Canadian Study of Health and Aging Clinical Frailty Scale, Hebrew Rehabilitation Center for Aged Vulnerability Index, and Vulnerable Elders Survey. [217,219,240,241]

2.3.2.7 Clinical judgment

Clinical judgements about frailty on the basis of the criteria of the medical evaluation team or patient characteristics are demonstrated to yield useful predictive information and to identify frailty.[242,243] For example, a study by Rodes-Cabau et al defined frailty on the basis of the criteria of the medical evaluation team.[244] Traynor et al used assisted care as a baseline patient characteristic to define frailty.[243]

2.3.3 Health administrative database frailty indices

Recently, there have been several efforts to develop frailty algorithms for use with health administrative databases or electronic medical records.[245,246,247,248,249] Health administrative database frailty algorithms have been based on the frailty index model. Derived and validated using health administrative data, administrative database algorithms have unique advantages. For example, these frailty indices can be used wherever electronic health data are available and encoded. Since administrative database frailty scores can potentially be incorporated into hospital information systems, the inter-operator variability and operationalization burden associated with manual scoring systems would be removed.[248,250,251]

In Canada, the Institute for Clinical Evaluative Sciences (IC/ES) houses administrative databases for healthcare research. Two administrative database frailty algorithms have been validated and incorporated into the IC/ES system: The Johns Hopkins Adjusted Clinical Groups (ACG) and the Hospital Frailty Risk Score.

The Johns Hopkins ACG frailty-defining diagnosis indicator is an instrument designed for use in health administrative data. The ACG frailty-defining diagnosis indicator is a binary variable, based on 12 clusters of frailty-defining diagnoses.[252,253] The ACG system is propriety and requires a license. Specific diagnostic codes underlying its clusters are not available for public dissemination.[252,253] Previous studies have used the ACG frailty-defining diagnosis indicator to study frailty-related health care resource use and surgical outcomes.[252,253]

The Hospital Frailty Risk Score is considered a low-cost, systematic way to screen for frailty and identify patients at higher risk of adverse outcomes.[248] The Hospital Frailty Risk Score was developed and validated based on a broad set of 109 International Statistical Classification of Diseases (ICD-10).[248] The Hospital Frailty Risk Score is a relatively new frailty score driven by administrative databases. Gilbert et al [248] suggested that the Hospital Frailty Risk Score overlapped fairly with dichotomized Fried and Rockwood frailty scales, and demonstrated moderate agreement with the Rockwood Frailty Index.

Key differences amongst the administrative database frailty algorithms may contribute to differences in performance for identifying frail patients. All of the algorithms assign weights to “deficits” identified by diagnostic codes but differ in the weights assigned to each deficit in calculating the frailty score.

2.4 Frailty and TAVI

The average age and complexity of patients undergoing cardiac surgery have increased, and the treatment options for heart disease have diversified, making frailty an essential topic in cardiac surgery.[254] The prevalence of frailty in patients undergoing TAVI is relatively high, depending on the measurement tools used. Current guidelines recommend assessing frailty for patients with aortic stenosis, but the lack of standard frailty measurement tools remains a primary barrier to the incorporation of frailty into perioperative management. Studies have

determined the association between frailty and relevant clinical outcomes. Recent studies also suggested that frailty may predict healthcare costs.

2.4.1 Prevalence of frailty in patients undergoing TAVI

Several factors may contribute to the high prevalence of frailty in TAVI. Cardiac surgery represents a typical stressor to which the patient's resiliency will determine their post-operative outcome, and thus cardiac surgery is an inherently relevant setting for frailty.[255] On the other hand, current guidelines for the management of valvular heart disease suggest that patients with low risk (STS <4%) with no specific indicators for TAVI should undergo SAVR; specific factors in favour of TAVI include severe comorbidity, age ≥75 years, history of cardiac surgery, frailty, and limited mobility.[93,256] Therefore, patients referred for TAVI typically have advanced age, multiple comorbidities, and frailty.[209]

Prevalent in older adults and patients with complex conditions, frailty plays an important role in the management of patients undergoing TAVI. Due to a large number of frailty measurement tools, the estimated prevalence of frailty in patients undergoing TAVI varies greatly across the literature. A narrative review by Afilalo et al suggested that the prevalence of frailty in patients referred for TAVI can be as high as 63%.[209] A systematic review by Kim et al showed that the prevalence of frailty in patients undergoing TAVI ranged from 5% to 85%.[231] The Frailty in Older Adults Undergoing Aortic Valve Replacement (FRAILTY-AVR) study found that within the same cohort of TAVI patients assessed with seven different frailty tools, the prevalence of frailty ranged from 35% to 74% depending on the frailty tool.[257]

2.4.2 Predictive ability of frailty

Frailty has been recognized as an important predictor for adverse outcomes after cardiac surgery, including mortality, morbidity and functional decline.[207] Emerging evidence has also revealed that frailty adds incremental predictive value to existing surgical risk prediction models in patients undergoing cardiac surgery.[207,258] A study by Afilalo et al. compared the

incremental predictive value of seven different frailty measures in predicting one-year mortality after TAVI or SAVR.[257] The study included 1,020 patients aged 70 or older and compared prediction accuracy statistics, including c-statistic, Bayesian information criterion and integrated discrimination improvement.[257] The study found that the addition of frailty measures to existing risk prediction models can improve performance with respect to predicting one-year mortality, regardless of the frailty measures used.[257] The study indicates that although the wide variations in frailty measurement tools may associate with discrepancies, it might be possible to incorporate frailty measures into existing risk prediction models in terms of predictive ability.

2.4.3 Frailty in preoperative assessment

Frailty is a missing parameter not captured by traditional risk scores such as STS score and EuroSCORE.[97,116] Previous studies have highlighted the limitations of these scoring systems and suggested that surgical risk scores cannot reflect a patient's actual biological status, and the comprehensive assessment of frailty score may add predictive value to assess the prognosis of elderly patients before cardiac surgery.[259] When considering valve procedures, clinical practice guidelines recommend assessing frailty as one component of risk.[117] Only selected patients benefit from TAVI, and frailty assessment can provide useful information for patient selection.[117] According to the AHA/ ACC, frailty is the most common reason for inoperability in patients with an STS score ≥15%, and frailty is one of the factors determining the choice of proceeding with SAVR versus TAVI.[96,117] Preoperative assessment of frailty, therefore, has been recommended for use in clinical setting.[257]

Due to a large number of frailty measurements, the quality of measurements varies widely.[216] With no single standard method of measuring frailty, the diversity of frailty measurements leaves little consensus on the optimal approach to assessing frailty in patients undergoing TAVI.[260] The lack of consensus surrounding frailty measurement tools limits their use in clinical practice. Some frailty measures are suited for population-level frailty screening, whereas others are suited for comprehensive assessment.[216] A two-step approach that one

frailty measurement is used for screening and a second one for a comprehensive assessment has been proposed for use in clinical setting.[216] Although there is no one perfect frailty measurement, there have been several universal criteria for a frailty measurement. A frailty measurement should be able to identify frailty and reliably predict adverse health outcomes accurately; it should be supported by a biological causative theory and be simple to apply.[212,216,261]

2.4.4 Frailty and patient outcomes after TAVI

When exposed to stressors, frail patients are more vulnerable to poor health outcomes. Given the association between frailty and adverse outcomes, previous literature has examined the relationship between frailty and patient outcomes after TAVI.

Studies have examined the relationship between frailty and 30-day mortality of patients after TAVI. [125,238,262,263,264,265,266,267] Most of the studies found no difference between frail and non-frail groups. For example, a prospective observational study by Bureau et al [266] suggested that there was no significant difference in the 30-day mortality between frail and non-frail patient groups; in another study, Green et al [267] showed that no significant difference was found in death at 30 days according to baseline frailty status. In contrast, a study by Alfredsson et al [265] showed that frailty defined by slow gait speed was independently associated with 30-day mortality after TAVI.

Existing research examining the relationship between frailty and 1-year mortality suggests that frailty is associated with mortality one year after TAVI.[121,125,237,263,268,269,270,271] For example, Green et al [271] showed that the Kaplan-Meier estimates of all-cause mortality in the frail and non-frail group were 32.7% and 15.9%, respectively (log-rank p=0.004). In another study by Steinvil et al,[269] Cox regression analysis demonstrated that frailty status was significantly associated with 1-year mortality (hazard ratio=2.2, 95% confidence interval 1.25-3.96; p=0.007), after adjusting for age, sex, end-stage renal disease, severe chronic obstructive pulmonary disease, non-transfemoral access, STS risk group, and baseline atrial

fibrillation. Findings on the relationship between frailty and mortality at one year are consistent.

Existing research also examines the association between frailty and other clinical outcomes. For example, Green et al [271] found that high frailty score was associated with a longer hospital stay before adjustment. A study by Yamamoto et al [236] suggested that after propensity matching, durations of Intensive Care Unit and hospital stay were longer in frail patients compared to non-frail. Zajarias et al [272] found that frailty score, derived per previous methods using four domains (i.e. serum albumin, gait speed, grip strength and Katz activity of daily living), was associated with an increased rate of peri-procedural bleeding in unadjusted analyses.

2.4.5 Frailty and healthcare costs of TAVI

Frailty has been identified as a driver of healthcare costs associated with TAVI. Frail patients are at greater risk of prolonged mechanical ventilation, longer intensive care unit stays, longer hospital stays, higher demand for rehabilitation care, and higher rehospitalization rates, leading to higher healthcare costs.[273,274,275,276,277,278] In a study by Goldfarb et al [278] testing the link between frailty and costs after cardiac surgery, frail patients were found to incur substantially higher hospitalization costs than non-frail patients, and the seven extreme-cost cases identified were frail at baseline.[278] The study by Goldfarb et al [278] investigated the incremental cost associated with preoperative frailty in patients undergoing cardiac surgery. This study gives insight into the effectiveness of frailty in predicting the financial burden associated with surgical treatment.

Although the connection between frailty and morbidity and between morbidity and costs has been clear, the link between preoperative frailty and cost and the predictive ability of frailty to identify high-cost TAVI cases is not clear.[278] With the expansion in the number of frail patients undergoing TAVI and their growing need for healthcare resources, accurately

identifying frail patients may provide clinicians, patients, and decision-makers with information for better patient selection and resource allocation.[278]

2.5 Pre-existing research

While frailty is expected to be highly prevalent amongst patients undergoing TAVI, it has not been assessed routinely in clinical settings. In the elderly population, frailty is an important risk factor for morbidity and mortality, with additional predictive validity beyond age, sex, comorbidities and other markers of risk. Since frailty has important prognostic value, clinicians have become increasingly interested in frailty measurement. The current research aims to address the research gap by performing a systematic review and meta-analyses of prognosis after TAVI in frail patients.

While there is no international standard for frailty measurement, specific tools are notable due to their common use and validation in a range of clinical populations. In the clinical setting, prospective use of a clinical frailty tool to risk stratify patients may optimize health care for patients undergoing TAVI. Recent retrospective analyses have derived and validated frailty indices using linked health administrative data. If database-driven frailty measures demonstrate consistent prediction of surgical outcomes, then incorporating administrative database frailty indices into electronic records as a prognostic indicator, holds promise for aiding clinicians in identifying frail patients prospectively. The current research aims to advance knowledge on more widespread use of these frailty indices and help clinicians determine the performance of frailty compared to conventional risk-adjustment methods.

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Chapter 3

3 Frailty in patients undergoing transcatheter aortic valve implantation: A protocol for a systematic review

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3.1 Introduction

Research on the benefits of transcatheter aortic valve implantation (TAVI) compared to surgical aortic valve replacement (SAVR) and medical management is ongoing, however it has been recognized that some patient populations fail to benefit from TAVI.[1] With increasing economic and clinical implications of TAVI, better understanding of how patient factors impact survival, functionality, complications, and quality of life remains a priority.[2]

Patients referred for TAVI typically have advanced age and multiple comorbidities, and the prevalence of frailty can be as high as 63%.[3,4] Frailty is defined as a syndrome of impaired physiological reserve and increased vulnerability to stressors.[5] When exposed to stressors, such as chronic illness and surgery, frail patients are prone to adverse events, procedural complications, prolonged recovery, functional decline, and mortality.[6] Although multiple studies have shown the value of frailty in predicting patient outcomes after TAVI, there is still a lack of consensus on the best way to assess frailty in clinical practice, with no single standard method of measuring frailty.[1,3] Without a clear consensus on frailty assessment practices, further review of frailty instruments and clinical outcomes of TAVI recipients becomes more important.[1]

This study aims to review the operationalization of frailty instruments for TAVI recipients, and to determine the mortality, clinical outcomes, and change in quality of life in frail patients undergoing TAVI. The specific review questions include: (1) How is frailty measured in patients undergoing TAVI? (2) What is the frequency of adverse clinical outcomes, including death, acute myocardial infraction, stroke, renal failure, pacemaker implantation, major bleeding, vascular complication, aortic regurgitation, readmission, and re-intervention, after TAVI in frail patients with aortic stenosis? (3) How does quality of life change after TAVI in frail patients with aortic stenosis?

3.2 Methods

The methods of this systematic review are reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses Protocols (PRISMA-P) 2015 checklist.[7]

3.2.1 Eligibility criteria

Participants: We will include patients with aortic stenosis, diagnosed as frail, who underwent a TAVI procedure. The mean age of the study population will be restricted to 65 years and older. Since the focus of this review is on frailty rather than baseline surgical risk, we will not use baseline surgical risk as exclusion criteria. We anticipate that the majority of studies will include patients at high or intermediate surgical risk.

We will include frail patients whose status had been assessed and measured prospectively using one of the following approaches: a) comprehensive geriatric assessment linked to a frailty index, such as the Rockwood Frailty index, b) a multidimensional frailty index such as the Fried scale, c) a single-item measure of frailty such as gait speed and d) clinical judgement without the use of specific frailty assessment tools.[8,9,10,11] We will consider assessments that are directly measured or self-reported. Since new frailty indices are continually being developed, we will include studies using frailty scores that we have not anticipated.

Some methods of frailty assessment do not have a defined 'frailty threshold'. Studies will be excluded if mean frailty scores are reported without dichotomizing the study population into frail and non-frail groups, or if frailty cut-off points were defined by the study sample (i.e. percentile or median). If different studies use the same frailty measure but use a different cut-off for frailty we will report frailty using the criteria defined by each individual study.[12] If a study reports separately on a 'pre-frail' group, we will not include this data in the frail group.

We will only include studies that intended to measure frailty, even if the method of frailty measurement has been newly developed. If studies do not specify the method of frailty

measurement, we will search the original protocol or cited references for the method used to measure frailty. Studies will be excluded if a method of frailty assessment is not referenced. We will not consider studies that used either comorbidity or disability alone as a marker of frailty, since these are related but distinct factors;[13] however we will consider studies where comorbidity or disability are measured as part of a multidimensional frailty assessment. Studies will be excluded if baseline frailty status is measured after the TAVI procedure or if the assessment is specifically focused on cognition, nutritional status, mood or mental health symptoms, or social relations or support. If multiple studies originating from the same patient population are found, we will include relevant data from all studies. If multiple frailty measurements were used in one study, we will extract all data, but will incorporate study data into data synthesis once, using the more established, more commonly used frailty measure.

Intervention: We will include all forms of TAVI, regardless of procedural approach, types of valves, and type of anesthesia We will exclude studies that investigated the effects of interventions such as health services and rehabilitation programs on patients undergoing TAVI.

Outcome measures: The primary outcome will be mortality. Secondary outcomes will be clinical outcomes and health-related quality of life. Both utility-based and psychometric measures of quality of life will be included. A complete list of outcome measures is summarized in **Table 3.1**. We will add additional outcomes to the list, if outcomes we have not anticipated are found in the literature.

Types of study: This review will include any study reporting mortality, clinical outcomes, or quality of life in patients meeting frailty criteria. We will include non-comparative cohorts of patients undergoing TAVI who have been diagnosed with frailty and comparative cohorts of frail and non-frail patients undergoing TAVI in which outcomes are reported separately for frail patients. In studies of comparative cohorts, only data in the frail cohorts will be extracted. Studies with sample size of fewer than 20 frail patients will be excluded. We will

include data from randomized controlled trials (RCTs) in which patients were randomized to TAVI or SAVR, if outcomes are reported separately by treatment and frailty status.

Table 3.1 Data extraction template

Publication details	First author.
	Year of publication.
	Name of the journal.
Study characteristics	Study design of the original study.
	Length of follow-up.
	Rates of loss to follow-up.
	Sample size of the frail group.
	Proportion frail.
Participant characteristics	Mean age of patients.
	Percentage female.
	Measures of surgical risk, including Society of Thoracic Surgery (STS) risk score or the European System for Cardiac Operative Risk Evaluation (EuroSCORE) (mean score or proportion of patients in each category).
	Measures of heart function including atrial fibrillation, left ventricular ejection fraction and New York Heart Association classification (mean score or proportion of patients in each category).
	Prior coronary artery bypass grafting.
	Prior myocardial infarction.

	Prior percutaneous coronary intervention.
	Prior stroke or transient ischemic attack.
	Approach of TAVI procedure.
	Other baseline clinical measures.
	Baseline quality of life measures.
Frailty assessment details	Measure of frailty.
	Frail cut-off/definition used.
	Type of frailty assessment.
	Dimensions included in the frailty measure (ie, comorbidity, disability, cognition, nutrition and physical function).
Outcomes of interest	Death.
	Myocardial infarction.
	Stroke.
	Bleeding complications.
	Acute kidney injury.
	Vascular complications.
	Conduction disturbances.
	New pacemaker implantation.
	Repeat coronary or valvular intervention.
	Neurocognitive dysfunction.

	Delirium.
	Length of ventilation.
	Length of hospitalization.
	Readmission.
	Post-procedure frailty.
	Post-procedure quality of life measures (mean scores and change from baseline).

TAVI, transcatheter aortic valve implantation.

3.2.2 Information sources

A systematic search strategy will be employed to identify published, unpublished, and ongoing studies. We will search the online database PubMed, EMBASE, PsycINFO, Cochrane Library, Web of Science and ClinicalTrial.gov for articles published in 2006 or later. A search of conference abstracts will be performed on relevant conferences held in the last three years. In the search strategy, the publication language will not be limited as study authors have the ability to read articles published in multiple languages. We will also search the reference lists of articles and relevant reviews identified in the search for any additional studies. Search strategies for each database will be reported and a PRISMA flow diagram presented.[14]

3.2.3 Search strategy

The specific search strategies for each database will be developed by an information specialist with experience conducting systematic reviews. The research team will provide input and feedback into the development of the strategy. A draft search strategy for EMBASE is given in **Table 3.2**. This strategy will be adapted for other databases.

Table 3.2 Search strategy for EMBASE

#	Searches
1	frailty/
2	frail elderly/
3	geriatric assessment/
4	frailty.mp.
5	or/1-4
6	geriatric patient/
7	very elderly/
8	aged/
9	aged hospital patient/
10	geriatrician/
11	*geriatrics/
12	(aged or aging or older or elderly or senior* or geriatric or centenarian or nonagenarian or octogenarian or septuagenarian or sexagenarian).mp.
13	or/6-12

14	exhaustion/
15	limited mobility/
16	"timed up and go test"/
17	exp walk test/
18	walking speed/
19	gait/
20	physical activity/
21	Performance Oriented Mobility Assessment/
22	grip strength/
23	hand strength/
24	muscle strength/
25	daily life activity/
26	exp "activity of daily living assessment"/
27	exp ADL disability/
28	exp disability/
29	exp functional status assessment/
30	exp neuropsychological test/

31	mental function assessment/
32	cognition assessment/
33	exp cognition/
34	exp cognitive defect/
35	memory assessment/
36	nutritional assessment/
37	((exhaustion or fatigue* or tired* or mobility or gait or walk* or stand or balance or bath* or dress* or toilet* or continence or feeding or cognition or memory or mental or disability or NYHA or Karnofsky or CSHA or functional* or Katz or Fried or Rockwood or frailty or nutrition*) adj7 (assess* or phenotype* or eval* or test* or exam* or instrument* or index or indices or scale* or score* or tool* or declin* or dependenc* or impair*)).mp.
38	(chair adj2 (rise or stand)).mp.
39	((grip* or grasp* or hand* or musc*) adj2 strength).mp.
40	weight loss.mp.
41	or/14-40
42	13 and 41
43	5 or 42
44	((transfemoral* or trans-femoral* or transapical* or trans-apical* or transaxillary or trans-axillary or transarterial* or trans-arterial* or subclavian* or sub-clavian* or

	transcatheter* or trans-catheter* or transcutaneous* or trans-cutaneous* or per-cutaneous* or percutaneous* or transcaval* or trans-caval* or "direct aortic" or tavi or tavr or pavi or pavr or sapien or cribier or revalv* or lotus or "direct flow" or jenavalve or portico or engager or evolut) adj3 aortic valv*).mp.
45	transcatheter aortic valve implantation/
46	or/44-45
47	43 and 46
48	limit 46 to yr=”2006 -Current"

3.2.4 Data management

We will use Covidence online software to manage data. The title and abstract of all articles identified in the search will be uploaded to Covidence for abstract screening. Full text articles will be uploaded for further screening and reasons for exclusion will be noted at the full text review stage. All included articles will be allocated a unique study ID code to track articles throughout the data screening and extraction process. Data extraction and quality appraisal will be managed in Microsoft Excel (2018).

3.2.5 Selection process

Two reviewers will independently review all abstracts identified in the initial search, and studies meeting the inclusion criteria will be included for full-text review. Full-text review of articles will be performed independently by two reviewers. Disagreement will be resolved by a third reviewer.

3.2.6 Data collection process

We plan to use a standardized data collection form constructed in Microsoft Excel. Data will be extracted by one reviewer and independently audited by another reviewer. Disagreements will be resolved by obtaining consensus between the two reviewers or consultation with a third reviewer when necessary. We will attempt to contact study authors to obtain missing data. Reasons for missing data and how each study dealt with missing data will be recorded.

3.2.7 Data items

The data collection form will include a list of fields given in **Table 3.1**. If any information is not reported, this will be recorded in the corresponding field. If two or more studies present Kaplan-Meier curves with time to death we will collect this data. If the numbers are not directly available, we will digitize the curves to retrieve patient level time to event data.[15]

3.2.8 Risk of bias in individual studies

Two reviewers will independently assess the risk of bias in individual studies using the Quality in Prognosis Studies (QUIPS) tool, which rates the studies as “high risk”, “moderate risk” or “low risk” of bias in the following domains: study population, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.[16] For our research purpose, we will not consider the study confounding and model development strategy sections of the tool as we anticipate they will not apply to the types of studies we will be reviewing.

3.2.9 Data synthesis

We will categorize clinical outcomes and report the frequency at each time point in tabular form. We will group results reported at similar times into pre-specified periods of interest. For example, results reported at 4-weeks and 8-weeks may be grouped with results at 6-weeks. For continuous outcomes we will report the mean value and standard deviation (SD).

Primary outcomes: For all studies, we will abstract the number of deaths and the median follow-up time to calculate the mortality rate per 100 person-years. We will pool mortality from multiple studies and model the death rate using a meta-analysis based on the Poisson distribution.[17] For studies reporting mortality, we will perform a meta-analysis of the odds of deaths at 30 days and 12 months, respectively. A single pooled Kaplan-Meier curve of time to death will be reproduced and presented by reconstructing the time to death data from individual studies.[15]

Clinical outcomes: For time-to-event outcomes, if studies present Kaplan-Meier curves with time to myocardial infarction, stroke, bleeding complications, acute kidney injury, vascular complications, conduction disturbances, new pacemaker implantation, repeat coronary or valvular intervention, neurocognitive dysfunction, delirium, and readmission, we will use the same methods described above to collect the information on numbers at risk and total number of events, and then create a single pooled Kaplan-Meier curve for each clinical outcome. If studies do not report time to event data, we will extract the number of events and the median follow-up time to calculate the event rate per 100-person years. Event rates from multiple studies will be pooled using a meta-analysis based on the Poisson distribution. For post-procedure length of hospitalization, we will pool data from multiple studies using a meta-analysis of the mean length of hospitalization.

Quality of life measures: When two or more studies report mean quality of life using the same measures at baseline and the same follow-up time point, we will pool mean scores to analyze changes in quality of life. We will calculate the mean change in quality of life along with the standard deviation (SD), from baseline (T_1) to the follow-up time point (T_2), using the formula $\frac{\mathrm{Qol\ T2}-\mathrm{Qol\ T1}}{\mathrm{SD\ T2}}$. When two or more studies report mean quality of life at baseline and the same follow-up time point, but using different overall measures, we will calculate standardized change scores for each study using the formula $\frac{Qol\ T2-Qol\ T1}{\sqrt{[(N1-1)*(SD\ Qol\ T2)\ \hat{}\ 2+(N2-1)*(SD\ Qol\ T1)\hat{}2]/(N1+N2-2)}}$.[18] We will report the standardized change scores for each time point and pool the standardized change scores from each study

using random effects model. If studies measure quality of life using the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), and report the mean mental component score (MCS) and the mean physical component score (PCS) separately, we will pool MCS and PCS separately.

3.2.10 Assessment of heterogeneity

For each meta-analysis, we will consider the studies included, to identify and characterize potential sources of heterogeneity. Differences across studies in the patient population (e.g. mean age, percentage female, and co-morbidity), may be potential sources of heterogeneity in study estimates. We will calculate the I-squared statistic to estimate the percentage of total variation across studies due to heterogeneity. Heterogeneity will be considered substantial if the I-squared value is greater than 50%.[19]

3.2.11 Subgroup analyses

We plan to perform the following sub-group analyses; however, the analysis will only be performed if we obtain sufficient data for the proposed groups. Studies will be grouped on the basis of: (1) surgical risk of the population (inoperable vs high risk vs intermediate risk), (2) approach (transfemoral vs non-transfemoral or alternative accesses), (3) type of frailty measure (multidimensional assessment vs single item assessment, objective measures vs clinical judgement, and established frailty measures vs newly developed tools), and (4) types of studies (observational studies vs RCTs).

3.2.12 Sensitivity analyses

We will perform sensitivity analyses to test if the findings are robust. If studies have a wide range of quality, we will exclude low-quality studies from sensitivity analysis. We may also perform sensitivity analysis restricting meta-analysis to frequently used, established frailty instruments only.

3.2.13 Meta-regression

Meta-regression will be performed to further investigate the potential source of clinical heterogeneity and to determine the influence of age, frailty (continuous variable), and quality of life measurements on outcomes if we obtain sufficient data.[20] The *metareg* function (STATA 14.0) will be used to undertake meta-regression with log-risk estimates, and the standard error will be determined from 95% confidence intervals for the log-risk estimates.

3.2.14 Quality of evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to conduct an evaluation of the body of work represented by the included studies.

3.3 Discussion

Frailty is increasingly being recognized as an important prognostic indicator to predict poor outcomes in patients undergoing TAVI procedures. Green et al analyzed data from the PARTNER (Placement of AoRtic TraNscathetER Valves) Trial and found that frailty was associated with increased mortality and a higher risk of poor outcome 1 year after TAVI.[2] Further to this, Zajarias et al evaluated patients in the PARTNER II randomized trial and demonstrated higher 30 day and 1 year mortality in frail patients.[21] However, since most studies have focused on improving surgical risk prediction, more research centered on patient outcomes and quality of life are needed.[22]

While frailty has been identified as an important concept, there is a lack of consensus in the literature on how it should be assessed, and that makes the field of study challenging. In this regard, Dent et al. reviewed the definitions and quality of more than a dozen frailty measurements used in research and clinical practice.[8] In a systematic review, Kim et al. identified 13 frailty instruments and evaluated their ability to predict negative outcomes for a range of cardiac surgical procedures, including TAVI.[22] The FRAILTY-AVR study found

that within the same cohort of TAVI patients assessed with seven different frailty tools, the prevalence of frailty ranged from 35-74% depending on the frailty tool.[23] With this review, we aim to summarize the frailty methods being used in TAVI patients, describe the domains of frailty being assessed in each study, and synthesize prognostic information. Our goal is to help move the field of frailty measurement in TAVI toward greater consensus.

Our review has several strengths. We will perform a comprehensive literature search to identify both published and unpublished studies, our search will include RCTs and observational studies, as well as references from previous reviews. Furthermore, two reviewers will independently use the QUIPS tool to assess the risk of bias and we will use GRADE to assess the quality of included studies. To the best of our knowledge, this will be the first review to investigate the frequency of adverse outcomes and to pool estimates of survival after TAVI in frail patients from multiple studies.

Our study also has some limitations. While many frailty assessments are similar in identifying frailty, different methods of frailty assessment cannot be assumed to be interchangeable.[24,25] Although we will perform sub-group analysis by type of frailty measure to account for these differences, the pooled results may be subject to heterogeneity. In addition, while we will perform sub-group analysis by type of frailty assessment, we do not anticipate being able to adjust for domains of frailty in our analysis. Our study will characterize prognosis for frail patients undergoing TAVI, and we will not compare prognosis to other groups of patients or treatments. While this provides a focused synthesis, interpretation of the results will occur in the context of previously conducted systematic reviews of TAVI and will be somewhat subjective. We expect to encounter studies that applied multiple frailty instruments in the same patient group and in this situation, we will only extract data from one frailty instrument, and this may introduce selection bias. Finally, some studies may define an intermediate “pre-frail” state. Though less vulnerable than the frail group, pre-frail patients are at higher risk than robust patients for experiencing adverse outcomes.[26,27] We may not find sufficient data to synthesize outcomes for this important sub-group.

With increased uptake of TAVI, the goal of our study to better understand how frailty impacts survival, functionality, complications, and quality of life is of great clinical importance.[2] Clinical practice guidelines recommend assessing frailty as one component of risk when considering heart valve procedures for patients.[28] The literature describes a number of different frailty measures capable of improving risk prediction in TAVI patients, suggesting that frailty assessment will help identify patients most likely to benefit from TAVI.[1] Pre-procedural frailty assessment can help identify potentially modifiable factors that may improve outcomes for frail patients.[29] Research into the impact of pre-operative interventions to improve outcomes for frail patients are ongoing but preliminary studies have demonstrated positive impacts on surgical outcomes of frail people.[30,31]

We believe the results of this review will inform clinicians, patients, and health care administrators, of the best available evidence about the impact of frailty in patients undergoing TAVI. We also expect that our findings will fill certain gaps, as well as trigger further research to enhance clinical decision making with a focus on patient-important outcomes.

3.4 References

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Chapter 4

4 Measurement and prognosis of frail patients undergoing transcatheter aortic valve implantation: a systematic review and meta-analysis

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4.1 Introduction

Transcatheter aortic valve implantation (TAVI) has become an alternative, less invasive treatment option for patients with severe symptomatic aortic stenosis.[1] The evidence continues to accumulate and synthesis of the evidence to better understand the prognosis of frail patients who undergo TAVI may be helpful.[2]

Frailty is a biological syndrome characterized by an increased vulnerability to stressors.[3] When exposed to stressors, such as chronic illness and surgery, frail patients are susceptible to adverse events, procedural complications, prolonged recovery, functional decline, and reduced survival.[4] Clinical research has identified frailty as an important risk factor for mortality and morbidity following TAVI.[5] Health economics research has shown that compared to non-frail patients, frail older adults undergoing cardiac surgery incurred substantially higher hospitalization costs.[6] Given the clinical and economic implications of TAVI, searching for and synthesizing outcomes of frail patients undergoing TAVI may provide information that can help optimize the selection of TAVI candidates and ultimately improve decision-making related to treatment of aortic stenosis.[2]

When considering valve procedures, clinical practice guidelines recommend assessing frailty as one component of risk.[7] We performed a systematic review of the literature to identify studies reporting the prognosis of frail patients undergoing TAVI. With no single standard method of measuring frailty and a diversity of frailty measurements, the optimal approach to assessing frailty in patients undergoing TAVI is unclear.[2,5] We catalogued frailty measures used in identified studies, to perform sub-group analyses for studies using the most common measures.

4.2 Methods

We searched PubMed, EMBASE, PsycINFO, Cochrane Library, Web of Science and ClinicalTrials.gov for articles published between January 2006 and October 10, 2018 (**S Table 4.1**). Conference abstracts from relevant conferences held in the last 3 years were also

searched. We included studies of patients who underwent a TAVI procedure that reported frailty and its impact on mortality, clinical outcomes, or health-related quality of life. The detailed inclusion and exclusion criteria were described in detail in the protocol.[8] This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines[9] and follows the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[10] The protocol was registered in PROSPERO (CRD42018090597) and published in *BJM Open*.[8]

Two authors independently assessed study eligibility and risk of bias and extracted data. Disagreements were resolved by consulting a third reviewer. The risk of bias in individual studies was appraised independently by two authors using the Quality in Prognosis Studies (QUIPS) tool.[11] The QUIPS tool offers a systematic approach to critical appraisal of bias in studies of prognostic factors.[11] The QUIPS was developed and validated based on basic epidemiologic principles and recommendations of quality assessment.[11] Previous literature demonstrated that the QUIPS was associated with moderate to substantial interrater reliability.[11] We classified studies with four or five low risk domains as having a low risk of bias overall, studies with two or more high risk domains as high risk of bias overall, and the remaining studies as moderate risk of bias overall.

We summarized the method of measuring frailty used in each study including the frailty tool used, dimensions of frailty measured, the cut-off for frail status, and the prevalence of frailty in the study population as measured by the frailty tool. We only extracted data from the most commonly used frailty instruments if multiple frailty instruments were applied in the same patient group. We categorized clinical outcomes and reported the frequency at each time point. Heterogeneity across studies was assessed using the Cochrane Q-statistic (I^2).[12] Given the substantial heterogeneity, we pooled and estimated outcomes using random effects model. We pooled dichotomous clinical outcomes using the DerSimonian and Laird random effects model and applying a logit transformation.[13] For the length of hospitalization, we pooled the values, estimating the mean and standard deviation using the random effects model for continuous variables.[14] For studies presenting Kaplan-Meier curves with time to death, we

collected the information on numbers at risk and total number of events, and then created a single pooled Kaplan-Meier curve. We pooled time to death data from individual studies to obtain an overall estimate of survival, using an algorithm developed by Guyot et al.[15]

We conducted a sub-group analysis to see if the estimates of mortality rates differed for studies that used the Fried phenotype, the most common multi-dimensional measure, compared to studies that did not use the Fried phenotype. A two-sided p-value of 0.05 or less was considered statistically significant. All analyses were conducted using R software (version 3.5.0). Pre-specified statistical details were described in the protocol.[8]

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to conduct an evaluation of the overall estimates based on considerations of risk of bias, consistency, precision, directness, and publication bias.[16] Given that cohort studies of prognosis exclude randomized controlled trial study designs, we did not downgrade the certainty of evidence due to observational study design.

4.3 Results

Our search identified 2,370 records with 1,559 articles remaining after removing duplicates. After screening, 35 studies[17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51] were identified as eligible for inclusion in the review (**S Figure 4.1**). The eligible studies enrolled a total of 11,323 frail patients with aortic stenosis undergoing TAVI.

The characteristics of the included studies are summarized in **S Table 4.2**. Three studies[38,41,51] enrolled patients from the Placement of Aortic Transcatheter Valves (PARTNER) trial reporting separately on outcomes of frail patients; the remaining studies reported on patients from a single cohort or registry. Most studies collected patient data prospectively; twelve studies[19,21,22,24,30,33,36,39,41,43,44,46] were conducted retrospectively.

S Table 4.3 summarizes the risk of bias assessment of individual studies. Of the 35 studies, 12[23,24,26,27,29,31,35,37,38,45,47,50] were rated at overall low risk of bias, 18[17-22, 30,33,34, 40-43, 46, 48,49, 51] at moderate risk and 5[25, 36, 39, 44, 48] at high risk of bias.

Table 4.1 summarizes frailty assessment in patients undergoing TAVI. Fifteen studies[17-31] used single-dimension measures, and 20 studies[32-51] used multi-dimensional measures. The prevalence of frailty varied widely among studies that assessed frailty with single dimension measures, ranging from 7.21% to 90.07%. Albumin, body mass index, and Katz Activity of Daily Living were the four most commonly used single-dimension measures when assessing frailty in TAVI patients. However, even with the same measure, different cut-points or definitions of frailty were used. For example, three studies[19,21,22] used the albumin to assess frailty; two[19,21] defined frailty as albumin level below 4g/dL, and one[22] as albumin level below 3.5g/dL.

The prevalence of frailty reported by studies that assessed frailty using multi-dimensional measures ranged from 15.23% to 84.67%. Most of these studies assessed frailty based on the Fried frailty phenotype; one study[32] assessed frailty based on the accumulated deficits frailty index. Of the 20 studies reporting multi-dimensional measures, four[44-46, 49] used the original Fried frailty phenotype and eight[33,36-39,41,42,51] modified the Fried frailty phenotype by examining fewer dimensions, altering cut-off values or measuring the same domains with different criteria. Among the eight studies[33,36-39,41,42,51] reporting the modified Fried frailty phenotype, measures used to assess mobility and disability were identical. Measures used to assess nutrition were different; seven studies[33,36-38,41,42,51] measured serum albumin, and 1 study[39] measured weight loss.

S Table 4.4 summarized prognosis of frail TAVI recipients reported for each study. Fifteen studies[17,19,25-29,32-34,38,39,41,48,51] reported 30-day mortality, which ranged from 2.83% to 25%; the combined 30-day mortality estimate was 7.73% (95% confidence interval 5.20% to 11.33%, **Table 4.2** and **S Figure 4.2**). Combining three studies[33,38,39] that measured frailty

using the modified Fried frailty phenotype, we observed a 30-day mortality of 7.86% (5.20% to 11.70%, **Table 4.2** and **S Figure 4.2**).

Twelve studies[23,28,29,32,33,35,38,41,44,47,48,51] reported 1-year mortality, ranging from 14.8% to 37.5%. The combined 1-year mortality estimate was 24.13% (20.91% to 27.68%, **Table 4.2** and **S Figure 4.3**).When pooling two studies[33,44] that used the Fried or modified Fried frailty phenotype to assess frailty, the estimated 1-year mortality was 26.91% (21.50% to 33.11%, **Table 4.2** and **S Figure 4.3**). Subgroup analyses of studies reporting frailty measurement using the Fried phenotype compared to non-Fried phenotype did not find statistical differences in effect estimates on 30-day and 1-year mortality (**S Figure 4.4**).

Fifteen studies[20,21,23-27,29,31,32,38,39,45,46,50] reported survival of frail patients after TAVI using a Kaplan-Meier curve. The combined survival estimates at 1, 2, and 3 years were 78.6% (77.1% to 80.1%, **Table 4.2**), 67.8% (65.7% to 70%, **Table 4.2**), and 50.8% (45.2% to 57.2%, **Table 4.2**), respectively. Combining the studies that used the Fried or modified Fried phenotype, we found survival estimates at 1, 2, and 3 years were 73% (68.8% to 77.5%, **Table 4.2**), 64.5% (56.4% to 73.9%, **Table 4.2**), and 58.9% (49% to 70.9%, **Table 4.2**), respectively. Details of survival are provided in **S Figure 4.5** and **S Table 4.5**.

Two studies[40, 42] measured health-related quality of life. Kobe et al[40] assessed quality of life before and 30 days after TAVI using the Short Form-36 questionnaire; they found that at 30-day follow-up, the mean scores of all but role physical and social functioning were significantly lower for frail patients. Okoh et al[42] assessed quality of life preoperatively and at 30-day follow-up using the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ); they found that at 30 days, frail patients reported worsening in two domains, KCCQ-symptoms and KCCQ physical limitation, but quality of life improved slightly overall (**S Table 4.6**).

Other commonly reported outcomes measuring the prognosis of frail TAVI recipients include procedural cardiac tamponade (ranging from 2% to 4%, reported by 3 studies[26,29,31]), convert to open heart surgery (ranging from 1.2% to 2.27%, reported by 2 studies[27,29]), procedural

life-threatening bleeding (ranging from 7.1% to 16.7%, reported by 5 studies[26, 28,29,31,37]) and 2-valve implantation (ranging from 1.8% to 2.55%, reported by 2 studies[29,31]). Seven studies[30,31,36,37,39,42,43] reported the mean length of hospitalization, ranging from 6 days to 12.1 days.

The GRADE certainty assessment per outcome, together with the pooled effects, is provided in table 2. Thirty-day mortality, procedural cardiac tamponade, procedural life-threatening bleeding, and conversion to open heart surgery were rated as low certainty of evidence; the remaining outcomes were rated as very low certainty of evidence.

Table 4.1 Frailty assessment in patients undergoing TAVI

Studies that used a single dimension assess frailty					
Study, year	**Measure**	**Dimensions**	**Definition**	**Total N**	**Frail n (%)**
[a] Alfredsson (2016) [17]	Gait speed	mobility	<0.83m/s or <6 s	8039	6100 (75.88%)
[b] Bagienski (2017) [18]	Katz ADL	disability	<6 points	141	127 (90.07%)
Bogdan (2016) [19]	Albumin	nutrition	≤4g/dl	150	79 (52.67%)
Cockburn (2015) [20]	Brighton mobility index	mobility	Poor mobility	312	65 (20.83%)
Grossman (2017) [21]	Albumin	nutrition	<4 g/dl	426	192 (45.07%)

[c] Koifman (2015) [22]	Albumin	nutrition	<3.5g/dl	476	238 (50%)
Kleczynski (2017) [23]	ISAR	unclear	≥2 points	101	53 (52.48%)
Mok (2016) [24]	Sarcopenia	nutrition	skeletal muscle mass index 2 SDs less than the mean SMM of young, healthy gender-specific reference ranges	460	293 (63.70%)
Martin (2018) [25]	CSHA score (1-7)	physical function	Scores 5-7	2624	1043 (39.75%)
Puls (2014) [26]	Katz ADL	disability	<6 points	300	144 (48%)
Rodes-Cabau (2010) [27]	Clinical judgment	subjective	Unclear	339	85 (25.07%)
Stortecky (2012) [28]	BMI	nutrition	<20kg/m^2	25	24 (9.38%)
Shimura	CFS	subjective	≥5 points (score ranges 0-9)	1215	353 (29.05%)

(2017) [29]						
Traynor (2017) [30]	Assisted care		unclear	Need assisted care	597	60 (10.05%)
Yamamoto (2015) [31]	BMI		nutrition	<20kg/m^2	777	56 (7.21%)
Studies that used multiple dimensions to assess frailty						
Study, year	**Name**	**Measures**	**Dimensions**	**Definition**	**Total N**	**Frail n (%)**
Bureau (2017) [32]	MPI	ADL	disability	MPI≥0.34 (the sum of all domain values is divided by 8 to obtain the MPI score between 0 and 1)	116	71 (61.21%)
		IADL	disability			
		SPMSQ	cognition			
		CIRS-CI	medical			
		MNA-SF	nutrition			
		ESS	medical			

		Number of medications	medical			
		Social support network	living status			
[d] Chauhan (2016) [33]	Modified Fried phenotype	ADL	disability	Presence of 2 or more criteria	343	233 (67.93%)
		Hand strength	muscle strength			
		Gait speed	mobility			
		Albumin	nutrition			
Capodanno (2014) [34]	GSS	Not reported	not reported	Value of 2 or 3	1256	306 (24.36%)
Eichler (2017) [35]	FI	MMSE	cognition	≥3 points (score ranges 0-7)	333	152 (45.65%)
		MNA	nutrition			
		ADL	disability			
		IADL	disability			

		Time up and go test	mobility			
		Subjective mobility disability	mobility			
Ghatak (2012) [36]	Modified Fried phenotype	Albumin	nutrition	Presence of 3 or more criteria	45	22 (48.89%)
		Katz ADL	disability			
		5MWT	mobility			
		Grip strength	muscle strength			
Green (2015) [37]	Modified Fried phenotype	Gait speed	mobility	Frailty score ≥6	244	110 (45.08%)
		Grip strength	muscle strength			
		Albumin	nutrition			
		ADL	disability			
Green		Gait speed	mobility	Frailty score ≥5 points	159	76 (47.80%)

(2012) [38]	Modified Fried phenotype	Grip strength	muscle strength			
		Albumin	nutrition			
		ADL	disability			
Huded (2016) [39]	Modified Fried phenotype	Unintentional weight loss	nutrition	Presence of 3 or more criteria	191	64 (33.51%)
		Grip strength	muscle strength			
		5MWT	mobility			
		Katz ADL	disability			
Kobe (2016) [40]	FORCAST	Chair rise	muscle strength	≥ 4 points (score ranges 0-12)	130	71 (54.62%)
		Weakness	muscle strength			
		Stair	mobility			
		CFS	subjective			

		Creatinine level	medical			
Maniar (2016) [41]	Modified Fried phenotype	Serum albumin	nutrition	≥6 points (score ranges 0-12)	219	73 (33.3%)
		Gait speed	mobility			
		Grip strength	muscle strength			
		Katz ADL	disability			
Okoh (2017) [42]	Modified Fried phenotype	Hand grip strength	muscle strength	FI ≥3/4	75	30 (40%)
		Gait speed	mobility			
		Serum albumin	nutrition			
		ADL	disability			
Patel (2016) [43]	NA	Gait speed	mobility	Gait speed≥6s or/and albumin<3.5g/dl	117	31 (26.50%)
		Albumin	nutrition			

Rabinovitz (2016) [44]	Fried phenotype	Unintentional weight loss	nutrition	Presence of 3 or more criteria	302	46 (15.23%)
		Exhaustion	exhaustion			
		Weakness	muscle strength			
		Walk speed	mobility			
		Low physical activity	physical activity			
Rodriguez-Pascual (2016) [45]	Fried phenotype	Unintentional weight loss	nutrition	Presence of 3 or more criteria	109	68 (62.39%)
		Exhaustion	exhaustion			
		Weakness	muscle strength			
		Walk speed	mobility			
		Low physical activity	physical activity			
Rogers	Fried phenotype	Unintentional weight loss	nutrition	Presence of 3 or more criteria	544	242 (44.49%)

(2018) [46]		Exhaustion	exhaustion			
		Weakness	muscle strength			
		Walk speed	mobility			
		Low physical activity	disability			
Schoenenberger (2018) [47]	NA	MMSE	cognition	≥3 points (score ranges 0-7)	330	169 (51.21%)
		Time up and go	mobility			
		MNA	nutrition			
		Basic ADL	disability			
		Incremental ADL	disability			
Steinvil (2018) [48]	NA	BMI	nutrition	Presence of 3 or more criteria	498	232 (46.59%)
		Albumin	nutrition			
		Katz ADL	disability			

		Grip strength	muscle strength			
		Walk test	mobility			
Shi (2018) [49]	Fried phenotype	Weight loss	nutrition	Presence of 3 or more criteria	137	116 (84.67%)
		Exhaustion	Exhaustion			
		Minnesota leisure time activity	Physical activity			
		5m walk test	mobility			
		Grip strength	muscle strength			
Skaar (2018) [50]	Geriatric assessment tool (0-9)	MMSE	cognition	Scores≥4	142	34 (23.94%)
		Nottingham extended ADL	disability			
		BMI<20.5	nutrition			
		Low energy	exhaustion			

		Weight loss	nutrition			
		Chair stand	muscle strength			
		Charlson comorbidity index	comorbidity			
		Hospital anxiety and depression scale	psychological			
Zajarias (2016) [51]	Modified Fried phenotype	Albumin	nutrition	≥6 points (score ranges 0-12)	553	265 (47.92%)
		Gait speed	mobility			
		Grip strength	muscle strength			
		Katz ADL	disability			

a. Alfredsson (2016) enrolled patient populations from the STS/ACC registry. Chauhan (2016), Green (2012), Green (2015), Huded (2016), Okoh (2017), Rogers (2018), Steinvil (2018), Traynor (2017), and Bagienski (2017) enrolled patients from the participating centres of STS/ACC registry.
b. Bagienski (2017) and Kleczynski (2017) enrolled patients from the same medical centre but used different frailty definitions.
c. Koifman (2015), Rogers (2018), and Steinvil (2018) enrolled patients from the same medical centre but used different frailty definitions.

d. Chauhan (2016) and Okoh (2017) enrolled patients from the same medical centre but used different frailty definitions.

N, the number of patients. **SMM**, skeletal muscle mass. **5MWT**, 5-meter walk test. **ADL**, activities of daily living. **MPI**, multidimensional prognostic index. **SPMSQ**, short portable mental status questionnaire. **CIRS-CI**, cumulative illness rating scale comorbidity index. **MNA-SF**, mini-nutritional assessment short form. **ESS**, Exton Smith scale. **FI**, frailty index. **GSS**, geriatric status scale. **MMSE**, mini-mental state examination. **BMI**, body mass index. **ISAR**, identification of seniors at risk. **FORCAST**, frailty predicts death one year after elective cardiac surgery test. **CFS**, clinical frailty scale. **NA**, not applicable

Table 4.2 Results of meta-analysis and GRADE assessment[**]

Effects					GRADE assessment						
# included study	Frailty measures[*]	# individuals	# events	Estimate (95% CI)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty
Procedural death											
4	Single	6682	350	6.49%	OBS	Serious	Strongly serious	Strongly serious	Not serious	None	Very low

				(2.46%-16.4%)							
30-day mortality											
9	All	8743	545	7.73% (5.20%-11.33%)	OBS	Strongly serious	Strongly serious	Strongly serious	Not serious	None	Very low
6	Multi	1016	82	8.31% (6.68%-10.28%)	OBS	Serious	Not serious	Strongly serious	Not serious	None	Low
3	Modified Fried	407	31	7.86% (5.20%-11.70%)	OBS	Serious	Not serious	Strongly serious	Serious	None	Very low
Cardiovascular death at 30 days											
2	Single	6453	259	3.37%	OBS	Serious	Serious	Strongly serious	Not serious	None	Very low

				(1.93%-5.81%)							
6-month mortality											
2	Multi	187	30	16.12% (11.50%-22.13%)	OBS	Serious	Not serious	Strongly serious	Strongly serious	None	Very low
1-year mortality											
8	All	922	217	24.13% (20.91%-27.68%)	OBS	Serious	Not serious	Strongly serious	Serious	None	Very low
6	Multi	845	191	22.75% (20.03%-25.71%)	OBS	Serious	Not serious	Strongly serious	Serious	None	Very low

2	Fried and modified Fried	223	60	26.91% (21.50%-33.11%)	OBS	Serious	Not serious	Strongly serious	Strongly serious	None	Very low
Survival											
15	All	3296	NA	1-year survival: 78.6% (77.1%-80.1%) 2-year survival: 67.8% (65.7%-70%) 3-year survival:	OBS	Strongly serious	Strongly serious	Strongly serious	Not serious	None	Very low

				50.8% (45.2%-57.2%)							
4	Fried and modified Fried	484	NA	1-year survival: 73% (68.8%-77.5%) 2-year survival: 64.5% (56.4%-73.9%) 3-year survival: 58.9%	OBS	Serious	Serious	Strongly serious	Strongly serious	None	Very low

				(49%-70.9%)							
Procedural acute kidney injury											
3	Single	6509	450	9.57% (5.28%-16.73%)	OBS	Serious	Strongly serious	Strongly serious	Not serious	None	Very low
Procedural cardiac tamponade											
3	Single	553	17	3.19% (1.99%-5.07%)	OBS	Not serious	Not serious	Strongly serious	Not serious	None	Low
Convert to open heart surgery											
2	Single	438	9	2.11% (1.10%-4.00%)	OBS	Not serious	Not serious	Strongly serious	Not serious	None	Low
Procedural life-threatening bleeding											

5	All	653	63	9.75% (7.69%-12.29%)	OBS	Not serious	Not serious	Strongly serious	Not serious	None	Low
Procedural major bleeding											
4	Single	791	104	9.93% (3.99%-22.63%)	OBS	Not serious	Strongly serious	Strongly serious	Not serious	None	Very low
Procedural minor bleeding											
3	Single	735	143	20.46% (11.35%-34.08%)	OBS	Serious	Strongly serious	Strongly serious	Serious	None	Very low
Procedural major vascular complications											
3	Single	647	63	10.49% (4.76%-21.54%)	OBS	Serious	Strongly serious	Strongly serious	Not serious	None	Very low

30-day major vascular complications											
2	All	189	7	2.97% (0.34%-21.67%)	OBS	Serious	Serious	Strongly serious	Not serious	None	Very low
Procedural minor vascular complications											
2	Single	591	43	7.37% (3.24%-15.93%)	OBS	Serious	Strongly serious	Strongly serious	Not serious	None	Very low
Procedural major access-site complications											
2	Single	109	14	13.07% (7.89%-20.88%)	OBS	Serious	Not serious	Strongly serious	Strongly serious	None	Very low
Procedural permanent pacemaker											
4	All	468	22	5.16%	OBS	Serious	Not	Strongly serious	Not serious	None	Very

				(3.01%-8.71%)			serious				low
Readmission within 30 days											
2	Modified Fried	174	11	6.63% (2.19%-18.37%)	OBS	Strongly serious	Serious	Strongly serious	Strongly serious	None	Very low
Procedural stroke											
6	All	761	24	3.66% (2.25%-5.91%)	OBS	Serious	Not serious	Strongly serious	Not serious	None	Very low
Stroke within 30 days											
2	Single	6185	132	2.14% (1.81%-2.53%)	OBS	Serious	Not serious	Strongly serious	Not serious	None	Very low
Transfusion											

3	All	458	191	41.01% (34.02%-48.39%)	OBS	Serious	Serious	Strongly serious	Strongly serious	None	Very low
2-valve implantation											
2	Single	409	10	2.46% (1.33%-4.51%)	OBS	Not serious	Not serious	Strongly serious	Not serious	None	Low
Length of hospitalization											
6	All	308	NA	8.25 (6.62-10.27)	OBS	Strongly serious	Strongly serious	Strongly serious	Strongly serious	None	Very low

**Meta-analyses conducted using random effects model

*Frailty measures are categorized as single, multi-measures, Fried, modified Fried and all.

Single indicates single measures

Multi indicates multi-measures

Fried indicates the Fried phenotype

Modified Fried indicates the modified Fried phenotype

Fried and modified Fried includes the Fried phenotype and modified Fried phenotype

All includes all single- and multi-measures

CI indicates confidence interval.

GRADE indicates Grading of Recommendations Assessment, Development and Evaluation

4.4 Discussion

We found that multi-dimensional measures are more commonly used than single-dimension measures. Even with the same frailty measure, different definitions or cut-offs were used. The most frequently used frailty measure in TAVI the studies we identified was the modified Fried phenotype, in which disability, muscle strength, mobility, and nutrition were assessed. Approaches to modifying the Fried phenotype included measuring fewer domains, using different cut-offs, or using different tools to assess the same domain.

Greater heterogeneity of meta-analyses that included single measures suggests single measures did not measure the same frailty construct and did not reliably measure frailty. Single measures included a mix of biological variables (albumin and BMI) or single performance measures (gait speed or activities of daily living), which address only a single component of the frailty construct. Thus, our study confirms that frailty is a multi-dimensional phenomenon that cannot be captured by a single construct.

The variety of frailty definitions and the diversity of TAVI populations in the studies contribute to the wide range and substantial heterogeneity of patient outcomes after TAVI. We identified studies on a wide array of clinical outcomes for frail patients post-TAVI, but few studies reported on quality of life measures. Using GRADE to assess confidence in prognosis estimates from the meta-analyses, we found very low or low confidence in the overall estimates, mainly due to inconsistency as influenced by heterogeneity of estimates and indirectness of frailty measures as influenced by lack of homogeneity across the TAVI populations identified in the studies.

Previous studies demonstrated that the assessment of frailty significantly enhances prediction of mortality after TAVI when combined with the European system for cardiac operative risk evaluation (EuroSCORE) or the Society of Thoracic Surgeons (STS) score.[47] There have been several studies reviewing frailty in cardiac surgical populations. Kim et al[5] conducted a systematic review of frailty instruments in older adults

undergoing cardiac surgical procedures. Kim et al[5] found high quality evidence that used mobility assessment as a single frailty measure and found mobility to be the most frequently assessed domain. Sepehri et al[52] performed a systematic review to demonstrate the association of frailty with negative postoperative outcomes in patients undergoing cardiac surgery. Our study adds to the existing literature as we investigate the frequency of adverse outcomes and pool estimates of survival after TAVI in frail patients from multiple studies.

The FRAILTY-AVR study[53] examined the validity of frailty measures in predicting mortality amongst TAVI recipients. The study added value to the literature by selecting frailty elements with the greatest predictive value, finding that the Essential Frailty Toolset (EFT) consisting of chair rise, cognition measured by the Mini-Mental State Examination, hemoglobin and serum albumin, performed best for predicting one-year mortality.[53] Due to the focus on predictive validity, the FRAILTY-AVR study[53] did not report outcomes separately for frail patients. As a result, the study[53] did not meet the inclusion criteria for our systematic review, which was focused on prognostic information amongst frail patients only. The FRAILTY-AVR study[53] makes important efforts to define a standard frailty assessment tool. Although the Fried and modified Fried were the most commonly used instruments amongst studies included in our meta-analysis, the FRAILTY-AVR showed the Fried did not perform as well as the EFT in predicting mortality amongst TAVI patients.[53] We suggest use of a standard measure, such as the EFT, can enhance the quality of frailty research in the TAVI patient population. We also recognize that use of a standard frailty measure is unlikely as researchers and clinicians may value use of diverse measures which reflect different aspects of frailty. If the EFT emerges as a standard, it may be used by clinicians to exclude frail patients from treatment, due to concerns about increased mortality. This would limit the opportunity to better understand the prognosis of frail patients undergoing TAVI, which was the primary goal of our study.

This review has several unique strengths. We performed a comprehensive literature search to identify both published and unpublished studies, in addition to searching citations from previous reviews. We included prognostic data from randomized

controlled trials and observational studies. Using the QUIPS tool, two reviewers independently assessed the risk of bias, and the use of the GRADE system to assess the certainty of evidence offers a structured and transparent evaluation of our findings. We systematically reviewed the operationalization of frailty assessment in TAVI patients, and pooled clinical outcomes of frail TAVI recipients. We tested for heterogeneity and attempted to address heterogeneity by performing sensitivity analysis and sub-group analysis.

This review has some important limitations. Given the limited data reported by the included studies, we were unable to perform meta-regression to further investigate the potential sources of heterogeneity and to determine the influence of mean age on outcomes. We therefore explored the causes and types of heterogeneity relying on the investigation of the I^2 statistic, which may be imprecise when the number of studies is small.[54] When extracting data, we encountered several studies that applied multiple frailty instruments in the same patient group, and in this situation, we only extracted data from the most commonly used frailty instrument, and this may introduce selection bias. Some studies defined an intermediate 'pre-frail' group, but we did not find sufficient data to synthesize outcomes for this important sub-group. Though less vulnerable than the frail group, pre-frail patients may be at higher risk than robust patients for experiencing adverse outcomes.[55,56] Individual-patient level data were not available, precluding adjustment for any study level differences in clinical or procedural variables that may have influenced prognosis across the cohorts. Therefore, clinical heterogeneity could not be ruled-out and along with high levels of heterogeneity, resulted in lower GRADE evaluations. Data on the quality of life was reported by few studies, so we were not able to assess the change in quality of life for frail patients after TAVI. The aim of this study was to characterize prognosis for frail patients undergoing TAVI, therefore, we did not directly compare prognosis to other groups of patients or to frail patients undergoing different therapies, nor were we able to determine which frailty measures perform best as prognostic tools for TAVI recipients.

When selecting candidates to undergo TAVI, several multivariate risk scores have been widely used to estimate operative mortality based on patient characteristics. The STS

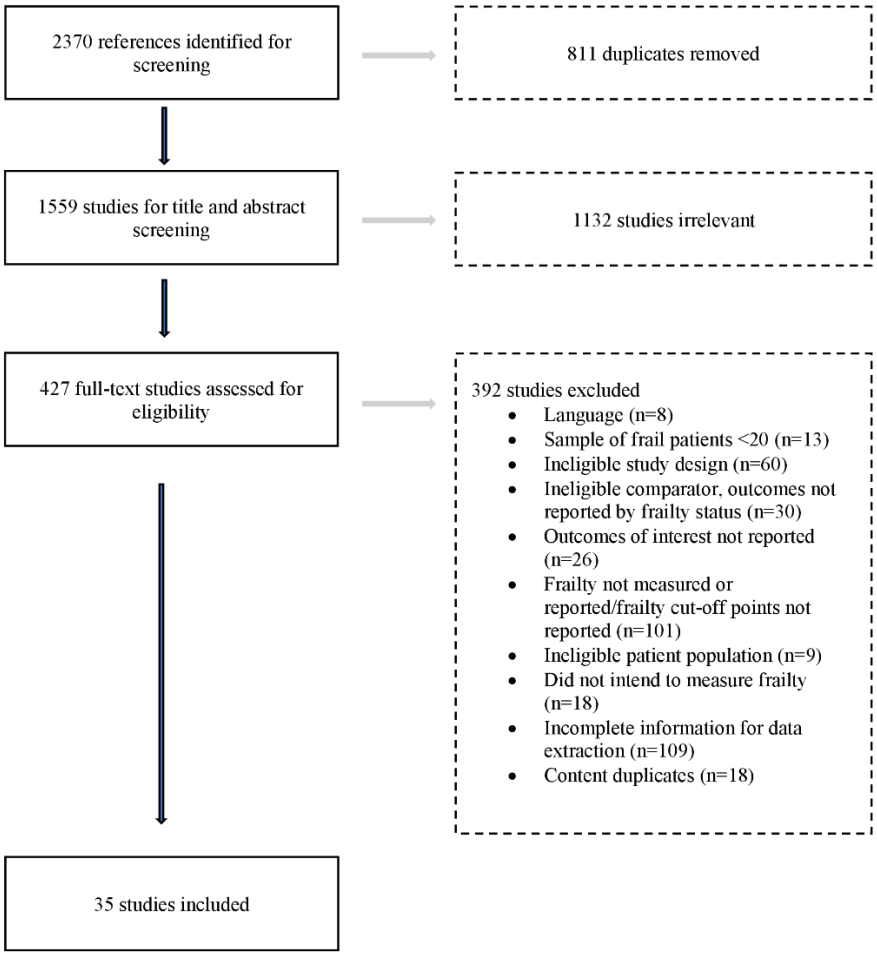
score and the EuroSCORE are the most commonly used scoring systems.[57,58] However, a disadvantage of both scores is that the main variables for scoring perioperative risk are medical diagnoses and comorbidities, which may not reflect the true 'biological status' of the patient.[57,58] When considering valve procedures for patients, clinical practice guidelines recommend assessing frailty as one component of risk.[5,7] Although a large number of frailty measures exist, there is currently little consensus on the optimal approach to assessing frailty in patients undergoing TAVI.[2] Frailty has consistently been shown to significantly predict mortality[52] and post-operative delirium,[59] even after controlling for other risk factors, suggesting that use of any frailty assessment is better than none when selecting patients for TAVI. Systematically reviewing the operationalization of frailty assessment in TAVI patients and pooling clinical outcomes of frail TAVI recipients will help better understand how frailty is assessed among TAVI patients, provide information on the prognosis of frail patients after TAVI, and can ultimately improve decisions related to treatment of AS.

To help achieve consensus on frailty measures to be applied in TAVI recipients, future studies should evaluate the prognostic value of frailty measures in TAVI recipients and determine the additional prognostic value of frailty measurement in addition to these established risk scores. Future studies should also compare prognosis of frail patients undergoing TAVI to frail patients undergoing surgical intervention or medical therapy. Few studies reported quality of life measures. In order to address the gaps in the literature future studies should measure quality of life before and after TAVI with use of standardized quality of life measurement tools such as the Short-Form 36.

In conclusion, frailty instruments for TAVI recipients varied across studies, leading to a range of frailty prevalence estimates and substantial heterogeneity. The results of this systematic review provide clinicians, patients, and health care administrators, with potentially useful evidence on the prognosis of frail patient

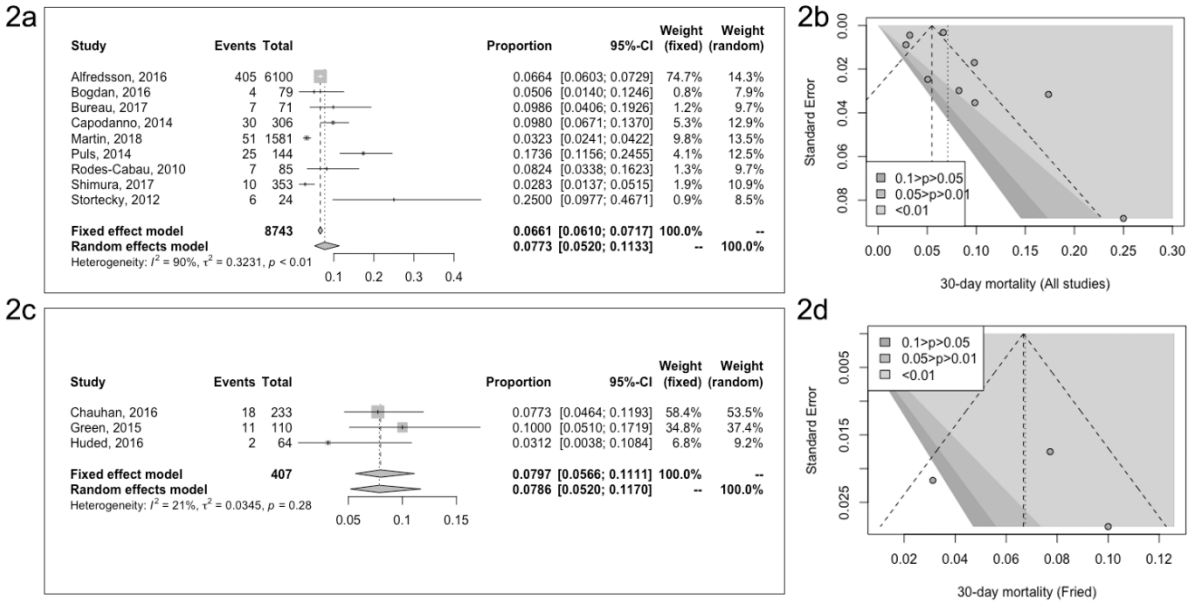
4.5 Supplementary figures

S Figure 4.1 PRISMA diagram of included studies



PRISMA, reporting in systematic reviews and meta-analyses. N, number of studies.

S Figure 4.2 Meta-analysis of 30-day mortality in frail patients after TAVI.



2a. Frailty was measured using sing and multi-dimensional measures.

2b. Funnel plots, using data from all studies that reported 30-day mortality

2c. Frailty was measured using modified Fried frailty phenotype.

2d. Funnel plots, using data from studies that frailty was measured using modified Fried frailty phenotype.

The squares indicate the 30-day mortality reported by each study

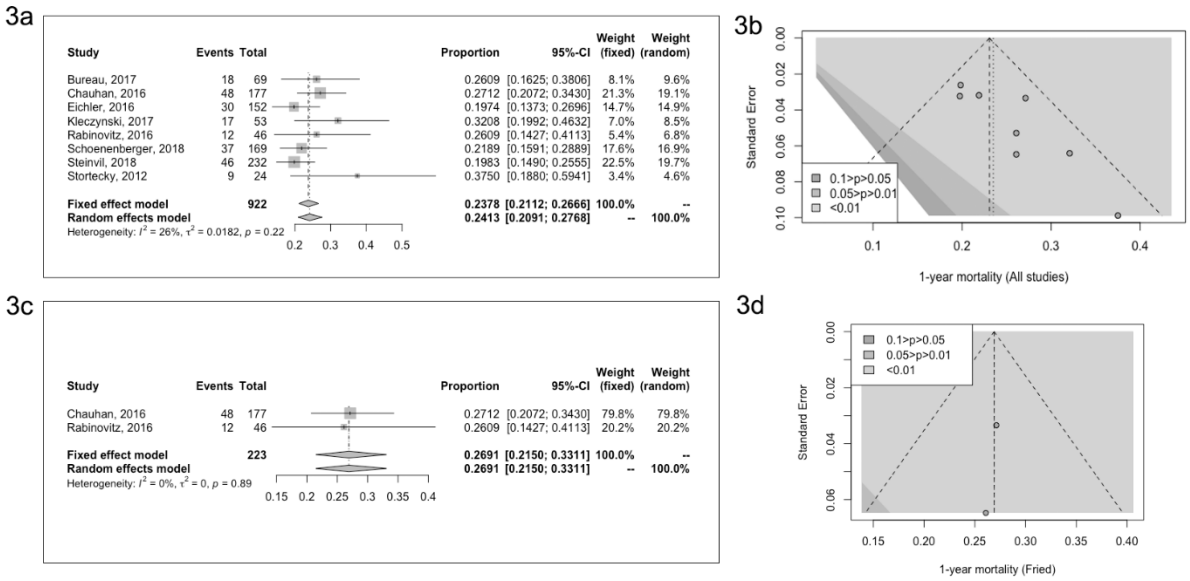
The horizontal lines indicate the magnitude of the confidence interval

The diamond indicates the pooled estimate for 30-day mortality

y-axis is the standard error of the 30-day mortality

x-axis is the 30-day mortality

S Figure 4.3 Meta-analysis of 1-year mortality in frail patients after TAVI.



3a. Frailty was measured using sing and multi-dimensional measures.

3b. Funnel plots, using data from all studies that reported 1-year mortality

3c. Frailty was measured using modified Fried frailty phenotype.

3d. Funnel plots, using data from studies that frailty was measured using modified Fried frailty phenotype.

The squares indicate the 1-year mortality reported by each study

The horizontal lines indicate the magnitude of the confidence interval

The diamond indicates the pooled estimate for 1-year mortality

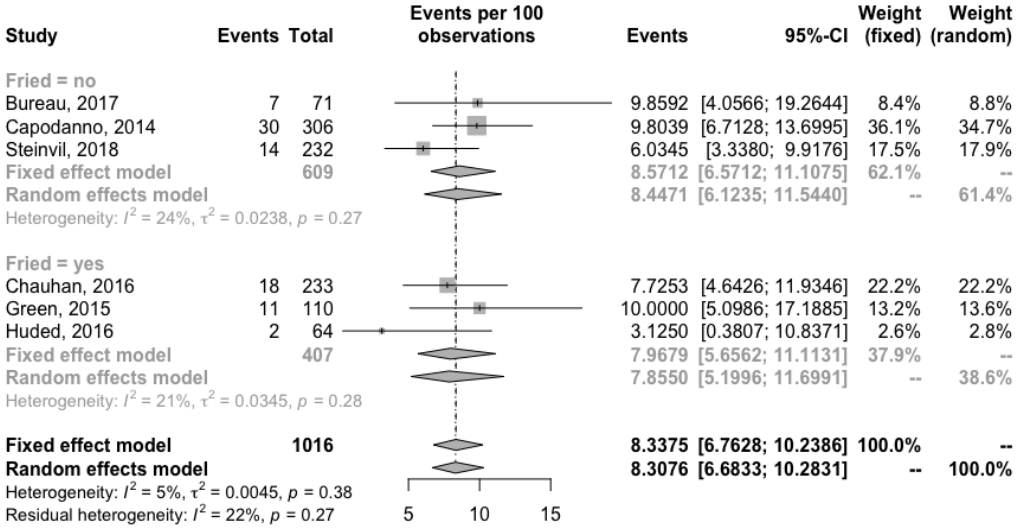
y-axis is the standard error of the 1-year mortality

x-axis is the 1-year mortality

S Figure 4.4 Subgroup analyses of studies reporting frailty measurement using the Fried phenotype compared to non-Fried phenotype

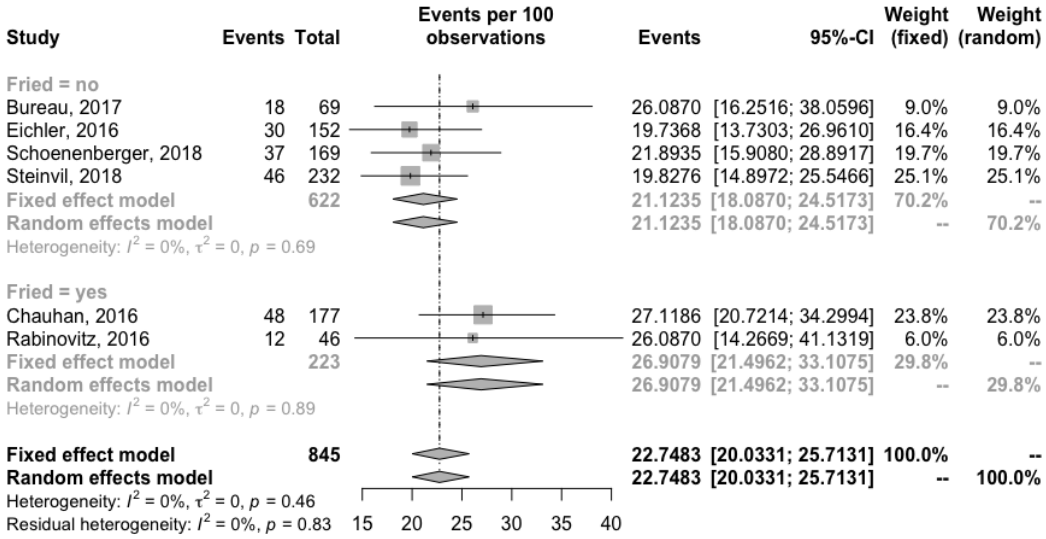
Subgroup analysis of 30-day mortality

Test for subgroup differences: Q=0.08 (p=0.78)



Subgroup analysis of 1-year mortality

Test for subgroup differences: Q=3.12 (p=0.08)

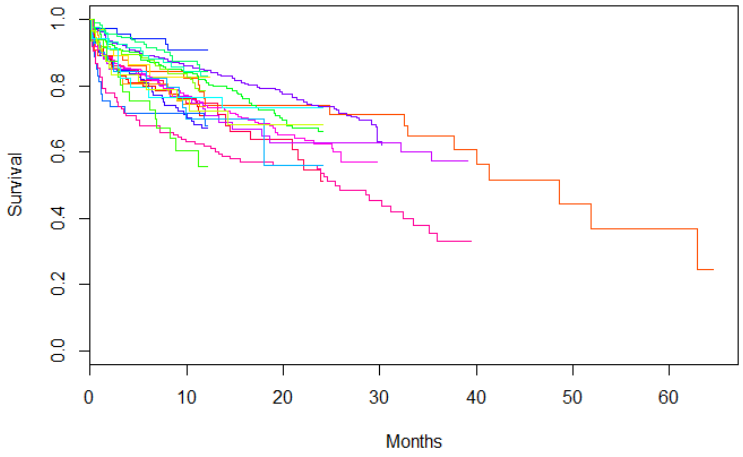


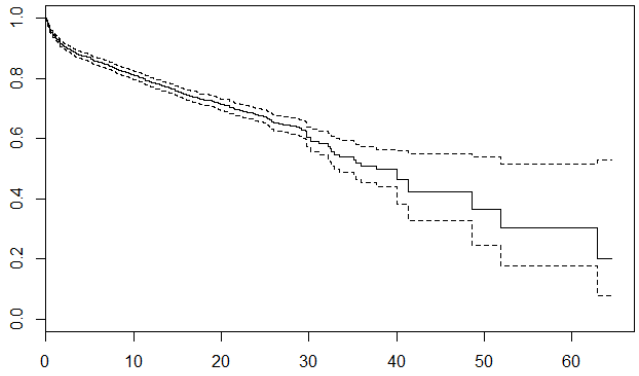
The squares indicate the mortality reported by each study.

The diamonds indicate the pooled estimates for mortality

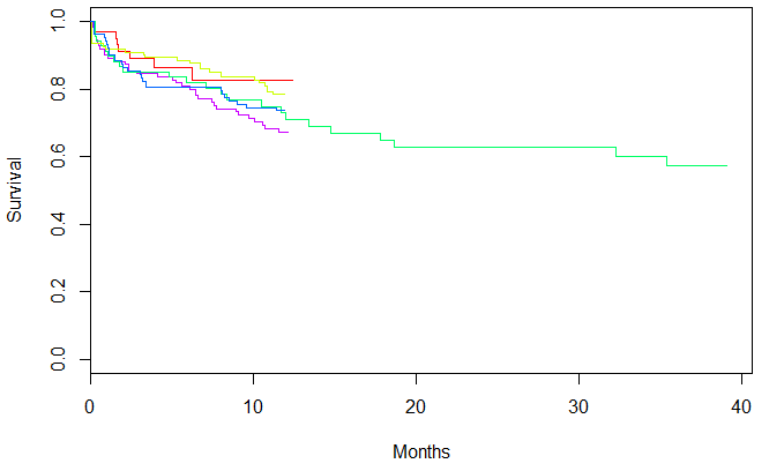
S Figure 4.5 Survival of frail patients after TAVI

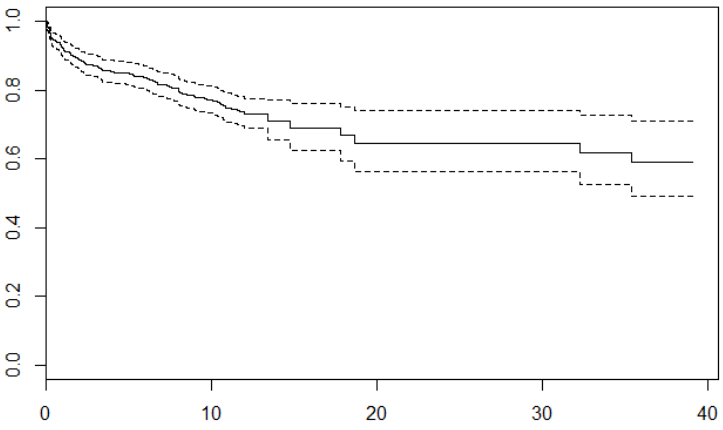
(frailty was measured using single- and multi-dimensional measures)





(frailty was measured using Fried and modified Fried)





4.6 Supplementary tables

S Table 4.1 Literature search

Search: TAVI in Frail Patients with Aortic Stenosis

Database: Embase Classic+Embase 1947 to 2018 October 08, 2018

Date run: Oct 09, 2018

#	Searches	Results
1	frailty/	4,474
2	frail elderly/	9,200
3	geriatric assessment/	14,090
4	frail*.mp.	29,693
5	fragile.mp.	25,961
6	or/1-5	66,792
7	geriatric patient/	22,004
8	very elderly/	148,862
9	aged/	2,835,855
10	aged hospital patient/	752
11	geriatrician/	1,701

12	*geriatrics/	25,458
13	(aged or aging or older or elderly or senior* or geriatric* or centenarian* or nonagenarian* or octogenarian* or septuagenarian* or sexagenarian*).mp.	4,829,113
14	or/7-13	4,829,113
15	exhaustion/	6,833
16	limited mobility/	1,507
17	"timed up and go test"/	1,775
18	exp walk test/	5,786
19	walking speed/	11,203
20	gait/	48,761
21	physical activity/	132,030
22	Performance Oriented Mobility Assessment/	283
23	grip strength/	17,571
24	hand strength/	3,100
25	muscle strength/	54,850
26	daily life activity/	78,985
27	exp "activity of daily living assessment"/	21,992

28	exp ADL disability/	13,335
29	exp disability/	180,851
30	exp functional status assessment/	121,162
31	exp neuropsychological test/	913,342
32	mental function assessment/	384
33	cognition assessment/	2,695
34	exp cognition/	2,059,036
35	exp cognitive defect/	433,929
36	memory assessment/	714
37	nutritional assessment/	26,256
38	((exhaustion or fatigue* or tired* or mobility or gait or walk* or stand or balance or bath* or dress* or toilet* or continence or feeding or cognition or memory or mental or disability or NYHA or Karnofsky or CSHA or functional* or Katz or Fried or Rockwood or frailty or nutrition*) adj7 (assess* or phenotype* or eval* or test* or exam* or instrument* or index or indices or scale* or score* or tool* or declin* or dependenc* or impair*)).mp.	854,212
39	(chair adj2 (rise or stand)).mp.	1,696
40	((grip* or grasp* or hand* or musc*) adj2 strength).mp.	82,777

41	(tug adj3 test).mp.	1,953
42	(timed* adj6 (up* or go)).mp.	6,854
43	timedupandgo.mp.	2
44	weight loss.mp.	129,598
45	(activit* adj3 (living or life)).mp.	100,405
46	(adl or iadl or badl).mp.	18,280
47	or/15-46	3,442,519
48	14 and 47	781,563
49	6 or 48	824,674
50	((transfemoral* or trans-femoral* or transapical* or trans-apical* or transaxillary or trans-axillary or transarterial* or trans-arterial* or subclavian* or sub-clavian* or transcatheter* or trans-catheter* or transcutaneous* or trans-cutaneous* or per-cutaneous* or percutaneous* or transcaval* or trans-caval* or "direct aortic" or tavi or tavr or pavi or pavr or sapien or cribier or revalv* or lotus or "direct flow" or jenavalve or portico or engager or evolut) adj3 aortic valv*).mp.	19,014
51	transcatheter aortic valve implantation/	16,180
52	or/50-51	19,014
53	49 and 52	1,414
54	limit 53 to yr="2006 -Current"	1,409

Database: Ovid MEDLINE(R) ALL 1946 to October 08, 2018

Date run: October 09, 2018

#	Searches	Results
1	Frailty/	662
2	Frail Elderly/	9,739
3	Geriatric Assessment/	24,413
4	frail*.mp.	21,060
5	fragile.mp.	19,323
6	or/1-5	61,189
7	"Aged, 80 and over"/	816,726
8	Aged/	2,823,799
9	Geriatricians/	42
10	*Geriatrics/	25,486
11	(aged or aging or older or elderly or senior* or geriatric* or centenarian* or nonagenarian* or octogenarian* or septuagenarian* or sexagenarian*).mp.	5,286,097
12	or/7-11	5,286,097
13	Physical Exertion/	55,505
14	Physical Endurance/	18,188

15	Walk Test/	677
16	Exercise Test/	59,444
17	Exercise Tolerance/	11,201
18	Walking Speed/	557
19	Gait/	24,764
20	Exercise/	94,223
21	mobility limitation/	3,922
22	Hand Strength/	12,733
23	Muscle Strength/	16,326
24	exp "Activities of Daily Living"/	64,195
25	"Quality of Life"/	167,141
26	exp Neuropsychological Tests/	164,970
27	exp Cognition/	142,641
28	Cognitive Dysfunction/	9,643
29	Cognition Disorders/	61,522
30	Nutritional Assessment/	13,529
31	Nutritional Status/	39,381

32	((exhaustion or fatigue* or tired* or mobility or gait or walk* or stand or balance or bath* or dress* or toilet* or continence or feeding or cognition or memory or mental or disability or NYHA or Karnofsky or CSHA or functional* or Katz or Fried or Rockwood or frailty or nutrition*) adj7 (assess* or phenotype* or eval* or test* or exam* or instrument* or index or indices or scale* or score* or tool* or declin* or dependenc* or impair*)).mp.	556,389
33	(chair adj2 (rise or stand)).mp.	1,106
34	((grip* or grasp* or hand* or musc*) adj2 strength).mp.	49,580
35	(tug adj3 test).mp.	1,150
36	(timed* adj6 (up* or go)).mp.	4,104
37	timedupandgo.mp.	1
38	weight loss.mp.	87,560
39	(activit* adj3 (living or life)).mp.	80,777
40	(adl or iadl or badl).mp.	10,012
41	or/13-40	1,308,674
42	12 and 41	555,051
43	6 or 42	592,801
44	((transfemoral* or trans-femoral* or transapical* or trans-apical* or transaxillary or trans-axillary or transarterial* or trans-	8,618

	arterial* or subclavian* or sub-clavian* or transcatheter* or trans-catheter* or transcutaneous* or trans-cutaneous* or per-cutaneous* or percutaneous* or transcaval* or trans-caval* or "direct aortic" or tavi or tavr or pavi or pavr or sapien or cribier or revalv* or lotus or "direct flow" or jenavalve or portico or engager or evolut) adj3 aortic valv*).mp.	
45	Transcatheter Aortic Valve Replacement/	2,879
46	or/44-45	8,618
47	43 and 46	479
48	limit 47 to yr="2006 -Current"	477

Database: Cochrane Central Register of Controlled Trials : Issue 4 of 12, April 2018

Date run: May 15, 2018

#	Searches	Results
1	MeSH descriptor: [Frailty] this term only	14
2	MeSH descriptor: [Frail Elderly] this term only	632
3	MeSH descriptor: [Geriatric Assessment] this term only	1357
4	frail*:ti,ab,kw (Word variations have been searched)	2,289
5	fragile:ti,ab,kw (Word variations have been searched)	1322
6	{OR #1-#5}	4,707
7	MeSH descriptor: [Aged, 80 and over] this term only	275
8	MeSH descriptor: [Aged] this term only	1,057
9	MeSH descriptor: [Geriatrics] this term only	194
10	aged or aging or older or elderly or senior* or geriatric* or centenarian* or nonagenarian* or octogenarian* or septuagenarian* or sexagenarian*:ti,ab,kw (Word variations have been searched)	543,310
11	{or #7-#10}	543,310
12	MeSH descriptor: [Mobility Limitation] this term only	383
13	MeSH descriptor: [Physical Exertion] this term only	3,745

14	MeSH descriptor: [Physical Endurance] this term only	3,066
15	MeSH descriptor: [Walk Test] this term only	133
16	MeSH descriptor: [Exercise Test] this term only	7,895
17	MeSH descriptor: [Exercise Tolerance] this term only	2,321
18	MeSH descriptor: [Walking Speed] this term only	61
19	MeSH descriptor: [Gait] this term only	1,711
20	MeSH descriptor: [Exercise] this term only	13,622
21	MeSH descriptor: [Hand Strength] this term only	1,237
22	MeSH descriptor: [Muscle Strength] this term only	3,554
23	MeSH descriptor: [Activities of Daily Living] explode all trees	4,849
24	MeSH descriptor: [Quality of Life] this term only	20,519
25	MeSH descriptor: [Neuropsychological Tests] explode all trees	14,997
26	MeSH descriptor: [Cognition] explode all trees	9,262
27	MeSH descriptor: [Cognition Disorders] this term only	3,300
28	MeSH descriptor: [Cognitive Dysfunction] this term only	682
29	MeSH descriptor: [Nutrition Assessment] this term only	643
30	MeSH descriptor: [Nutritional Status] this term only	2,164

31	((exhaustion or fatigue* or tired* or mobility or gait or walk* or stand or balance or bath* or dress* or toilet* or continence or feeding or cognition or memory or mental or disability or NYHA or Karnofsky or CSHA or functional* or Katz or Fried or Rockwood or frailty or nutrition*) next/7 (assess* or phenotype* or eval* or test* or exam* or instrument* or index or indices or scale* or score* or tool* or declin* or dependenc* or impair*)):ti,ab,kw (Word variations have been searched)	71,128
32	(chair next/2 (rise or stand)):ti,ab,kw (Word variations have been searched)	577
33	((grip* or grasp* or hand* or musc*) next/2 strength):ti,ab,kw (Word variations have been searched)	12,819
34	(tug next/3 test):ti,ab,kw (Word variations have been searched)	277
35	(timed* next/6 (up* or go)):ti,ab,kw (Word variations have been searched)	1,747
36	"weight loss":ti,ab,kw (Word variations have been searched)	14,222
37	(activit* next/3 (living or life)):ti,ab,kw (Word variations have been searched)	8,991
38	adl or iadl or badl:ti,ab,kw (Word variations have been searched)	2,433
39	{or #12-#38}	147,840
40	#11 and #39	94,059
41	#6 or #40	96,452

42	((transfemoral* or trans-femoral* or transapical* or trans-apical* or transaxillary or trans-axillary or transarterial* or trans-arterial* or subclavian* or sub-clavian* or transcatheter* or trans-catheter* or transcutaneous* or trans-cutaneous* or per-cutaneous* or percutaneous* or transcaval* or trans-caval* or "direct aortic" or tavi or tavr or pavi or pavr or sapien or cribier or revalv* or lotus or "direct flow" or jenavalve or portico or engager or evolut) next/3 aortic valv*):ti,ab,kw (Word variations have been searched)	730
43	MeSH descriptor: [Transcatheter Aortic Valve Replacement] this term only	111
44	#42 or #43	730
45	#41 and #44	72

Database: PsycINFO (ProQuest) - updated weekly

Date run: October 09, 2018

#	Searches	Results
1	MAINSUBJECT.EXACT("Health Impairments" OR "Geriatric Assessment")	9,138
2	AB,TI,SU(frail* OR fragile)	10,660
3	1 OR 2	18,152
4	MAINSUBJECT.EXACT("Geriatric Patients" OR "Geriatrics" OR "Gerontology")	31,680
5	AB,TI,SU(aged OR aging OR older OR elderly OR senior* OR geriatric* OR centenarian* OR nonagenarian* OR octogenarian* OR septuagenarian* OR sexagenarian*)	1,926,992
6	4 OR 5	1,927,152
7	MAINSUBJECT.EXACT("Fatigue" OR "Physical Mobility" OR "Locomotion" OR "Physical Agility" OR "Physical Activity" OR "Physical Endurance" OR "Physical Fitness" OR "Physical Strength" OR "Exercise" OR "Ability Level" OR "Activity Level" OR "Walking" OR "Gait" OR "Activities of Daily Living" OR "Daily Activities" OR "Quality of Life" OR "Neuropsychological Assessment" OR "Cognition" OR "Cognitive Impairment" OR "Memory Disorders" OR "Nutritional Deficiencies")	257,149
8	AB,TI,SU(exhaustion OR fatigue* OR tired* OR mobility OR gait OR walk* OR stand OR balance OR bath* OR dress* OR toilet* OR continence OR feeding OR cognition OR memory OR mental OR disability OR NYHA OR Karnofsky OR CSHA OR functional* OR Katz OR Fried OR	882,574

	Rockwood OR frailty OR nutrition*) AND AB,TI,SU(assess* OR phenotype* OR eval* OR test* OR exam* OR instrument* OR index OR indices OR scale* OR score* OR tool* OR declin* OR dependenc* OR impair*)	
9	chair NEAR/2 (rise OR stand)	356
10	strength NEAR/2 (grip* OR grasp* OR hand* OR musc*)	6,781
11	tug NEAR/3 test	218
12	timed* NEAR/6 (up* OR go)	1,197
13	activit* NEAR/3 (living OR life)	32,094
14	AB,TI,SU(timedupandgo OR weight loss OR adl OR iadl OR badl)	17,547
15	7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14	1,008,472
16	6 AND 15	555,046
17	3 OR 16	563,316
18	(transfemoral* OR trans-femoral* OR transapical* OR trans-apical* OR transaxillary OR trans-axillary OR transarterial* OR trans-arterial* OR subclavian* OR sub-clavian* OR transcatheter* OR trans-catheter* OR transcutaneous* OR trans-cutaneous* OR per-cutaneous* OR percutaneous* OR transcaval* OR trans-caval* OR "direct aortic" OR tavi OR tavr OR pavi OR pavr OR sapien OR cribier OR revalv* OR lotus OR "direct flow" OR jenavalve OR portico OR engager OR evolut) AND (aortic valv*)	18
19	TAVI	27

20	18 OR 19	34
21	17 AND 20	9

Database: Web of Science Core Collection (Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years) updated daily

Date run: October 09, 2018

#	Searches	Results
1	TS=(frail*)	22,247
2	TS=(fragile)	37,652
3	#1 OR #2	59,834
4	TS=(aged OR aging OR older OR elderly OR senior* OR geriatric* OR centenarian* OR nonagenarian* OR octogenarian* OR septuagenarian* OR sexagenarian*)	3,797,370
5	TS=((exhaustion OR fatigue* OR tired* OR mobility OR gait OR walk* OR stand OR balance OR bath* OR dress* OR toilet* OR continence OR feeding OR cognition OR memory OR mental OR disability OR NYHA OR Karnofsky OR CSHA OR functional* OR Katz OR Fried OR Rockwood OR frailty OR nutrition*) NEAR/7 (assess* OR phenotype* OR eval* OR test* OR exam* OR instrument* OR index OR indices OR scale* OR score* OR tool* OR declin* OR dependenc* OR impair*))	773,498
6	TS=(chair NEAR/2 (rise OR stand))	2,002

7	TS=((grip* OR grasp* OR hand* OR musc*) NEAR/2 strength)	39,945
8	TS=(tug NEAR/3 test)	1,187
9	TS=(timed* NEAR/6 (up OR go))	3,859
10	TS=(weight loss)	174,213
11	TS=(activit* NEAR/3 (living OR life))	43,381
12	TS=(ADL OR IADL OR BADL)	11,123
13	#12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5	1,000,842
14	#13 AND #4	263,645
15	#14 OR #3	315,519
16	TS=((transfemoral* OR trans-femoral* OR transapical* OR trans-apical* OR transaxillary OR trans-axillary OR transarterial* OR trans-arterial* OR subclavian* OR sub-clavian* OR transcatheter* OR trans-catheter* OR transcutaneous* OR trans-cutaneous* OR per-cutaneous* OR percutaneous* OR transcaval* OR trans-caval* OR "direct aortic" OR tavi OR tavr OR pavi OR pavr OR sapien OR cribier OR revalv* OR lotus OR "direct flow" OR jenavalve OR portico OR engager OR evolut) NEAR/3 aortic valv*)	12,250
17	#16 AND #15	403

Search numbers for PRISMA

Database	Search results	Internal and cross-database duplicates	De-duped results for screening
Ovid Embase	1,409	158	1,251
Ovid MEDLINE	477	373	104
Cochrane Library	72	68	4
PsycINFO	9	7	2
Web of Science	403	347	56
TOTALS:	2,370	953	1,417
	Search updates (to October 09 2018):		142
	Total screened (from databases):		**1,559**

S Table 4.2 Baseline demographics and population characteristics

Study	Recruitment period	N (frail)	Age (mean±SD)	Female (n,%)	NYHA III/IV (n,%)	STS (mean±SD)	Logistic Euro score (mean±SD)	TF-approach (n, %)	TA-approach (n,%)	AVA, cm^2 (mean±SD)	Creatinine (mg/dL) (mean±SD)	Haemoglobin, g/dL (mean±SD)	LVEF (mean±SD)	Aortic gradient, mmHg (mean±SD)
Alfredsson (2016)	2011-2014	6100	NR	3421 (56.08 %)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bureau (2017)	2013-2015	71	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bagienski (2017)	NR	127	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bogdan (2016)	2009-2012	79	82±5	43 (55%)	46 (58.2%)	5.8±3.12	19.44±14.98	NR	NR	0.66±0.14	1.35±0.93	11.27±1.58	53.22±12.64	43.54±15.19
Capodanno (2014)	2010-2012	306	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Chauhan (2016)	2012-2015	233	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cockburn (2016)	2008-2014	65	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Eichler (2017)	2013-2015	152	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ghatak (2012)	NR	22	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Green (2015)	PARTNER[1]	110	87.1** (82.7-90.3)	58 (53%)	NR	11.3** (9.6-13.8)	NR	57 (52%)	NR	0.62** (0.51-0.72)	NR	NR	55** (35-60)	45.2** (34.9-59.7)
Green (2012)	PARTNER[1]	76	87.1±6.6	40 (53%)	NR	11.9±4	NR	NR	30 (39%)	0.6±0.2	NR	11.1±1.6	47±15	45±15
Grossman (2017)	2008-2014	192	84.3±7.5	109 (56.8)	122 (66%)	6.2±4.5	20.8±16	132 (73%)	42 (23%)	NR	NR	NR	NR	NR
Huded	2012-2015	64	83.1±7.5	42	53	6.8±2.8	NR	57	NR	NR	1.19±0.45	11.8±1.8	NR	NR

(2016)				(66%)	(90%)			(89%)						
Koifman (2015)	2007-2014	238	84±8	81 (21%)	210 (94%)	10±4.7	NR	181 (76%)	NR	0.64±0.13	1.3±0.9	11±1.4	NR	NR
Kleczynski (2017)	NR	53	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kobe (2016)	2011-2014	71	NR	37 (52.11 %)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Martin (2018)	2013-2014	1466	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mok (2016)	NR	293	81.3±7.5	105 (36%)	240 (82%)	7.1±4	NR	174 (59.4%)	119 (40.6%)	0.68±0.21	NR	NR	54±14	NR
Maniar (2016)	PARTNER II[2]	73	84±7	49 (67.6%)	NR	12.3±5.7	NR	NR	NR	NR	NR	NR	NR	NR
Okoh (2017)	NR	30	92±2	24 (80%)	24 (80%)	8.4±5.4	NR	20 (67%)	NR	NR	NR	NR	NR	NR

Patel (2016)	2012-2015	31	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Puls (2014)	2008-2012	144	83.1±5.2	106 (74%)	136 (94.4%)	8.8±6.7	28.8±16.3	NR	NR	NR	NR	NR	NR	NR
Rabinovitz (2016)	2009-2013	46	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rodes-Cabau (2010)	2005-2009	85	83±7	58 (68.2%)	NR	11.6±8.3	NR	42 (49.4%)	43 (50.6%)	NR	112±73 (umol/L)	NR	NR	NR
Rodriguez-Pascual (2016)	2010-2015	68	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rogers (2018)	Since 2007	242	83±7.6	140 (58%)	NR	8.8±6.1	NR	NR	NR	NR	NR	NR	NR	NR
Schoenenberger (2018)	2009-2013	169	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Shimura (2017)	2013-2016	353	NR	276 (78.2%)	208 (58.92%)	NR	NR	285 (80.74%)	58 (16.43%)	NR	NR	NR	NR	NR
Steinvil (2018)	2011-2016	232	83±7	132 (57%)	193 (83%)	8.8±6.1	NR	NR	NR	0.7 ±0.2	NR	NR	NR	43±13
Shi (2018)	2014-2016	116	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Skaar (2018)	2011-2015	34	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stortecky (2012)	2007-2010	24	84±4	NR	NR	NR	24.8±16	NR	NR	0.5±0.2	NR	NR	52±19	NR
Traynor (2017)	2008-2015	60	85.4±7.4	38 (63.3%)	49 (81.7%)	12.7±11.2	NR	34 (56.67%)	NR	NR	1.4±1.1	NR	56±14	NR
Yamamoto (2015)	2010-2011	56	85±6.7	38 (67.90 %)	47 (83.9%)	10.9±7.3	23.6±11.2	41 (73.2%)	NR	0.58±0.19	NR	NR	NR	53.3±21.5
Zajarias	PARTNER II[2]	265	85±6	157	NR	11.8±5.8	NR	NR	NR	NR	NR	NR	NR	NR

(2016)				(59.7%)										

Baseline demographics and population characteristics (continued)

Study	AF (n, %)	Active cancer (n, %)	BMI (mean±SD)	COPD (n,%)	Cerebrovascular Disease (n,%)	CAD (n, %)	Chronic Lung disease (n,%)	Chronic Dialysis (n,%)	Chronic Kidney disease (n, %)	dyslipidemia (n,%)	Diabetes Mellitus (n,%)	Hyperlipidemia (n,%)	Hypertension (n,%)
Alfredsson, (2016)	NR	NR	NR	NR	NR	NR	1611 (26.41%)	186 (3.05%)	NR	NR	2137 (35.03%)	NR	5510 (90.33%)
Bureau (2017)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bagienski (2017)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bogdan (2016)	14 (17%)	NR	NR	23 (29%)	NR	NR	NR	NR	NR	39 (49%)	27 (34%)	NR	56 (70%)

Capodanno (2014)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chauhan (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cockburn (2015)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Eichler (2017)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ghatak (2012)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Green (2015)	NR	NR	NR	46 (42%)	26 (26%)	91 (83%)	NR	NR	NR	NR	28 (26%)	NR	95 (86%)
Green (2012)	NR	NR	25±6.4	NR	NR	NR	NR	NR	NR	NR	19 (25%)	38 (50%)	58 (76%)
Grossman (2017)	57 (32%)	NR	NR	NR	NR	100 (56%)	NR	NR	NR	NR	71 (39%)	136 (74%)	160 (86%)

Huded (2016)	26 (41%)	NR	29.1±6.9	5 (8%)	NR	54 (84%)	NR	NR	14 (22%)	NR	24 (38%)	37 (58%)	50 (78%)
Koifman (2015)	101 (44%)	NR	NR	77 (34%)	32 (16%)	NR	NR	NR	NR	NR	79 (35%)	NR	211 (92%)
Kleczynski (2017)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kobe (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Martin (2018)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mok (2016)	107 (37%)	NR	25.4±4.9	NR	NR	206 (71%)	94 (32%)	NR	NR	208 (71%)	85 (29%)	NR	246 (84%)
Maniar (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Okoh (2017)	11 (37%)	NR	25.4±3.7	NR	NR	22 (73%)	7 (23%)	1 (3%)	NR	17 (57%)	NR	NR	28 (93%)

Patel (2016)	19 (61.3%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Puls (2014)	NR	NR	26.9±5.1	NR	NR	101 (70%)	NR	NR	NR	NR	50 (34%)	NR	NR
Rabinovitz (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rodes-Cabau (2010)	NR	NR	25±5	23 (27.1%)	15 (17.7%)	57 (67.1%)	NR	3 (3.5%)	NR	55 (65.5%)	21 (26.6%)	NR	58 (68.2%)
Rodriguez-Pascual (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rogers (2018)	109 (45%)	NR	29±11	116 (48%)	NR	NR	NR	15 (6%)	90 (37%)	NR	82 (34%)	198 (82%)	223 (92%)
Schoenenberger (2018)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shimura	NR	8	NR	NR	NR	NR	NR	NR	203	NR	94	NR	258

(2017)		(2.3%)							(57.5%)		(26.6%)		(73.1%)
Steinvil (2018)	102 (44%)	NR	29±11	114 (49%)	NR	NR	NR	14 (6%)	86 (37%)	NR	79 (34%)	190 (82%)	216 (93%)
Shi (2018)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Skaar (2018)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stortecky (2012)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Traynor (2017)	NR	NR	NR	NR	18 (30%)	NR	32 (55.2%)	2 (3.3%)	NR	NR	28 (46.7%)	NR	57 (95%)
Yamamoto (2015)	NR	NR	NR	17 (30.40%)	NR	NR	NR	1 (1.80%)	42 (75%)	19 (33.90%)	5 (8.90%)	NR	37 (66.10%)
Zajarias (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Baseline demographics and population characteristics (continued)

Study	Liver disease (n,%)	Previous stroke (n, %)	Previous MI (n, %)	Previous BVA (n, %)	Previous PCI (n, %)	Previous CABG (n,%)	Pulmonary disease (n,%)	Peripheral arterial disease (n,%)	Peripheral Vascular disease (n, %)	Permanent pacemaker (n,%)	Valve type
Alfredsson (2016)	NR	753 (12.34%)	1422 (23.31%)	774 (12.69%)	2103 (34.48%)	1800 (29.51%)	NR	1930 (31.64%)	NR	NR	NR
Bureau (2017)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bagienski (2017)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	CoreValve Edwards Sapien Jena Lotus NVT
Bogdan (2016)	1 (1%)	NR	NR	NR	NR	NR	NR	NR	9 (11%)	NR	CoreValve: 60 (75.94%) Edwards Sapien: 19 (24.06%)

Capodanno (2014)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chauhan (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cockburn (2015)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	CoreValve: 277 (89%) Edwards Sapien: 24 (7.7%) Lotus: 10 (3.2%)
Eichler (2017)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	CoreValve (classic, Evolut R) Edwards Sapien Edwards Sapien XT
Ghatak (2012)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Edwards Sapien
Green (2015)	9 (8%)	NR	NR	35 (32%)	45 (41%)	47 (43%)	NR	NR	46 (42%)	27 (25%)	Edwards Sapien
Green	NR	9	NR	NR	NR	27	22	NR	16	24	Edwards Sapien

(2012)		(12%)				(36%)	(29%)		(21%)	(32%)	
Grossman (2017)	NR	6 (3%)	NR	NR	NR	NR	NR	NR	19 (11%)	13 (7%)	CoreValve Edwards Sapien XT
Huded (2016)	NR	13 (20%)	NR	NR	NR	17 (27%)	NR	6 (9%)	NR	NR	Edwards Sapien Edwards Sapien XT Edwards Sapien 3 CoreValve Direct Flow Medical
Koifman (2015)	NR	NR	NR	NR	60 (26%)	67 (29%)	NR	NR	76 (34%)	37 (21%)	
Kleczynski (2017)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Edwards Sapien Edwards Sapien XT Edwards Sapien 3 CoreValve JenaValve
Kobe	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

(2016)											
Martin (2018)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mok (2016)	NR	56 (19%)	84 (29%)	NR	NR	57 (20%)	NR	NR	87 (30%)	NR	NR
Maniar (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Okoh (2017)	NR	NR	NR	1 (3%)	4 (13%)	4 (13%)	NR	NR	7 (23%)	7 (23%)	
Patel (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Puls (2014)	NR	NR	NR	NR	40 (28%)	16 (11%)	43 (30%)	NR	42 (29%)	NR	CoreValve Edwards Sapien
Rabinovitz (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rodes-Cabau	NR	NR	39	NR	26	20	NR	NR	29	NR	Cribier-Edwards

(2010)			(45.9%)		(30.6%)	(23.5%)			(34.1%)		Edwards Sapien Edwards Sapien XT
Rodriguez-Pascual (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rogers (2018)	NR	17 (7%)	41 (17%)	53 (22%)	80 (33%)	58 (24%)	NR	NR	58 (24%)	65 (27%)	Balloon expandable (67%) Self-expanding (33%)
Schoenenberger (2018)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	CoreValve Edwards Sapien XT
Shimura (2017)	17 (4.8%)	65 (18.4%)	28 (7.9%)	NR	94 (26.6%)	21 (5.9%)	108 (30.6%)	67 (19%)	NR	NR	NR
Steinvil (2018)	NR	16 (7%)	42 (18%)	49 (21%)	79 (34%)	58 (25%)	NR	NR	53 (23%)	67 (29%)	NR
Shi (2018)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Skaar (2018)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Stortecky (2012)	NR	NR	NR	NR	NR	1 (4.2%)	NR	NR	NR	NR	NR
Traynor (2017)	NR	NR	18 (30%)	NR	NR	15 (25%)	NR	NR	38 (63.3%)	12 (20%)	NR
Yamamoto (2015)	NR	6 (10.70%)	5 (8.90%)	NR	NR	NR	NR	8 (14.30%)	NR	10 (17.90%)	CoreValve Edwards Sapien
Zajarias (2016)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Edwards Sapien XT

N, sample size of frail TAVI recipients. SD, standard deviation. NYHA, New York Heart Association. STS, Society of Thoracic Surgeons. TF, transfemoral approach. TA, transapical approach. AVA, aortic valve area. LVEF, left ventricular ejection fraction. AF, atrial fibrillation. BMI, body mass index. COPD, chronic obstructive pulmonary disease. CAD, coronary artery disease. MI, myocardial infarction. BVA, balloon aortic valvuloplasty. PCI, percutaneous coronary intervention. CABG, coronary artery bypass grafting.

NR, not reported

§ = Euro score II

**= median and IQR

1, recruitment period, 2007-2010

2, recruitment period, 2011-2016

S Table 4.3 Assessment of quality in individual studies

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Statistical Analysis Reporting	Overall Risk of Bias	Study Design	Abstract
Alfredsson (2016)	high	moderate	low	low	low	moderate	prospective	no
Bureau (2017)	high	moderate	low	low	low	moderate	prospective	no
Bagienski (2017)	moderate	moderate	low	low	low	moderate	prospective	no
Bogdan (2016)	moderate	high	low	low	moderate	moderate	retrospective	no
Capodanno	moderate	moderate	low	low	low	moderate	prospective	no

(2014)								
Chauhan (2016)	moderate	high	low	low	low	moderate	retrospective	no
Cockburn (2015)	moderate	low	moderate	low	moderate	moderate	prospective	no
Eichler (2017)	high	low	low	low	low	low	prospective	no
Ghatak (2012)	high	high	moderate	low	moderate	high	retrospective	yes
Grossman (2017)	moderate	high	moderate	low	low	moderate	retrospective	no
Green (2012)	moderate	low	low	low	low	low	prospective	no

Green (2015)	moderate	low	low	low	low	low	prospective	no
Huded (2016)	high	high	low	low	low	high	retrospective	no
Kleczynski (2017)	low	low	low	low	low	low	prospective	no
Kobe (2016)	moderate	moderate	low	low	low	moderate	prospective	no
Koifman (2015)	moderate	high	low	low	low	moderate	retrospective	no
Martin (2018)	high	high	low	low	low	high	prospective	no
Maniar	high	moderate	moderate	low	low	moderate	retrospective	yes

(2016)								
Mok (2016)	high	low	low	low	low	low	retrospective	no
Okoh (2017)	Low	high	moderate	low	low	moderate	prospective	no
Patel (2016)	moderate	high	low	low	low	moderate	retrospective	no
Puls (2014)	moderate	low	low	low	low	low	prospective	no
Rabinovitz (2016)	high	high	moderate	low	low	high	retrospective	no
Rodes-Cabau (2010)	low	low	high	low	low	low	prospective	no

Rodriguez-Pascual (2016)	low	low	low	low	low	low	prospective	no
Rogers (2018)	moderate	moderate	low	low	low	moderate	retrospective	no
Schoenenberger (2018)	high	low	low	low	low	low	prospective	no
Shimura (2017)	low	moderate	low	low	low	low	prospective	no
Steinvil (2018)	moderate	moderate	low	low	low	moderate	prospective	no
Shi (2018)	moderate	high	low	low	low	moderate	prospective	no
Skaar	low	low	low	low	low	low	prospective	no

(2018)								
Stortecky (2012)	high	moderate	moderate	moderate	high	high	prospective	yes
Traynor (2017)	low	low	moderate	moderate	low	moderate	retrospective	no
Yamamoto (2015)	moderate	low	low	low	low	low	prospective	no
Zajarias (2016)	high	moderate	low	low	low	moderate	prospective	yes

*Risk of bias was assessed using the Quality in Prognostic Studies tool (QUIPS)

Low risk= studies with four or five low risk domains

High risk=studies with two or more high risk domains

Moderate risk=remaining studies

S Table 4.4 Prognosis of frail TAVI recipients

Study	Procedural/in-hospital	30 days	6 months	8 months	1 year	2 year
Death						
Alfredsson, 2016	300/6100 (4.9%)	405/6100 (6.6%)				
Bureau, 2017		7/71 (9.9%)	13/71 (18.3%)		18/69 (26.1%)	
Bogdan, 2016		4/79 (5.1%)				35.4% (2.1 years)
Capodanno, 2014		30/306 (9.8%)				
Chauhan, 2016		18/233 (7.7%)			48/177 (27.1%)	
Eichler, 2017					30/152 (19.7%)	
Green, 2015		11/110 (10%)			32.7%	
Huded, 2016		2/64 (3.13%)				

Kleczynski, 2017					17/53 (32.1%)	
Martin, 2018		51/1581(3.23%)				
Maniar, 2016		12.3%			36.5%	
Okoh, 2017						30%
Puls, 2014	33/144 (23%)	25/144 (17%)				
Rabinovitz, 2016					12/46 (26.1%)	
Rodriguez-Pascual, 2016						39.7%*(98weeks)
Rodes-Cabau, 2010	2/85 (2.4%)	7/85 (8.2%)		19/85 (22.4%)		
Schoenenberger, 2018					37/169(21.9%)	
Shimura, 2017	15/353 (4.25%)	10/353 (2.83%)				
Steinvil, 2018		14/232 (6.03%)			46/232 (19.8%)	

Shi, 2018			17/116 (15%)			
Skaar, 2018						9/34 (26.47%)
Stortecky, 2012		6/24 (25%)			9/24 (37.5%)	
Traynor, 2017	2/60 (3.3%)				14.8%	
Zajarias, 2016		17/265 (6.4%)			88/265 (33.2%)	
Death (cardiovascular cause)						
Alfredsson, 2016		251/6100 (4.1%)				
Green, 2015		8/110 (7%)				
Shimura, 2017	4/353(1.13%)	8/353 (2.27%)				
Acute kidney injury						
Alfredsson, 2016	397/6100 (6.5%)					

Bogdan, 2016		25/79 (31.6%)				
Green, 2012	3/76 (3.95%)					
Okoh, 2017	2/30 (6.67%)					
Shimura, 2017	47/353 (13.31%)					
Yamamoto, 2015	6/56 (10.7%)					
Arrhythmia						
Rodes-Cabau, 2010	9/85 (10.6%)					
Annulus rupture						
Yamamoto, 2015	1/56 (1.8%)					
Bleeding						
Zajarias, 2016	15/265 (43.4%)					

Cardiac tamponade						
Puls, 2014	3/144 (2%)					
Shimura, 2017	11/353 (3.11%)					
Yamamoto, 2015	3/56 (5.4%)					
Conversion to open surgery						
Rodes-Cabau, 2010	1/85 (1.2%)					
Shimura, 2017	8/353 (2.27%)					
Coronary obstruction						
Shimura, 2017	3/353 (0.85%)					
Delirium						
Bagienski, 2017	105/127 (82.68%)					

Life-threatening bleeding						
Alfredsson, 2016		391/6100 (6.4%)				
Green, 2012	7/76 (9.21%)					
Puls, 2014	15/144 (10%)					
Stortecky, 2012	4/24 (16.7%)					
Shimura, 2017	33/353 (9.35%)					
Yamamoto, 2015	4/56 (7.1%)					
Major bleeding						
Green, 2015		10/110 (9%)				
Koifman, 2015	6/238 (3%)					
Puls, 2014	12/144 (8%)					

Shimura, 2017	77/353 (21.81%)					
Yamamoto, 2015	9/56 (16.1%)					
Minor bleeding						
Koifman, 2015	31/238 (13%)					
Puls, 2014	50/144 (35%)					
Shimura, 2017	62/353 (17.56%)					
Major vascular complications						
Bogdan, 2016		0/79 (0%)				
Green, 2015		7/110 (6%)				
Koifman, 2015	37/238 (16%)					
Shimura, 2017	18/353 (5.1%)					

Yamamoto, 2015	8/56 (14.3%)					
Minor vascular complications						
Bogdan, 2016		2/79 (2.5%)				
Koifman, 2015	26/238 (11%)					
Shimura, 2017	17/353 (4.82%)					
Major access site complications						
Rodes-Cabau, 2010	12/85 (14.1%)					
Stortecky, 2012	2/24 (8.3%)					
Major vascular injury						
Huded, 2016		4/64 (6%)				
Myocardial infarction						

Rodes-Cabau, 2010		2/85 (2.4%)				
Yamamoto, 2015	0/56 (0%)					
Need for second valve						
Rodes-Cabau, 2010	1/85 (1.2%)					
Permanent pacemaker						
Green, 2015		10/110 (9%)				
Koifman, 2015	12/238 (5%)					
Okoh, 2017	2/30 (6.67%)					
Puls, 2014	3/144 (2%)					
Rodes-Cabau, 2010		7/85 (8.2%)				
Yamamoto, 2015	5/56 (8.9%)					
Percutaneous closure device failure						

Bogdan, 2016		10/79 (12.7%)				
Renal failure						
Green, 2015		9/110 (8%)				
Respiratory failure						
Huded, 2016		1/64 (2%)				
Readmission						
Green, 2015		4/110(4%)				
Huded, 2016		7/64 (11%)				
Stroke						
Alfredsson, 2016		129/6100 (2.1%)				
Green, 2015		1/110 (1%)				
Huded, 2016		4/64 (6%)				

Koifman, 2015	11/238 (5%)					
Rodes-Cabau, 2010		3/85 (3.5%)				
Okoh, 2017	0/30 (0%)					
Shimura, 2017	6/353 (1.7%)					
Stortecky, 2012	2/24 (8.3%)					
Traynor, 2017	2/60 (3.3%)					
Yamamoto, 2015	3/56 (5.4%)					
Sepsis						
Rodes-Cabau, 2010		4/85 (4.7%)				
Transfusion						
Green, 2012	24/76 (32.9%)					
Koifman, 2015	100/238 (43%)					

Puls, 2014	67/144 (47%)					
Valve embolization						
Rodes-Cabau, 2010	1/85 (1.2%)					
Vascular complications						
Bogdan, 2016		12/79 (15.18%)				
2-valve implantation						
Shimura, 2017	9/353 (2.55%)					
Yamamoto, 2015	1/56 (1.8%)					
Length of hospital stay for frail TAVI recipients, days						
Ghatak, 2012	12.1±8.4					
Green, 2012	9±6					
Huded, 2016	6±3.5					

Okoh, 2017	7±8
Patel, 2016	9**
Traynor, 2017	6.8±5.2
Yamamoto, 2015	10.3±7.5
Intensive care unit (ICU) stay, days	
Patel, 2016	2.7**
Yamamoto, 2015	4.9±4

*= median + IQR

**=mean without standard deviation reported

S Table 4.5 Survival rate of frail patients after TAVI

a. combined all studies

Time (Months)	n.risk	n.event	survival	Std.err	Lower 95%CI	Upper 95% CI
1	3088	198	0.94	0.00411	0.932	0.949
2	2915	307	0.907	0.00506	0.897	0.917
3	2790	359	0.89	0.00546	0.88	0.901
4	2668	399	0.878	0.00575	0.866	0.889
5	2573	422	0.87	0.00592	0.858	0.882
6	2458	463	0.856	0.00621	0.844	0.868
7	2371	491	0.846	0.00641	0.834	0.859
8	2279	525	0.834	0.00666	0.821	0.847
9	2183	556	0.822	0.00688	0.809	0.836
10	2103	587	0.811	0.0071	0.797	0.825
11	2005	613	0.8	0.00728	0.786	0.815
12	1756	648	0.786	0.00754	0.771	0.801
13	1274	660	0.779	0.00774	0.764	0.794
14	1194	676	0.769	0.00804	0.753	0.785
15	1116	696	0.756	0.00843	0.739	0.773

16	1043	713	0.744	0.00877	0.727	0.761
17	974	721	0.738	0.00895	0.721	0.756
18	915	734	0.728	0.00926	0.71	0.746
19	835	737	0.725	0.00934	0.707	0.744
20	775	753	0.711	0.00982	0.692	0.731
21	720	762	0.702	0.0101	0.683	0.722
22	662	768	0.696	0.0103	0.676	0.717
23	606	777	0.687	0.0107	0.666	0.708
24	554	784	0.678	0.011	0.657	0.7
25	363	787	0.673	0.0113	0.651	0.696
26	327	799	0.65	0.0128	0.625	0.675
27	284	801	0.645	0.0131	0.62	0.671
28	244	803	0.64	0.0134	0.614	0.667
29	198	805	0.634	0.014	0.607	0.662
30	134	813	0.604	0.017	0.571	0.638
31	71	815	0.591	0.019	0.555	0.63
32	65	816	0.583	0.0205	0.544	0.624
33	61	820	0.547	0.0259	0.498	0.6
34	57	821	0.538	0.0271	0.487	0.593

35	56	821	0.538	0.0271	0.487	0.593
36	51	824	0.508	0.0305	0.452	0.572
37	49	824	0.508	0.0305	0.452	0.572
38	46	825	0.497	0.0317	0.439	0.564
39	45	825	0.497	0.0317	0.439	0.564

TAVI, transcatheter aortic valve implantation. N, number of patients. STD, standard deviation. Err, error. CI, confidence interval.

b. combined studies used Fried/modified Fried phenotype

Time (Months)	n.risk	n.event	survival	Std.err	Lower 95%CI	Upper 95% CI
1	422	36	0.922	0.0125	0.898	0.947
2	398	52	0.887	0.0148	0.858	0.916
3	382	59	0.871	0.0157	0.841	0.902
4	367	67	0.853	0.0166	0.821	0.886
5	359	69	0.848	0.0169	0.816	0.882
6	347	74	0.836	0.0175	0.803	0.871
7	333	82	0.817	0.0184	0.781	0.853
8	319	88	0.802	0.019	0.765	0.84
9	305	96	0.782	0.0198	0.744	0.821
10	297	100	0.771	0.0202	0.733	0.812
11	284	109	0.748	0.0211	0.708	0.79
12	108	114	0.73	0.0223	0.688	0.775
13	36	114	0.73	0.0223	0.688	0.775
14	35	115	0.71	0.0295	0.655	0.77
15	34	116	0.69	0.0349	0.625	0.762

16	32	116	0.69	0.0349	0.625	0.762
17	32	116	0.69	0.0349	0.625	0.762
18	30	117	0.668	0.0403	0.593	0.751
19	28	118	0.645	0.0447	0.564	0.739
20	28	118	0.645	0.0447	0.564	0.739
21	28	118	0.645	0.0447	0.564	0.739
22	28	118	0.645	0.0447	0.564	0.739
23	27	118	0.645	0.0447	0.564	0.739
24	27	118	0.645	0.0447	0.564	0.739
25	26	118	0.645	0.0447	0.564	0.739
26	26	118	0.645	0.0447	0.564	0.739
27	26	118	0.645	0.0447	0.564	0.739
28	25	118	0.645	0.0447	0.564	0.739
29	25	118	0.645	0.0447	0.564	0.739
30	24	118	0.645	0.0447	0.564	0.739
31	24	118	0.645	0.0447	0.564	0.739
32	23	118	0.645	0.0447	0.564	0.739
33	22	119	0.617	0.0508	0.525	0.725
34	22	119	0.617	0.0508	0.525	0.725

35	22	119	0.617	0.0508	0.525	0.725
36	21	120	0.589	0.0557	0.49	0.709
37	21	120	0.589	0.0557	0.49	0.709
38	21	120	0.589	0.0557	0.49	0.709
39	21	120	0.589	0.0557	0.49	0.709

TAVI, transcatheter aortic valve implantation. N, number of patients. STD, standard deviation. Err, error. CI, confidence interval.

S Table 4.6 Quality of life among frail TAVI recipients

Study	QoL measures	Baseline, Mean (SD)	30-day Mean (SD)	Change in QoL at 30 days
Okoh, 2017	KCCQ overall score			-5.86 (p=.62)
	KCCQ physical limitation			-8.34 (p=0.46)
	KCCQ symptoms			-5.68 (p=0.65)
	KCCQ quality of life			6.36 (p=0.63)
	KCCQ social limitation			-7.57 (p=0.58)
Kobe, 2016 Subgroup of frail patients with a frailty score 4-6	SF-36 physical functioning	55.8 (15.3)	49.6 (22.2)	
	SF-36 role physical	37.9 (32.8)	33.8 (43.1)	
	SF-36 bodily pain	88.1 (23.2)	74.4 (23.7)	
	SF-36 role emotional	88.2 (23.6)	38.3 (42.3)	

	SF-36 general health	73.4 (18.7)	62 (15.5)	
	SF-36 vitality	45.5 (24.6)	43.4 (15.5)	
	SF-36 social functioning	91.5 (17.8)	68.8 (26.4)	
	SF-36 mental health	80.4 (16.8)	67.2 (23.2)	
	SF-36 physical component summary	42.9 (6.54)	42.3 (8.02)	
	SF-36 mental component summary	55 (8.79)	42.8 (9.86)	
Kobe, 2016 Subgroup of frail patients with a frailty score 6-14	SF-36 physical functioning	40.9 (20.5)	46.5 (30.2)	
	SF-36 role physical	25.6 (33.2)	27.5 (39.7)	
	SF-36 bodily pain	69.1 (35.6)	60.4 (34.8)	
	SF-36 role emotional	82.5 (32.9)	45 (46.2)	
	SF-36 general health	63.1 (22.7)	50.6 (20.9)	
	SF-36 vitality	35.4 (25.8)	44.1 (24.9)	

	SF-36 social functioning	79.7 (28.7)	67.9 (23.9)	
	SF-36 mental health	75 (16.3)	66 (23.3)	
	SF-36 physical component summary	36.1 (9.57)	38.6 (8.68)	
	SF-36 mental component summary	53 (9.23)	45.2 (11.6)	

KCCQ, Kansas City Cardiomyopathy Questionnaire. SF-36, Short Form-36 questionnaire. SD, standard deviatio

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Chapter 5

5 Performance of frailty indices in predicting clinical outcomes of patients undergoing transcatheter aortic valve implantation

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5.1 Introduction

Transcatheter aortic valve implantation (TAVI) has been an alternative, less invasive treatment option for patients with severe symptomatic aortic stenosis for those who cannot undergo surgery or those at high risk for poor outcomes with surgical aortic valve replacement (SAVR).[1,2] Research on the benefits of TAVI compared to SAVR and medical management is ongoing. However, it has been recognized that some patients fail to benefit from TAVI.[3] Economic and clinical implications of TAVI are substantial.[4,5,6] Therefore, accurately identifying patient populations who are most likely to benefit from TAVI is of great significance to clinical decision-makers.[3]

Currently, indications for TAVI are mainly based on operative surgical risk. The majority of commonly used perioperative risk tools were adapted from the European system for cardiac operative risk evaluation (Euro SCORE) and the Society of Thoracic Surgeons (STS) score.[7] Although the two scoring systems have been used to estimate operative mortality after TAVI for many years, both scores have been criticized for not capturing the true 'biological status' of the patient.[7,8]

Frailty is a biological syndrome characterized by an increased vulnerability to stressors, and previous research has identified frailty as an important predictor of mortality and poor outcomes after TAVI. [9,10,11,12] When considering procedures for patients with valvular diseases, clinical guidelines recommend assessing frailty as one component of risk.[13] Despite a large number of frailty measures, there is little consensus on the optimal approach to assessing frailty in patients undergoing TAVI.[14,15]

Recent studies have derived and validated frailty indices using health administrative databases or electronic medical records.[16,17] Emerging evidence examined the impact of frailty on mortality, readmission and resource utilization after TAVI, suggesting that frailty, diagnosed using the administrative driven frailty indices, was associated with increased rates of mortality and readmission.[18] However, studies comparing the predictive performance of frailty indices remain limited. This study aims to examine the performance of databases driven frailty indices in predicting clinical outcomes of patients undergoing TAVI compared to a reference risk prediction model. If database driven

frailty measures demonstrate improved prediction of post-TAVI outcomes, then incorporating administrative database frailty indices into electronic records as a prognostic indicator may be a promising approach to implement in clinical settings.

5.2 Methods

5.2.1 Data sources

This retrospective cohort study utilized data from the CorHealth Ontario TAVI registry. Data from the CorHealth registry were linked to the administrative databases housed at the Institute for Clinical Evaluative Sciences (IC/ES) in Ontario, Canada. Linked administrative databases include Continuing Care Reporting System (CCRS), Discharge Abstract Database (DAD), Home Care Database (HCD), National Ambulatory Care Reporting System (NACRS), National Rehabilitation Reporting System (NRS), Ontario Drug Benefit Claims (ODB), Ontario Health Insurance Plan Claims Database (OHIP), Ontario Mental Health Reporting System (OMHRS), Same Day Surgery Database (SDS), Congestive Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD), Ontario Hypertension Dataset (HYPER), Ontario Census Area Profiles (CENSUS), Registered Persons Database (RPDB), Assistive Devices Program (ADP), Home Care Database (HCDMOH), Client Agency Program Enrolment (CAPE) and the Ontario Case Costing Initiative (OCCI). These datasets were linked using unique encoded identifiers and analyzed at ICES. Additional information about the databases, including the purpose of the database and the key parameters taken from the database, is provided in **Appendix A**.

5.2.2 Study cohort

Patients aged 66 or older who underwent a TAVI procedure in Ontario, Canada from April 1, 2012 to March 31, 2018 were included. Patient data were linked using encoded identifiers derived from the OHIP number to the administrative databases at the IC/ES. For patients who underwent repeat TAVI procedures, we considered the first procedure as the index event. Patients without a valid personal identification number were excluded.

5.2.3 Administrative database frailty indices

Two administrative database frailty indices, the Johns Hopkins Adjusted Clinical Group (ACG) frailty indicator and the Hospital Frailty Risk Score (HFRS), were used to assign frailty status, based on preprocedural patient characteristics. The Johns Hopkins ACG frailty indicator is a binary variable that dichotomizes patients as frail and non-frail based on 12 clusters of frailty-defining diagnoses (**Appendix B**).[17,19] The Johns Hopkins ACG frailty indicator is a proprietary index. Thus, specific diagnostic codes used to assign the clusters are not publicly available. The Johns Hopkins ACG frailty indicator has been used to identify frail patients in previous research.[17,19] The HFRS is a frailty score developed and validated based on more than 100 International Statistical Classification of Diseases (ICD-10) diagnostic codes.[20] Each diagnostic code is assigned a score and the HFRS is calculated based on the codes (**Appendix C**). The HFRS dichotomized patients as frail (>5 points) and non-frail (≤5 points).[20] The HFRS also categorized patients as high-risk (>15 points), intermediate-risk (5-15 points) and low-risk (<5 points) based on frailty risk.[20] To facilitate comparison between the two indices, this study focused on the dichotomous measure of the HFRS.

5.2.4 Outcomes

The primary outcome was death from any cause at 1 year and secondary outcomes were in-hospital death and 1-year rehospitalization. In-hospital deaths during the index hospitalization were identified from the DAD. Deaths after discharge were identified from the RPDB. Rehospitalization was identified from the NACRS and DAD (**Appendix D**).

5.2.5 Baseline variables

Demographic data, including age, gender, rural residence and income quintile, were collected from the RPDB. Comorbidities, including myocardial infarction, ischemic heart disease, atrial fibrillation, peripheral vascular disease, cerebrovascular disease, cancer and dialysis, were identified based on ICD diagnostic codes from the DAD and OHIP fee codes in the 3 years preceding TAVI. Cardiac history, including previous coronary artery bypass graft surgery, valve surgery, percutaneous coronary intervention, valve-in-valve

surgery, permanent pacemaker and implantable cardiac defibrillator, were identified from the DAD and OHIP the 20 years preceding TAVI. Coronary heart failure, chronic obstructive pulmonary disease, hypertension and diabetes mellitus were identified from the corresponding IC/ES databases. Dyslipidemia and dementia were identified using validated algorithms.[21,22] Preprocedural and procedural data, including serum creatinine, anesthesia, hemoglobin, transvalvular gradient, STS score, access site and valve type, were collected from the CorHealth database (**Appendix D**). Several baseline covariates were adjusted in frailty indices. Dementia is a frailty-defining diagnose in Johns Hopkins ACG frailty indicator. Dementia and cardiovascular diseases are health deficits included in HFRS.

5.2.6 Statistical analysis

Characteristics were compared between frail and non-frail groups for both the ACG and HFRS. Continuous variables were presented as mean (standard deviation [SD]) and compared using the t-test. Categorical variables were presented as proportions and compared using the chi-square test. Less sensitive to large sample sizes, standardized differences were calculated.[23] Standardized differences greater than 0.1 were considered meaningful differences.[23]

The prevalence of frailty was estimated by dividing the number of frail patients by the total number of patients. Kappa was calculated to assess the agreement between the ACG frailty indicator and HFRS.[24] To better understand the differences between the frailty indices we compared frailty categorization within subgroups of demographic and clinical variables.

A hierarchical clustering regression model adjusting for demographics, baseline comorbidities, cardiac history and preprocedural characteristics was fitted as the reference model. The reference model was pre-specified. Given the data availability, the reference model included demographic and clinical variables that have been shown to predict post-TAVI prognosis and adjusted for as many of the EuroSCORE and STS score variables as possible. Frailty indices were added to the reference model individually to test the significance of frailty in predicting death at one year, in-hospital death and 1-year

rehospitalization. Multicollinearity in the model was examined using the variance inflation factor and tolerance.

To compare the reference model and each model with frailty indices, we reported the following performance statistics: c-statistic, Akaike information criterion (AIC), Bayesian information criterion (BIC), integrated discrimination improvement (IDI) and net reclassification index (NRI).[25] The c-statistic, or the receiver-operating-characteristic (ROC) curve, is a traditional measure of discrimination.[26] The c-statistic assesses each risk prediction model's ability to separate patients who will develop the event of interest from patients who will not.[25,26] A larger c-statistic indicates improved discrimination.[25,26] The AIC and BIC are widely used tools in model selection. The AIC and BIC allow for simultaneous comparison of multiple models, with more negative values indicating improved prediction.[27,28,29] Both the IDI and NRI are considered novel measures to assess improvement in model performance offered by a new predictor.[25,30] The IDI assesses the ability of a new model to improve average sensitivity without sacrificing average specificity, with more positive values indicating improved prediction.[25,30] The NRI quantifies the improvement in model performance and is calculated based on the number of patients correctly reclassified by adding a new predictor, with more positive value indicating improved prediction.[25,30]

We performed a sensitivity analysis, to account for death as a competing risk for rehospitalization. We built a competing risk Cox model, with sandwich variance estimators to account for clustering by institution, in order to estimate the effect of frailty on the hazard of rehospitalization with death as a competing risk.[31,32] We compared the findings on the association between frailty and rehospitalization, with that of the frailty in hierarchical clustering regression model.

SAS Enterprise 7.1 was used for all analyses; p-values of <0.05 were considered significant.

5.3 Results

5.3.1 Characteristics of the cohort

A total of 3,866 patients were included. A total of 867 patients (22.4%) were diagnosed as frail using the Johns Hopkins ACG indicator and 870 patients (22.5%) were diagnosed as frail using the HFRS (**Table 5.1**).

Table 5.1 Prevalence of frailty

Frailty assessed with Johns Hopkins ACG frailty indicator	Frail	867 (22.4%)
	Non-frail	2999 (77.6%)
Johns Hopkins ACG frailty score, mean (SD)		12.81 (3.64)
Frailty assessed with HFRS	Frail (>5)	870 (22.5%)
	Non-frail (≤5)	2996 (77.5%)
HFRS, mean (SD)		3.21 (4.64)
Frailty assessed with HFRS	<5	2974 (76.9%)
	5≤ and ≤15	739 (19.1%)
	>15	153 (4.0%)

ACG, adjusted clinical groups. HFRS, Hospital Frailty Risk Score. SD, standard deviation.

Overall, the agreement between the Johns Hopkins ACG frailty indicator and the HFRS was fair (Kappa statistic=0.3236, 95% confidence interval [CI], 0.2888-0.3582) (**Table 5.2**). Comparison of frailty categorization within subgroups of demographic and clinical variables indicated fair agreement between the frailty indices (**Table 5.3**). The Kappa statistic between the two frailty indices ranged from 0.1084 (dementia) to 0.4544 (cognitive impairment/ dementia) (**Table 5.3**).

Table 5.2 Agreement between the HFRS and Johns Hopkins ACG frailty indicator

	Non-frail defined by HFRS	Frail defined by HFRS	Total
Non-frail defined by ACG	2,524	457	2,999
Frail defined by ACG	454	413	867
Total	2,996	870	3,866
Kappa: 0.3236 (SE:0.0177); 95% CI: 0.2888-0.3583			

ACG, adjusted clinical groups. HFRS, Hospital Frailty Risk Score. CI, confidence interval.

Table 5.3 Comparison of frailty categorization within subgroups of demographic and clinical variables

Variables	**Total N**	**Frail defined by ACG**	**Frail defined by HFRS**	**Frail defined by ACG and HFRS**	**Kappa statistic**
Age 66-70	160	31 (19.38%)	50 (31.25%)	22 (13.75%)	0.3996 (0.2455-0.5537)
Age 71-75	388	84 (21.65%)	96 (24.74%)	44 (11.34%)	0.3354 (0.2274-0.4434)
Age 76-80	706	151 (21.39%)	159 (22.52%)	76 (10.76%)	0.3471 (0.2655-0.4286)

Age 81-85	1,138	267 (23.46%)	252 (22.14%)	122 (10.72%)	0.3138 (0.2500-0.3776)
Age 86-90	1,143	261 (22.83%)	247 (21.61%)	113 (9.89%)	0.2864 (0.2222-0.3507)
Age >90	331	73 (22.05%)	66 (19.94%)	36 (10.88%)	0.3903 (0.2707-0.5099)
Female	1,739	421 (24.21%)	407 (23.40%)	202 (11.62%)	0.3280 (0.2771-0.3788)
Male	2,127	446 (20.97%)	463 (21.77%)	211 (9.92%)	0.3187 (0.2711-0.3663)
Income quintile 1	748	194 (25.94%)	191 (25.53%)	99 (13.24%)	0.3460 (0.2705-0.4215)
Income quintile 2	843	198 (23.49%)	197 (23.37%)	98 (11.63%)	0.3421 (0.2688-0.4153)
Income quintile 3	802	158 (19.70%)	175 (21.82%)	72 (8.89%)	0.2842 (0.2060-0.3624)
Income quintile 4	709	156 (22.00%)	154 (21.72%)	69 (9.73%)	0.2899 (0.2079-0.3720)

Income quintile 5	764	161 (21.07%)	153 (20.03%)	75 (9.82%)	0.3427 (0.2626-0.4229)
Rural residence	430	93 (21.63%)	88 (20.47%)	42 (9.77%)	0.3214 (0.2151-0.4277)
Myocardial infarction	460	145 (31.52%)	211 (45.87%)	105 (22.83%)	0.3452 (0.2621-0.4283)
Ischemic heart disease	2,746	605 (22.03%)	658 (23.96%)	306 (11.14%)	0.3310 (0.2901-0.3718)
History of heart failure	2,723	677 (24.86%)	740 (27.18%)	352 (12.93%)	0.3202 (0.2807-0.3599)
Heart failure hospitalization within 90 days	461	138 (29.93%)	193 (41.87%)	89 (19.31%)	0.2899 (0.2030-0.3767)
Previous PCI	1,276	279 (21.87%)	324 (25.39%)	153 (11.99%)	0.3562 (0.2973-0.4151)
Previous CABG	826	140 (16.95%)	158 (19.13%)	58 (7.02%)	0.2554 (0.1751-0.3358)
Previous ICD	57	12 (21.05%)	15 (26.32%)	7 (12.28%)	0.3715 (0.0954-0.6476)

Previous valve surgery	421	83 (19.71%)	96 (22.80%)	41 (9.74%)	0.3128 (0.2059-0.4196)
Previous permanent pacemaker	356	95 (26.69%)	95 (26.69%)	57 (16.01%)	0.4544 (0.3502-0.5586)
COPD	1,373	327 (23.82%)	370 (26.95%)	167 (12.16%)	0.3029 (0.2467-0.3592)
Cognitive impairment/ dementia	294	253 (86.05%)	116 (39.46%)	109 (37.07%)	0.1084 (0.0465-0.1703)
Hypertension	3,643	818 (22.45%)	832 (22.84%)	393 (10.79%)	0.3231 (0.2874-0.3588)
Dyslipidemia	2,520	534 (21.19%)	569 (22.58%)	260 (10.32%)	0.3236 (0.2802-0.3669)
Cancer	271	68 (25.09%)	94 (34.69%)	40 (14.76%)	0.2859 (0.1670-0.4048)
Cerebrovascular disease	214	95 (44.39%)	127 (59.35%)	75 (35.05%)	0.3409 (0.2216-0.4602)
Atrial fibrillation	1,145	316 (27.60%)	393 (34.32%)	186 (16.24%)	0.3151 (0.2573-0.3730)

Peripheral vascular disease	253	60 (23.72%)	85 (33.60%)	38 (15.02%)	0.3409 (0.2183-0.4634)
Dialysis	117	39 (33.33%)	73 (62.39%)	32 (27.35%)	0.2421 (0.0903-0.3849)
ED visit before TAVI (within 1 year)	2,781	727 (26.14%)	788 (28.34%)	375 (13.48%)	0.3064 (0.2676-0.3453)
Anemia	1,600	390 (24.38%)	434 (27.13%)	196 (12.25%)	0.2946 (0.2426-0.3466)
Creatinine (u mol/L) ≥120	61	SC	SC	SC	0.3453 (0.0610-0.6295)

ACG, Johns Hopkins Adjusted Clinical Groups frailty indicator. **HFRS,** Hospital Frailty Risk Score. **N**, sample size. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department. **STS**, Society of Thoracic Surgeons. **SC**, small cell.

Frail and non-frail groups had marked differences in their demographics and procedural characteristics (**S Table 5.1, S Table 5.2, S Table 5.3** and **S Table 5.4**). Diagnosed using the Johns Hopkins ACG frailty indicator, frailty prevalence was significantly higher in patients with myocardial infarction, history of heart failure, heart failure hospitalization, dementia, cerebrovascular disease, atrial fibrillation and emergency department visit before TAVI procedure (**S Table 5.1**). In addition to these patient factors, ischemic heart disease, previous percutaneous coronary intervention, chronic obstructive pulmonary disease, hypertension, cancer, peripheral vascular disease, dialysis and anemia were

associated with a higher frailty prevalence when frailty was diagnosed using the HFRS (**S Table 5.2**). Regardless of the frailty indices, frailty prevalence was significantly lower in patients with previous coronary artery bypass graft surgery (**S Table 5.1** and **S Table 5.2**). Differences in patient characteristics were more dramatic when frailty was diagnosed using the HFRS as higher standardized differences were observed, except baseline dementia. Standardized differences in dementia between frail and non-frail patients when frailty was diagnosed using the Johns Hopkins ACG frailty indicator and the HFRS were 0.84 and 0.25, respectively (**S Table 5.1** and **S Table 5.2**).

Clinical outcomes by frailty were shown in **S Table 5.5** and **S Table 5.6**. At one-year follow-up, a total of 556 deaths occurred. In-hospital death and 12-month rehospitalization occurred in 164 and 2,577 cases, respectively. Regardless of the frailty indices, frail patients were significantly associated with increased rates of death at 1-year, bleeding, readmission, emergency department visit after discharge and rehospitalization. Frail patients, diagnosed with the HFRS, were also associated with an increased rate of in-hospital death (**S Table 5.6**). Regardless of the frailty indices, frail patients were associated with a longer hospital stay. Differences in clinical outcomes were more dramatic when frailty was diagnosed using the HFRS that using the Johns Hopkins ACG frailty indicator.

5.3.2 Frailty and one-year mortality, in-hospital mortality and rehospitalization

Adjusting for demographics and comorbidities, both the Johns Hopkins ACG indicator (odds ratio [OR], 1.424; 95% CI, 1.128-1.798) and HFRS (OR, 1.278; 95% CI, 1.018-1.605) were significantly associated with one-year mortality (**S Table 5.7** and **S Table 5.8**). Neither the Johns Hopkins ACG indicator (OR, 1.230; 95% CI, 0.825-1.834) nor the HFRS (OR, 1.110; 95% CI, 0.751-1.642) were significantly associated with in-hospital mortality (**S Table 5.9** and **S Table 5.10**). Both Johns Hopkins ACG indicator (OR, 1.681; 95% CI, 1.346-2.098) and HFRS (OR, 1.526; 95% CI, 1.232-1.890) were significantly associated with rehospitalization at one year (**S Table 5.11** and **S Table 5.12**).

S Table 5.13 and **S Table 5.14** display the sensitivity analysis results. Adjusting for death as a competing risk for rehospitalization, the competing risk Cox model suggested that both Johns Hopkins ACG frailty indicator (hazard ratio, 1.195; 95% CI, 1.083-1.318) and HFRS (hazard ratio, 1.177; 95% CI, 1.073-1.291) were significantly increased the hazard of rehospitalization.

5.3.3 Predictive performance of Johns Hopkins ACG frailty indicator and HFRS

Compared to a reference model, both the Johns Hopkins ACG frailty indicator (ΔAIC, -7; ΔBIC, -6; Δc-statistics, 0.002 [p=0.3548]; IDI, 0.003 [p=0.0033]; NRI, 0.154 [p=0.0008]) and HFRS (ΔAIC, -3; ΔBIC, -2; Δc-statistics, 0.03 [p=0.1747]; IDI, 0.001 [p=0.2043]; NRI, 0.116 [p=0.0115)] demonstrated improved prediction for one-year mortality (**Table 5.4**). Neither the Johns Hopkins ACG frailty indicator (ΔAIC, 1; ΔBIC, 2; Δc-statistics, 0.000 [p=0.9408]; IDI, -0.001 [p=0.1023]; NRI, -0.046 [p=0.5653]) nor the HFRS (ΔAIC, 1; ΔBIC, 3; Δc-statistics, 0.000 [p=0.8008]; IDI, 0.000 [p=0.3746]; NRI, -0.114 [p=0.1526]) demonstrated improved prediction for in-hospital mortality (**Table 5.4**). Compared to a reference model, both the Johns Hopkins ACG frailty indicator (ΔAIC, -19; ΔBIC, -20; Δc-statistics, 0.006 [p=0.0362]; IDI, 0.005 [p<0.0001]; NRI, 0.205 [p<0.0001]) and HFRS (ΔAIC, -14; ΔBIC, -13; Δc-statistics, 0.005 [p=0.0691]; IDI, 0.004 [p=0.0002]; NRI, 0.142 [p<0.0001]) demonstrated improved prediction for rehospitalization (**Table 5.4**).

The reclassification table shows the number of patients correctly reclassified by adding frailty to the reference model (**S Table 5.15**). As shown, when predicting death at 1-year and rehospitalization, both the Johns Hopkins ACG frailty indicator and HFRS improved the ability to classify patients without outcomes but decreased the ability to classify those with outcomes. In contrast, when predicting in-hospital death, both the Johns Hopkins ACG frailty indicator and HFRS improved the ability to classify patients with outcomes but decreased the ability to classify those without outcomes.

Table 5.4 Predictive performance of Johns Hopkins ACG frailty indicator and HFRS compared to a reference model

Models	**Adjusted OR (95% CI)**	**ΔAIC**	**ΔBIC**	**Δc statistic**	**IDI**	**NRI**
1-year mortality						
Johns Hopkins ACG frailty indicator (**S Table 5.7**)	**1.424 (1.128-1.798)**	-7	-6	0.002 (p=0.3548)	**0.003 (p=0.0033)**	**0.154 (p=0.0008)**
HFRS (**S Table 5.8**)	**1.278 (1.018-1.605)**	-3	-2	0.003 (p=0.1747)	0.001 (p=0.2043)	**0.116 (p=0.0115)**
In-hospital mortality						
Johns Hopkins ACG frailty indicator (**S Table 5.9**)	1.230 (0.825-1.834)	1	2	0.000 (p=0.9408)	-0.001 (p=0.1023)	-0.046 (p=0.5653)
HFRS (**S Table 5.10**)	1.110 (0.751-1.642)	1	3	0.000 (p=0.8008)	0.000 (p=0.3746)	-0.114 (p=0.1526)
Rehospitalization						
Johns Hopkins ACG frailty indicator	**1.681 (1.346-2.098)**	-19	-20	**0.006 (p=0.0362)**	**0.005 (p<0.0001)**	**0.205 (p<0.0001)**

(**S Table 5.11**)						
HFRS (**S Table 5.12**)	**1.526** **(1.233-1.890)**	-14	-13	0.005 (p=0.0691)	**0.004** **(p=0.0002)**	**0.142** **(p<0.0001)**

Reference model covariates include age, gender, income quintile, rural residence, MI, ischemic heart disease, heart failure, previous CABG, previous PCI, previous valve surgery, previous ICD, valve-in-valve, previous permanent pacemaker, COPD, dementia, hypertension, dyslipidemia, cancer, CVD, AF, PVD, dialysis, ED visit before TAVI, anemia, creatinine, access site, and year of procedure.

5.4 Discussion

Drawing on data from the Ontario TAVI cohort and the linked data derived from administrative databases housed at the IC/ES, we found poor agreement between the Johns Hopkins ACG frailty indicator and the HFRS, despite similar proportions of frail patients diagnosed. Adjusting for demographics and baseline comorbidities, both the Johns Hopkins ACG frailty indicator and the HFRS were significantly associated with one-year mortality and rehospitalization at 12 months following TAVI, but not in-hospital mortality. Comparing predictive accuracy between the reference model and each model with frailty indices, we found that Johns Hopkins ACG frailty indicator and HFRS improved classification in predicting one-year mortality and rehospitalization at 12 months.

Key differences amongst the administrative database frailty algorithms may contribute to differences in performance for identifying frail patients. Despite similar proportions of frail patients identified, the agreement between the two frailty indices was poor. An important reason might be the frailty indices included different health deficits. Literature has listed frailty-defining diagnoses in Johns Hopkins ACG frailty indicator, including

malnutrition, dementia, impaired vision, decubitus ulcer, incontinence of urine, loss of weight, poverty, barriers to access to care, difficulty in walking and fall.[33] The HFRS is a frailty risk score developed and validated based on 109 ICD-10 codes.[20] Some deficits are included in both the Johns Hopkins ACG frailty indicator and the HFRS, such as dementia in Alzheimer's disease, unspecified fall, blindness and low vision, decubitus ulcer, fall involving bed and fall on and from stairs and steps. However, most of deficits are included in the HFRS but not included in Johns Hopkins ACG frailty indicator.[20] Additionally, different weights assigned to the diagnoses may also lead to a low agreement between Johns Hopkins ACG frailty indicator and HFRS. Each ICD-10 code in the HFRS is assigned a weight, which was proportional to the association between the diagnosis code and adverse outcomes.[20] Of the 109 ICD-10 codes, dementia in Alzheimer's disease, hemiplegia, Alzheimer's disease, sequelae of cerebrovascular disease and other symptoms and signs involving the nervous and musculoskeletal systems are the five codes assigned with highest weights.[20] Due to the proprietary nature of the ACG system, specific codes are not public available and thus it is not possible to compare the weighting between the two codes.[33]

The clinical significance of our findings is that preoperative frailty assessment may add predictive value for clinical outcomes after TAVI. The performance of a statistical prediction model is usually assessed using discrimination and calibration.[30] Assessment of discrimination with the c-statistic has been criticized because the increase in the c-statistic is often small.[25] Emerging evidence has suggested that the reclassification index offers insights into the value of adding a new predictor to a reference model, and the NRI can quantify the improvement in reclassification.[30] While we did not find statistically significant improvements in the c-statistic, we found that both Johns Hopkins ACG frailty indicator and HFRS improved classification in predicting one-year mortality and rehospitalization at 12 months, suggesting frailty measurably improve the predictive value compared to the reference model. The improvement in classification, or NRI, considers the ability to classify patients who develop adverse outcomes and classify those who do not develop adverse outcomes separately.[25] Reclassification tables show that the improved classification of the models with frailty indices is mainly attributed to the

increased ability to classify patients without adverse outcomes. The decreased ability to classify those with adverse outcomes correctly may limit the utility in identifying patients at high risk for outcomes after TAVI, such as death at one-year, in-hospital death and rehospitalization at 12 months.

Previous research has demonstrated that frailty is independently associated with adverse outcomes after TAVI, suggesting the value of frailty measures in predicting clinical outcomes after TAVI.[18,34,35,36] However, few studies investigated the impacts of frailty diagnosed using the administrative driven indices. Malik et al[18] examined the impact of frailty diagnosed using the HFRS on post-TAVI outcomes. The authors categorized patients into three frailty categories, and found that an increasing frailty was associated with poorer post-TAVI outcomes.[18] Further to this, emerging research reveals the incremental predictive value of frailty compared with existing risk prediction models for TAVI recipients. Afilalo et al.[37] compared the predictive value of seven different frailty scales to predict poor outcomes after TAVI or SAVR, and found that frailty, regardless of the measure, adds incremental value above existing risk prediction models. This study [37] reported c-statistic, BIC and IDI but did not calculate NRI. The study [37] concluded that frailty, defined with weakness, cognitive impairment, anemia and hypoalbuminemia, performed the best amongst other frailty measures. Current guidelines recommend assessing frailty in preoperative risk assessment, as existing risk prediction models for TAVI do not capture frailty and may not reflect patients' true biological status. [13,38] Preoperative assessment of frailty also provides additional information for patient selection, ultimately assisting in medical decision-making regarding therapeutic options for patients with aortic stenosis.[13]

While frailty has been increasingly recognized as an essential predictor of outcomes after TAVI, assessment of frailty has not been widely adopted in preoperative evaluation and decision-making. An important barrier to the preoperative assessment of frailty is the lack of an international standard measurement of frailty.[15] Fried frailty phenotype remains the most commonly used frailty measure.[15] However, assessment of frailty phenotype can be time-consuming and subject to inter-operator variability, limiting its extensive use in surgical populations. In settings where clinical frailty measures are rarely available,

administrative database frailty indices have been strongly recommended.[39] Derived and validated using health administrative data, administrative database algorithms have unique advantages. For example, administrative database frailty indices can potentially be encoded and utilized wherever electronic health data are available.[20,39] On the other hand, use of administrative database frailty indices can remove the inter-operator variability and operationalize burden associated with manual scoring systems.[20,39]

This study has several unique strengths. We captured all patients aged 66 or older who underwent a TAVI procedure from 2012 to 2018 in Ontario, Canada. The inclusion of this representative patient cohort reduces selection bias, ensuring the generalizability of our findings. In addition, since both Johns Hopkins ACG frailty indicator and HFRS have been encoded and validated in the IC/ES system, the two frailty indices being tested were calculated accurately with linked health administrative data. Furthermore, we comprehensively examined the performance of the two administrative database frailty indices in predicting clinical outcomes. We believe our findings will help advance knowledge on more widespread use of these frailty indices and help clinicians determine the performance of frailty when compared to common risk-adjustment methods.

Our study has some important limitations. First, the HFRS was developed and validated based on a cohort of patients aged 75 years and older with elective, non-elective and day-case admissions to hospitals,[20] while our study cohort was restricted to patients aged 66 years and older who underwent a TAVI procedure. HFRS has been increasingly used as a tool to identify high-risk patients for in-hospital death and complications, and recent research has investigated its use in TAVI recipients.[40] Second, we only tested the performance of frailty indices in predicting outcomes for up to one year. Long-term outcomes were not examined. Third, restricted by the availability of data housed at IC/ES, we were unable to adjust for all variables that have been demonstrated to have impacts on outcome variables, such as New York Heart Association classification and left ventricular ejection fraction.[41,42,43] Fourth, given the limitations underlying linked health administrative data, our study may be subject to possible inaccuracies in administrative database codes. For example, there might be variations or errors in documentation and coding, leading to measurement errors. Fifth, for the purpose of risk

prediction, our study only focused on the predictive value of binary frailty measures. Using of a binary variable may lose information offered by a continuous variable.

In conclusion, the agreement between the Johns Hopkins ACG frailty indicator and the HFRS was low. Key differences amongst the two frailty indices may lead to differences in performance for identifying frail patients. Preoperative assessment of frailty may add predictive value for clinical outcomes after TAVI.

5.5 Supplementary tables

S Table 5.1 Preprocedural characteristics of patients undergoing TAVI frail versus non-frail diagnosed with the Johns Hopkins ACG frailty indicator

Variable name	**Frail (N=867)**		**Non-frail (N=2,999)**		**Standardized difference***	**p-value**
	N	%	N	%		
Demographics						
Age						0.8112
66-70	31	3.6%	129	4.3%	-0.04	
71-75	84	9.7%	304	10.1%	-0.01	
76-80	151	17.4%	555	18.5%	-0.03	
81-85	267	30.8%	871	29.0%	0.04	
86-90	261	30.1%	882	29.4%	0.02	
>90	73	8.4%	258	8.6%	-0.01	

Females	421	48.6%	1,318	43.9%	0.09	0.0162
Income quintile						0.0381
1	194	22.4%	554	18.5%	0.10	
2	198	22.8%	645	21.5%	0.03	
3	158	18.2%	644	21.5%	-0.08	
4	156	18.0%	553	18.4%	-0.01	
5	161	18.6%	603	20.1%	-0.04	
Rural residence	93	10.7%	337	11.2%	-0.02	0.6737
Comorbidities						
Myocardial infarction	145	16.7%	315	10.5%	0.18	<0.0001
Ischemic heart disease	605	69.8%	2,141	71.4%	-0.04	0.3575
History of heart failure	677	78.0%	2,046	68.2%	0.22	<0.0001
Heart failure hospitalization within 90 days	138	15.9%	323	10.8%	0.15	<0.0001
Previous PCI	279	32.2%	997	33.2%	-0.02	0.5572
Previous CABG	140	16.1%	686	22.9%	-0.17	<0.0001
Previous valve surgery	83	9.6%	338	11.2%	-0.05	0.1577
Previous ICD	12	1.4%	45	1.5%	-0.01	0.8022

Previous permanent pacemaker	95	11.0%	261	8.7%	0.08	0.0432
COPD	327	37.7%	1,046	34.9%	0.06	0.1241
Cognitive impairment/ dementia	253	29.2%	41	1.4%	0.84	<0.0001
Hypertension	818	94.3%	2,825	94.2%	0.01	0.8673
Dyslipidemia	534	61.6%	1,986	66.2%	-0.10	0.0117
Cancer	68	7.8%	203	6.8%	0.04	0.2752
Cerebrovascular disease	95	11.0%	119	4.0%	0.27	<0.0001
Atrial fibrillation	316	36.4%	829	27.6%	0.19	<0.0001
Peripheral vascular disease	60	6.9%	193	6.4%	0.02	0.6111
Dialysis	39	4.5%	78	2.6%	0.10	0.0041
ED visit before TAVI (within 1 year)	727	83.8%	2,054	68.5%	0.37	<0.0001
Anemia						<0.05
No	159	18.3%	674	22.5%	-0.10	
Yes	390	45.0%	1,210	40.3%	0.09	
Missing	318	36.7%	1,115	37.2%	-0.01	
Mean hemoglobin (data available in 2,433 patients)	118.80	16.56	122.60	17.84	0.22	<0.0001

Creatinine (u mol/L)						0.9808
<120	522	60.2%	1,816	60.6%	-0.01	
≥120	14	1.61%	47	1.57%	-0.00	
Missing	331	38.2%	1,136	37.9%	0.01	
Mean creatinine (data available in 2,399 patients)	52.86	42.83	55.16	35.14	0.06	0.2050
STS score (data available in 2,887 patients)	7.02	5.75	6.44	5.09	0.11	<0.05
Transvalvular gradient (data available in 2,359 patients)	44.18	16.36	44.11	16.24	0.004	0.9325

ACG, adjusted clinical groups. **N**, sample size. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department. **STS**, Society of Thoracic Surgeons

S Table 5.2 Preprocedural characteristics of patients undergoing TAVI frail versus non-frail diagnosed with the HFRS

Variable name	Frail (N=870)		Non-frail (N=2,996)		Standardized difference*	p-value
	N	%	N	%		
Demographics						
Age						0.0755
66-70	50	5.8%	110	3.7%	0.10	
71-75	96	11.1%	292	9.7%	0.04	
76-80	159	18.3%	547	77.5%	0.00	
81-85	252	29.1%	886	29.5%	-0.01	
86-90	247	28.5%	896	30.0%	-0.03	
>90	66	7.6%	265	8.8%	-0.04	
Females	407	46.9%	1,332	44.4%	0.05	0.2255
Income quintile						0.1137
1	191	22.0%	557	18.6%	0.09	
2	197	22.7%	646	21.5%	0.03	
3	175	20.2%	627	21.0%	-0.02	
4	154	17.8%	555	18.5%	-0.02	
5	153	17.6%	611	20.4%	-0.07	

Rural residence	88	10.1%	342	11.4%	-0.04	0.2829
Comorbidities						
Myocardial infarction	211	24.3%	249	8.3%	0.44	<0.0001
Ischemic heart disease	658	75.9%	2,088	69.6%	0.14	<0.001
History of heart failure	740	85.4%	1,983	66.1%	0.46	<0.0001
Heart failure hospitalization within 90 days	193	22.3%	268	8.9%	0.37	<0.0001
Previous PCI	324	37.4%	952	31.7%	0.12	<0.01
Previous CABG	158	18.2%	668	22.3%	-0.10	<0.01
Previous valve surgery	96	11.1%	325	10.8%	0.01	0.8763
Previous ICD	15	1.73%	42	1.40%	0.03	0.4875
Previous permanent pacemaker	95	11.0%	261	8.70%	0.08	<0.05
COPD	370	42.7%	1,003	33.4%	0.19	<0.0001
Cognitive impairment/ dementia	116	13.4%	178	5.94%	0.25	<0.0001
Hypertension	832	96.0%	2,811	93.7%	0.10	<0.05
Dyslipidemia	569	65.6%	1,951	65.0%	0.01	0.8778
Cancer	94	10.8%	177	5.9%	0.18	<0.0001
Cerebrovascular disease	127	14.6%	87	2.9%	0.42	<0.0001
Atrial fibrillation	393	45.3%	752	25.1%	0.43	<0.0001

Peripheral vascular disease	85	9.8%	168	5.6%	0.16	<0.0001
Dialysis	73	8.4%	44	1.5%	0.32	<0.0001
ED visit before TAVI (within 1 year)	788	90.9%	1,993	66.4%	0.62	<0.0001
Anemia						<0.0001
No	118	13.6%	715	23.8%	-0.26	
Yes	434	50.1%	1,166	38.9%	-0.23	
Missing	318	36.7%	1,115	37.2%	-0.01	
Mean hemoglobin (data available in 2,433 patients)	115.6	16.49	123.5	17.55	0.46	
Creatinine (u mol/L)						0.2076
<120	531	61.2%	1,807	60.3%	0.02	
≥120	8	0.9%	53	1.8%	-0.07	
Missing	331	38.2%	1,136	37.9%	0.01	
Mean creatinine (data available in 2,399 patients)	46.74	23.62	56.93	39.76	0.31	<0.0001
STS score (data available in 2,887 patients)	7.87	6.17	6.20	4.89	0.30	<0.0001
Transvalvular gradient	42.51	15.78	44.58	16.37	0.13	<0.05

(data available in 2,359 patients)						

HFRS, Hospital Frailty Risk Score. **N**, sample size. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department. **STS**, Society of Thoracic Surgeons.

S Table 5.3 Procedural characteristics of patients undergoing TAVI frail versus non-frail diagnosed with the Johns Hopkins ACG frailty indicator

Variable name	Frail (N=867)		Non-frail (N=2,999)		Standardized difference*	p-value
	N	%	N	%		
Anesthesia						0.8029
General	568	65.5%	1,949	65.0%	0.01	
Local	277	31.9%	983	32.8%	-0.02	
Missing	22	2.5%	67	2.2%	0.02	
Access site						0.4504
Transfemoral	761	87.8%	2,603	86.8%	0.03	
Non-transfemoral	106	12.2%	396	13.2%	-0.03	
Procedure status						<0.05
Elective	774	89.3%	2,764	92.2%	-0.10	
Urgent/ emergent	93	10.7%	235	7.8%	0.10	
Valve type						0.7247
Edwards Life Sciences	380	43.8%	1,378	45.9%	-0.04	
Medtronic Core Vale	264	30.4%	889	29.6%	0.02	
Other	64	7.4%	215	7.2%	0.01	
Missing	159	18.3%	517	17.2%	0.03	

Valve-in-valve	74	8.5%	301	10.0%	-0.05	0.1883
Year of procedure						0.4800
2012	67	7.7%	230	7.7%	0.00	
2013	95	11.0%	355	11.8%	-0.03	
2014	120	13.8%	491	16.4%	-0.07	
2015	165	19.0%	542	18.1%	0.02	
2016	191	22.0%	643	21.4%	0.01	
2017	229	26.4%	738	24.6%	0.04	

ACG, adjusted clinical groups. **N**, sample size. **TAVI**, transcatheter aortic valve implantatio

S Table 5.4 Procedural characteristics of patients undergoing TAVI frail versus non-frail diagnosed with the HFRS

Variable name	**Frail (N=870)**		**Non-frail (N=2,996)**		**Standardized difference***	**p-value**
	N	%	N	%		
Anesthesia						0.0979
General	593	68.4%	1,924	64.2%	0.09	
Local	258	29.8%	1,002	33.4%	-0.08	
Missing	19	2.2%	70	2.3%	-0.01	
Access site						<0.05
Transfemoral	738	85.1%	2,626	87.6%	-0.07	
Non-transfemoral	132	15.2%	370	12.3%	0.08	
Procedure status						<0.0001
Elective	764	88.1%	2,774	92.5%	-0.15	
Urgent/ emergent	106	12.2%	222	7.4%	0.16	
Valve type						0.5051
Edwards Life Sciences	379	43.7%	1,379	46.0%	-0.05	
Medtronic Core Vale	269	31.0%	884	29.5%	0.03	

Other	60	6.9%	219	7.3%	-0.01	
Missing	162	18.7%	514	17.1%	0.04	
Valve-in-valve	94	10.8%	281	9.4%	0.05	0.2111
Year of procedure						0.2770
2012	60	6.9%	237	7.9%	-0.04	
2013	109	12.6%	341	11.4%	0.04	
2014	150	17.3%	461	15.4%	0.05	
2015	168	19.4%	539	18.0%	0.04	
2016	186	21.5%	648	21.6%	-0.004	
2017	197	22.7%	770	25.7%	-0.07	

HFRS, Hospital Frailty Risk Score. **N**, sample size. **TAVI**, transcatheter aortic valve implantation.

S Table 5.5 Clinical outcomes of patients undergoing TAVI frail versus non-frail diagnosed with the Johns Hopkins ACG frailty indicator

Variable name	Frail (N=867)		Non-frail (N=2,999)		Standardized difference*	p-value
	N	%	N	%		
Death at 1-year (N=3,866)	172	19.8%	384	12.8%	0.19	<0.0001
In-hospital outcomes (N=3,866)						
In-hospital death	49	5.7%	115	3.8%	0.09	<0.05
Stroke	25	2.9%	62	2.1%	0.05	0.1536
Permanent pacemaker	110	12.7%	394	13.1%	-0.01	0.7287
Bleeding						<0.01
Major	70	8.1%	151	5.0%	0.12	
Minor	38	4.4%	107	3.6%	0.04	
No bleeding	759	87.5%	2,741	91.4%	-0.13	
Length of hospitalization	12.50	20.33	9.26	17.53	0.17	<0.0001
Outcomes after discharge (N=3,702)						
Readmission	452	52.1%	1,215	40.5%	0.23	<0.0001

ED visit after discharge	636	73.4%	1,851	61.7%	0.25	<0.0001
Rehospitalization	655	75.5%	1,922	64.1%	0.25	<0.0001

ACG, adjusted clinical groups. **N**, sample size. **TAVI**, transcatheter aortic valve implantation. **ED**, emergency department.

S Table 5.6 Clinical outcomes of patients undergoing TAVI frail versus non-frail diagnosed with the HFRS

Variable name	**Frail (N=870)**		**Non-frail (N=2,996)**		**Standardized difference***	**p-value**
	N	%	N	%		
Death at 1-year (N=3,866)	177	20.4%	379	12.6%	0.21	<0.0001
In-hospital outcomes (N=3,866)						
Death	53	6.1%	111	3.7%	0.11	<0.01
Stroke	28	3.2%	59	2.0%	0.08	<0.05
Permanent pacemaker	123	14.2%	381	12.7%	0.04	0.2732
Bleeding						<0.01
Major	71	8.2%	150	5.0%	0.13	
Minor	34	3.9%	111	3.7%	0.01	
No bleeding	765	88.2%	2,735	91.2%	-0.10	
Length of hospitalization	13.60	23.53	8.94	16.25	0.23	<0.0001
Outcomes after discharge (N=3,702)						
Readmission	473	54.6%	1,194	39.8%	0.30	<0.0001

ED visit after discharge	648	74.7%	1,839	61.3%	0.29	<0.0001
Rehospitalization	664	76.6%	1,913	63.8%	0.28	<0.0001

HFRS, Hospital Frailty Risk Score. **N**, sample size. **TAVI**, transcatheter aortic valve implantation. **ED**, emergency department.

S Table 5.7 Prediction of 1-year mortality with the Johns Hopkins ACG frailty indicator

Parameter	Odds ratio	95% CI	p-value
Frailty (Johns Hopkins ACG frailty indicator)	**1.424**	**1.128-1.798**	**0.0029**
Demographics			
Age			
66-70	Referent		
71-75	0.973	0.560-1.690	0.9220
76-80	0.994	0.593-1.667	0.9819
81-85	0.936	0.565-1.550	0.7965
86-90	1.210	0.731-2.004	0.4574
>90	**1.997**	**1.153-3.458**	**0.0136**
Gender			
Males	Referent		
Females	0.858	0.699-1.053	0.1432
Income quintile			
1	Referent		

2	1.107	0.834-1.470	0.4806
3	0.878	0.651-1.183	0.3918
4	0.911	0.671-1.236	0.5487
5	0.968	0.718-1.306	0.8324
Rural residence	**1.485**	**1.125-1.960**	**0.0053**
Comorbidities			
Myocardial infarction	1.054	0.794-1.400	0.7161
Ischemic heart disease	0.930	0.735-1.176	0.5446
History of heart failure	**1.419**	**1.108-1.818**	**0.0056**
Heart failure hospitalization within 90 days	0.987	0.749-1.301	0.9256
Previous PCI	0.902	0.725-1.122	0.3525
Previous CABG	**0.726**	**0.556-0.948**	**0.0185**
Previous valve surgery	0.928	0.470-1.831	0.8291
Previous ICD	1.585	0.806-3.119	0.1819
Valve-in-valve	0.654	0.314-1.364	0.2579
Previous permanent pacemaker	1.153	0.845-1.573	0.3692
COPD	**1.241**	**1.023-1.504**	**0.0282**
Cognitive impairment/ dementia	1.140	0.799-1.626	0.4698

Hypertension	0.862	0.572-1.298	0.4767
Dyslipidemia	1.147	0.933-1.409	0.1932
Cancer	1.156	0.818-1.632	0.4112
Cerebrovascular disease	0.942	0.645-1.377	0.7581
Atrial fibrillation	**1.503**	**1.230-1.836**	**<0.0001**
Peripheral vascular disease	**1.674**	**1.207-2.321**	**0.0020**
Dialysis	**1.733**	**1.090-2.756**	**0.0201**
ED visit before TAVI (within 1 year)	**1.394**	**1.082-1.796**	**0.0101**
Anemia			
Absent	Referent		
Present	**1.658**	**1.237-2.223**	**0.0007**
Missing	2.157	0.931-5.000	0.0731
Creatinine (u mil/mol)			
<120	Referent		
≥120	1.720	0.871-3.397	0.1181
Missing	0.786	0.351-1.761	0.5591
Access site			
Transfemoral	Referent		
Non-transfemoral	**1.843**	**1.425-2.385**	**<0.0001**

Year of procedure			
2012	Referent		
2013	1.052	0.694-1.595	0.8116
2014	1.141	0.757-1.720	0.5279
2015	0.978	0.645-1.482	0.9160
2016	0.815	0.537-1.235	0.3346
2017	0.899	0.598-1.351	0.6069

ACG, adjusted clinical groups. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department.

S Table 5.8 Prediction of 1-year mortality with the HFRS

Parameter	Odds ratio	95% CI	p-value
Frailty (HFRS)	**1.278**	**1.018-1.605**	**0.0346**
Demographics			
Age			
66-70	Referent		
71-75	0.981	0.565-1.702	0.9443
76-80	1.010	0.603-1.693	0.9685
81-85	0.954	0.576-1.579	0.8544
86-90	1.234	0.746-2.041	0.4127
>90	**2.043**	**1.181-3.537**	**0.0107**
Gender			
Males	Referent		
Females	0.864	0.704-1.060	0.1603
Income quintile			
1	Referent		
2	1.105	0.832-1.466	0.4902
3	0.870	0.645-1.172	0.3592

4	0.910	0.671-1.234	0.5443
5	0.972	0.721-1.311	0.8528
Rural residence	**1.506**	**1.140-1.988**	**0.0039**
Comorbidities			
Myocardial infarction	1.039	0.781-1.382	0.7950
Ischemic heart disease	0.923	0.730-1.167	0.5046
History of heart failure	**1.411**	**1.101-1.808**	**0.0065**
Heart failure hospitalization within 90 days	0.972	0.737-1.282	0.8392
Previous PCI	0.899	0.722-1.118	0.3366
Previous CABG	**0.729**	**0.558-0.951**	**0.0201**
Previous valve surgery	0.954	0.482-1.889	0.8920
Previous ICD	1.591	0.812-3.119	0.1760
Valve-in-valve	0.630	0.301-1.318	0.2197
Previous permanent pacemaker	1.166	0.855-1.589	0.3323
COPD	**1.226**	**1.011-1.486**	**0.0387**
Cognitive impairment/ dementia	1.374	0.993-1.901	0.0548
Hypertension	0.859	0.570-1.294	0.4668
Dyslipidemia	1.136	0.925-1.396	0.2241

Cancer	1.149	0.814-1.622	0.4291
Cerebrovascular disease	0.929	0.634-1.362	0.7074
Atrial fibrillation	**1.485**	**1.214-1.816**	**0.0001**
Peripheral vascular disease	**1.650**	**1.190-2.287**	**0.0027**
Dialysis	**1.657**	**1.038-2.647**	**0.0344**
ED visit before TAVI (within 1 year)	**1.399**	**1.085-1.802**	**0.0095**
Anemia			
Absent	Referent		
Present	**1.652**	**1.232-2.216**	**0.0008**
Missing	2.162	0.935-5.000	0.0715
Creatinine (u mil/mol)			
<120	Referent		
≥120	1.800	0.914-3.548	0.0893
Missing	0.789	0.353-1.764	0.5639
Access site			
Transfemoral	Referent		
Non-transfemoral	**1.845**	**1.426-2.386**	**<0.0001**
Year of procedure			
2012	Referent		

2013	1.046	0.690-1.587	0.8315
2014	1.122	0.745-1.691	0.5818
2015	0.978	0.645-1.482	0.9147
2016	0.816	0.538-1.237	0.3374
2017	0.908	0.604-1.366	0.6443

HFRS, Hospital Frailty Risk Score. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department.

S Table 5.9 Prediction of in-hospital mortality with the Johns Hopkins ACG frailty indicator

Parameter	Odds ratio	95% CI	p-value
Johns Hopkins ACG frailty indicator	1.230	0.825-1.834	0.3099
Demographics			
Age			
66-70	Referent		
71-75	0.637	0.265-1.534	0.3146
76-80	0.607	0.270-1.365	0.2272
81-85	0.622	0.285-1.356	0.2324
86-90	0.786	0.363-1.701	0.5410
>90	1.172	0.501-2.737	0.7144
Gender			
Males	Referent		
Females	1.373	0.967-1.949	0.0761
Income quintile			
1	Referent		
2	0.918	0.565-1.490	0.7283

3	0.699	0.413-1.185	0.1835
4	1.081	0.662-1.764	0.7550
5	0.845	0.503-1.418	0.5235
Rural residence	1.247	0.775-2.009	0.3630
Comorbidities			
Myocardial infarction	1.137	0.717-1.805	0.5849
Ischemic heart disease	1.087	0.712-1.658	0.6991
History of heart failure	1.291	0.846-1.971	0.2358
Heart failure hospitalization within 90 days	1.135	0.718-1.794	0.5889
Previous PCI	1.075	0.746-1.548	0.6973
Previous CABG	**0.615**	**0.379-0.999**	**0.0494**
Previous valve surgery	**0.191**	**0.042-0.872**	**0.0326**
Previous ICD	0.688	0.153-3.102	0.6269
Valve-in-valve	3.108	0.726-13.303	0.1264
Previous permanent pacemaker	1.370	0.817-2.298	0.2324
COPD	1.016	0.725-1.423	0.9281
Cognitive impairment/ dementia	1.081	0.575-2.036	0.8083
Hypertension	1.419	0.605-3.328	0.4212

Dyslipidemia	1.079	0.760-1.533	0.6693
Cancer	1.705	0.588-1.967	0.8133
Cerebrovascular disease	1.096	0.599-2.006	0.7661
Atrial fibrillation	1.202	0.847-1.707	0.3034
Peripheral vascular disease	**1.974**	**1.204-3.236**	**0.0071**
Dialysis	1.470	0.681-3.172	0.3267
ED visit before TAVI (within 1 year)	1.252	0.805-1.949	0.3186
Anemia			
Absent	Referent		
Present	**2.004**	**1.166-3.444**	**0.0119**
Missing	1.560	0.399-6.092	0.5226
Creatinine (u mil/mol)			
<120	Referent		
≥120	**2.809**	**1.022-7.716**	**0.0452**
Missing	1.300	0.358-4.716	0.6897
Access site			
Transfemoral	Referent		
Non-transfemoral	**2.630**	**1.800-3.842**	**<0.0001**
Year of procedure			

2012	Referent		
2013	1.192	0.614-2.314	0.6044
2014	1.500	0.792-2.839	0.2134
2015	0.896	0.453-1.776	0.7539
2016	0.571	0.279-1.169	0.1253
2017	0.690	0.345-1.380	0.2938

ACG, adjusted clinical groups. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department. **STS**, Society of Thoracic Surgeons.

S Table 5.10 Prediction of in-hospital mortality with the HFRS

Parameter	Odds ratio	95% CI	p-value
HFRS	1.110	0.751-1.642	0.6001
Demographics			
Age			
66-70	Referent		
71-75	0.641	0.267-1.541	0.3204
76-80	0.612	0.272-1.376	0.2346
81-85	0.629	0.289-1.373	0.2445
86-90	0.794	0.367-1.717	0.5571
>90	1.190	0.509-2.784	0.6874
Gender			
Males	Referent		
Females	1.384	0.976-1.964	0.0684
Income quintile			
1	Referent		
2	0.918	0.566-1.490	0.7301
3	0.696	0.411-1.179	0.1780

4	1.080	0.662-1.763	0.7576
5	0.849	0.506-1.425	0.5353
Rural residence	1.253	0.778-2.019	0.3534
Comorbidities			
Myocardial infarction	1.137	0.714-1.808	0.5892
Ischemic heart disease	1.084	0.711-1.652	0.7089
History of heart failure	1.290	0.845-1.970	0.2378
Heart failure hospitalization within 90 days	1.131	0.714-1.790	0.6004
Previous PCI	1.073	0.745-1.541	0.7035
Previous CABG	**0.612**	**0.377-0.993**	**0.0468**
Previous valve surgery	**0.189**	**0.041-0.871**	**0.0325**
Previous ICD	0.703	0.157-3.159	0.6458
Valve-in-valve	3.118	0.724-13.423	0.1268
Previous permanent pacemaker	1.383	0.825-2.318	0.2181
COPD	1.010	0.721-1.415	0.9539
Cognitive impairment/ dementia	1.210	0.674-2.170	0.5230
Hypertension	1.415	0.603-3.318	0.4246
Dyslipidemia	1.074	0.757-1.525	0.6894

Cancer	1.077	0.588-1.971	0.8103
Cerebrovascular disease	1.104	0.600-2.031	0.7496
Atrial fibrillation	1.197	0.841-1.704	0.3173
Peripheral vascular disease	**1.972**	**1.202-3.233**	**0.0071**
Dialysis	1.463	0.673-3.180	0.3363
ED visit before TAVI (within 1 year)	1.262	0.810-1.966	0.3035
Anemia			
Absent	Referent		
Present	**2.007**	**1.167-3.451**	**0.0118**
Missing	1.565	0.402-6.089	0.5179
Creatinine (u mil/mol)			
<120	Referent		
≥120	**2.877**	**1.050-7.883**	**0.0399**
Missing	1.301	0.360-4.704	0.6877
Access site			
Transfemoral	Referent		
Non-transfemoral	**2.631**	**1.801-3.844**	**<0.0001**
Year of procedure			
2012	Referent		

2013	1.192	0.614-2.314	0.6041
2014	1.489	0.786-2.819	0.2219
2015	0.898	0.453-1.779	0.7568
2016	0.571	0.279-1.170	0.1260
2017	0.695	0.348-1.390	0.3036

HFRS, Hospital Frailty Risk Score. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department. **STS**, Society of Thoracic Surgeons.

S Table 5.11 Prediction of rehospitalization at 12 months with the Johns Hopkins ACG frailty indicator

Parameter	Odds ratio	95% CI	p-value
Johns Hopkins ACG frailty indicator	**1.681**	**1.346-2.098**	**<0.0001**
Demographics			
Age			
66-70	Referent		
71-75	1.171	0.765-1.793	0.4674
76-80	1.197	0.801-1.788	0.3806
81-85	1.147	0.776-1.695	0.4927
86-90	1.320	0.889-1.959	0.1683
>90	1.493	0.946-2.354	0.0849
Gender			
Males	Referent		
Females	**1.243**	**1.057-1.461**	**0.0085**
Income quintile			
1	Referent		
2	1.104	0.874-1.394	0.4058
3	1.014	0.803-1.280	0.9062

4	0.935	0.735-1.190	0.5839
5	0.985	0.778-1.248	0.9026
Rural residence	1.211	0.942-1.555	0.1353
Comorbidities			
Myocardial infarction	1.189	0.918-1.541	0.1897
Ischemic heart disease	0.938	0.782-1.124	0.4885
History of heart failure	1.033	0.868-1.229	0.7167
Heart failure hospitalization within 90 days	1.049	0.811-1.358	0.7143
Previous PCI	1.045	0.880-1.243	0.6140
Previous CABG	0.933	0.766-1.137	0.4929
Previous valve surgery	0.992	0.587-1.676	0.9760
Previous ICD	0.884	0.473-1.653	0.7003
Valve-in-valve	0.786	0.456-1.352	0.3839
Previous permanent pacemaker	1.046	0.796-1.376	0.7456
COPD	**1.426**	**1.215-1.673**	**<0.0001**
Cognitive impairment/ dementia	1.112	0.791-1.562	0.5417
Hypertension	1.323	0.977-1.791	0.0700
Dyslipidemia	1.007	0.856-1.184	0.9355

Cancer	**1.465**	**1.069-2.006**	**0.0175**
Cerebrovascular disease	0.991	0.696-1.412	0.9612
Atrial fibrillation	**1.481**	**1.239-1.770**	**<0.0001**
Peripheral vascular disease	**1.475**	**1.035-2.066**	**0.0239**
Dialysis	**2.092**	**1.216-3.597**	**0.0077**
ED visit before TAVI (within 1 year)	**1.881**	**1.591-2.224**	**<0.0001**
Anemia			
Absent	Referent		
Present	1.190	0.974-1.455	0.0887
Missing	1.819	0.949-3.486	0.0717
Creatinine (u mil/mol)			
<120	Referent		
≥120	0.769	0.425-1.393	0.3861
Missing	0.534	0.284-1.002	0.0507
Access site			
Transfemoral	Referent		
Non-transfemoral	**1.326**	**1.031-1.706**	**0.0282**
Year of procedure			
2012	Referent		

2013	0.838	0.591-1.189	0.3221
2014	0.967	0.682-1.369	0.8480
2015	0.848	0.601-1.195	0.3455
2016	0.873	0.624-1.221	0.4268
2017	0.786	0.564-1.097	0.1568

ACG, adjusted clinical groups. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department. **STS**, Society of Thoracic Surgeons.

S Table 5.12 Prediction of rehospitalization at 12 months with the HFRS

Parameter	Odds ratio	95% CI	p-value
HFRS	**1.526**	**1.233-1.890**	**0.0001**
Demographics			
Age			
66-70	Referent		
71-75	1.205	0.787-1.844	0.3916
76-80	1.237	0.828-1.848	0.2984
81-85	1.190	0.805-1.759	0.3817
86-90	1.362	0.918-2.021	0.1251
>90	1.552	0.984-2.448	0.0587
Gender			
Males	Referent		
Females	**1.243**	**1.058-1.461**	**0.0083**
Income quintile			
1	Referent		
2	1.100	0.871-1.388	0.4239
3	1.003	0.795-1.266	0.9786
4	0.935	0.735-1.189	0.5817

5	0.977	0.772-1.237	0.8496
Rural residence	1.227	0.955-1.577	0.1089
Comorbidities			
Myocardial infarction	1.133	0.872-1.473	0.3483
Ischemic heart disease	0.930	0.776-1.115	0.4353
History of heart failure	1.019	0.857-1.213	0.8279
Heart failure hospitalization within 90 days	1.019	0.787-1.320	0.8861
Previous PCI	1.037	0.872-1.233	0.6811
Previous CABG	0.945	0.775-1.152	0.5743
Previous valve surgery	1.025	0.608-1.726	0.9268
Previous ICD	0.868	0.465-1.621	0.6559
Valve-in-valve	0.748	0.436-1.285	0.2934
Previous permanent pacemaker	1.061	0.807-1.395	0.6717
COPD	**1.402**	**1.195-1.645**	**<0.0001**
Cognitive impairment/ dementia	**1.503**	**1.107-2.040**	**0.0090**
Hypertension	1.298	0.959-1.755	0.0911
Dyslipidemia	1.000	0.850-1.175	0.9976
Cancer	**1.433**	**1.046-1.963**	**0.0250**

Cerebrovascular disease	0.956	0.669-1.368	0.8067
Atrial fibrillation	**1.447**	**1.209-1.731**	**<0.0001**
Peripheral vascular disease	**1.418**	**1.012-1.987**	**0.0423**
Dialysis	**1.918**	**1.111-3.313**	**0.0194**
ED visit before TAVI (within 1 year)	**1.888**	**1.597-2.231**	**<0.0001**
Anemia			
Absent	Referent		
Present	1.173	0.960-1.434	0.1186
Missing	1.757	0.915-3.372	0.0902
Creatinine (u mil/mol)			
<120	Referent		
≥120	0.815	0.451-1.474	0.4994
Missing	0.549	0.292-1.032	0.0625
Access site			
Transfemoral	Referent		
Non-transfemoral	**1.335**	**1.038-1.717**	**0.0245**
Year of procedure			
2012	Referent		
2013	0.828	0.584-1.174	0.2886

2014	0.939	0.663-1.329	0.7220
2015	0.841	0.597-1.185	0.3221
2016	0.869	0.621-1.216	0.4138
2017	0.793	0.569-1.105	0.1698

HFRS, Hospital Frailty Risk Score. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department. **STS**, Society of Thoracic Surgeons.

S Table 5.13 Sensitivity analysis of rehospitalization with Johns Hopkins ACG frailty indicator

Parameter	Hazard ratio	95% CI	p-value
Johns Hopkins ACG frailty indicator	**1.195**	**1.083-1.318**	**0.0004**
Demographics			
Age			
66-70	Referent		
71-75	1.010	0.825-1.236	0.9242
76-80	0.985	0.813-1.192	0.8734
81-85	0.983	0.815-1.185	0.8571
86-90	1.009	0.836-1.219	0.9254
>90	0.991	0.797-1.232	0.9353
Gender			
Males	Referent		
Females	**1.123**	**1.041-1.212**	**0.0029**
Income quintile			
1	Referent		
2	1.002	0.899-1.116	0.9760

3	1.026	0.920-1.144	0.6480
4	1.016	0.907-1.138	0.7812
5	0.994	0.889-1.111	0.9120
Rural residence	1.059	0.943-1.191	0.3332
Comorbidities			
Myocardial infarction	1.091	0.972-1.225	0.1390
Ischemic heart disease	0.972	0.892-1.059	0.5156
History of heart failure	0.996	0.915-1.084	0.9238
Heart failure hospitalization within 90 days	1.002	0.893-1.124	0.9696
Previous PCI	1.024	0.944-1.110	0.5657
Previous CABG	1.027	0.934-1.129	0.5860
Previous valve surgery	0.961	0.738-1.252	0.7687
Previous ICD	0.945	0.687-1.298	0.7249
Valve-in-valve	0.952	0.724-1.253	0.7276
Previous permanent pacemaker	0.966	0.849-1.099	0.5984
COPD	**1.129**	**1.049-1.215**	**0.0012**
Cognitive impairment/ dementia	1.020	0.877-1.187	0.7942
Hypertension	1.116	0.960-1.298	0.1531

Dyslipidemia	0.987	0.915-1.065	0.7334
Cancer	1.140	0.992-1.310	0.0647
Cerebrovascular disease	1.006	0.860-1.177	0.9375
Atrial fibrillation	**1.152**	**1.062-1.249**	**0.0006**
Peripheral vascular disease	1.143	0.983-1.328	0.0829
Dialysis	**1.271**	**1.022-1.580**	**0.0308**
ED visit before TAVI (within 1 year)	**1.265**	**1.165-1.373**	**<0.0001**
Anemia			
Absent	Referent		
Present	1.052	0.957-1.156	0.2954
Missing	1.192	0.866-1.642	0.2819
Creatinine (u mil/mol)			
<120	Referent		
≥120	0.919	0.685-1.231	0.5704
Missing	0.821	0.604-1.117	0.2093
Access site			
Transfemoral	Referent		
Non-transfemoral	1.071	0.953-1.203	0.2479
Year of procedure			

2012	Referent		
2013	0.926	0.784-1.094	0.3685
2014	0.981	0.830-1.159	0.8200
2015	0.950	0.804-1.121	0.5420
2016	0.956	0.812-1.125	0.5880
2017	0.895	0.761-1.053	0.1807

ACG, adjusted clinical groups. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department. **STS**, Society of Thoracic Surgeons.

S Table 5.14 Sensitivity analysis of rehospitalization with HFRS

Parameter	Hazard ratio	95% CI	p-value
HFRS	**1.177**	**1.073-1.291**	**0.0005**
Demographics			
Age			
66-70	Referent		
71-75	1.018	0.832-1.247	0.8608
76-80	0.995	0.821-1.205	0.9567
81-85	0.995	0.825-1.200	0.9555
86-90	1.017	0.842-1.228	0.8635
>90	1.005	0.808-1.249	0.9664
Gender			
Males	Referent		
Females	**1.114**	**1.032-1.203**	**0.0055**
Income quintile			
1	Referent		
2	1.003	0.900-1.118	0.9557

3	1.028	0.922-1.147	0.6158
4	1.024	0.914-1.147	0.6790
5	0.992	0.887-1.109	0.8849
Rural residence	1.064	0.946-1.196	0.3000
Comorbidities			
Myocardial infarction	1.069	0.951-1.201	0.2634
Ischemic heart disease	0.967	0.888-1.054	0.4497
History of heart failure	0.992	0.912-1.080	0.8612
Heart failure hospitalization within 90 days	0.998	0.889-1.120	0.9714
Previous PCI	1.016	0.937-1.102	0.7001
Previous CABG	1.037	0.943-1.141	0.4510
Previous valve surgery	0.982	0.753-1.282	0.8946
Previous ICD	0.918	0.668-1.261	0.5973
Valve-in-valve	0.924	0.701-1.219	0.5769
Previous permanent pacemaker	0.979	0.861-1.113	0.7446
COPD	**1.125**	**1.045-1.211**	**0.0016**
Cognitive impairment/ dementia	1.124	0.982-1.287	0.0894
Hypertension	1.111	0.955-1.292	0.1713

Dyslipidemia	0.982	0.910-1.060	0.6427
Cancer	1.129	0.982-1.297	0.0884
Cerebrovascular disease	0.991	0.847-1.160	0.9150
Atrial fibrillation	**1.137**	**1.048-1.234**	**0.0020**
Peripheral vascular disease	1.128	0.970-1.311	0.1174
Dialysis	1.239	0.995-1.543	0.0551
ED visit before TAVI (within 1 year)	**1.268**	**1.168-1.377**	**<0.0001**
Anemia			
Absent	Referent		
Present	1.045	0.951-1.149	0.3599
Missing	1.187	0.861-1.636	0.2958
Creatinine (u mil/mol)			
<120	Referent		
≥120	0.930	0.694-1.246	0.6264
Missing	0.825	0.606-1.123	0.2214
Access site			
Transfemoral	Referent		
Non-transfemoral	1.074	0.957-1.207	0.2255
Year of procedure			

2012	Referent		
2013	0.925	0.783-1.093	0.3615
2014	0.979	0.829-1.156	0.8027
2015	0.953	0.807-1.125	0.5694
2016	0.959	0.815-1.129	0.6159
2017	0.902	0.767-1.060	0.2109

HFRS, Hospital Frailty Risk Score. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department. **STS**, Society of Thoracic Surgeons.

S Table 5.15 Reclassification table

	Events moving up, N (%)	**Events moving down, N (%)**	**Non-events moving up, N (%)**	**Non-events moving down, N (%)**
Outcome: death at 1 year (the number of events=556; the number of non-events=3,310)				
ACG	161 (29.68%)	391 (70.32%)	727 (21.96%)	2,583 (78.04%)
HFRS	201 (36.15%)	355 (63.85%)	1,005 (30.36%)	2,305 (69.64%)
Outcome: in-hospital death (the number of events=164; the number of non-events=3,702)				
ACG	117 (71.34%)	47 (28.66%)	2,726 (73.64%)	976 (26.36%)
HFRS	99 (60.37%)	65 (39.63%)	2,446 (66.07%)	1,256 (33.93%)
Outcome: rehospitalization (the number of events=2,577; the number of non-events=1,125)				
ACG	660 (25.61%)	1,917 (74.39%)	173 (15.38%)	952 (84.62%)
HFRS	778 (30.19%)	1,799 (69.81%)	260 (23.11%)	865 (76.89%)

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Chapter 6

6 Performance of frailty indices in predicting cost outcomes in patients undergoing transcatheter aortic valve implantation

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6.1 Introduction

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative, less invasive treatment option for patients with severe symptomatic aortic stenosis who cannot undergo surgery or who are at high risk for poor outcomes with surgical aortic valve replacement (SAVR).[1,2,3] Research on the benefits of TAVI compared to SAVR has continued to inform clinical decision-making around treatments of aortic stenosis.[1,2,3] Current indications for TAVI have expanded to include younger and lower surgical risk patients, but the high cost of TAVI limits its use in a larger number of eligible candidates.[4,5,6,7]

Patients referred for TAVI typically have advanced age and multiple comorbidities.[8,9] The prevalence of frailty in patients undergoing TAVI can be as high as 85%.[8,9] Frailty is a biological syndrome characterized by an increased vulnerability to stressors.[10,8] In patients undergoing TAVI, frailty has been identified as an important predictor of mortality and significant complications.[9,11] Frailty has been associated with longer hospital stays, higher rates of readmission, and higher demands for organ support, all of which may increase healthcare costs.[12,13]

In addition to clinical outcomes, healthcare cost is an essential component in clinical decision-making.[14,15] Recent studies have shown significant association between preoperative frailty and hospitalization costs in patients undergoing TAVI, suggesting that the cost-effectiveness of TAVI may be jeopardized in those who are frail.[12,15] Given the significant association between frailty and poor outcomes and the link between poor outcomes and health care costs, clinicians may need more information about the costs of care for frail patients. [12,15]

Studies exploring the relation of frailty to health care costs of TAVI are limited. On the other hand, the best approach to measuring preoperative frailty in patients undergoing TAVI remains controversial. Accordingly, the objective of this study was to examine the performance of frailty, diagnosed using two administrative database driven frailty indices, in predicting cost outcomes of patients undergoing TAVI. This study aims to

better understand how frailty impacts health care cost of TAVI, ultimately improving medical decision-making around TAVI.

6.2 Methods

This retrospective study was conducted in the province of Ontario in Canada. All residents in Ontario receive publicly funded universal medical coverage provided by the Ontario Ministry of Health and Long-Term Care (MOHLTC).

6.2.1 Data sources

All patients who underwent a TAVI procedure in Ontario, Canada from April 1, 2012 to March 31, 2018 were identified through the CorHealth Ontario TAVI registry. The CorHealth Ontario is an organization formed by the merger of the Cardiac Care Network and the Ontario Stroke Network. The CorHealth Ontario advises the MOHLTC, and data entry into the CorHealth TAVI registry is mandatory for provincial funding.[16]

Patient data from the CorHealth TAVI registry were linked to the administrative databases at the Institute for Clinical Evaluative Sciences (IC/ES), including the Continuing Care Reporting System (CCRS), Discharge Abstract Database (DAD), Home Care Database (HCD), National Ambulatory Care Reporting System (NACRS), National Rehabilitation Reporting System (NRS), Ontario Drug Benefit Claims (ODB), Ontario Health Insurance Plan Claims Database (OHIP), Ontario Mental Health Reporting System (OMHRS), Same Day Surgery Database (SDS), Congestive Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD), Ontario Hypertension Dataset (HYPER), Ontario Diabetes Dataset (ODD), Ontario Census Area Profiles (CENSUS), Registered Persons Database (RPDB), Assistive Devices Program (ADP), Home Care Database (HCDMOH), Client Agency Program Enrolment (CAPE) and the Ontario Case Costing Initiative (OCCI). Additional information about the databases is provided in **Appendix A**.

6.2.2 Study cohort

Patients aged 66 or older who underwent a TAVI procedure in Ontario, Canada from April 1, 2012 to March 31, 2018 were included. Data were linked using unique encoded identifiers and analyzed at ICES. The first procedure was considered as the index event if a patient underwent repeat TAVI procedure. Patients without a valid linkage number were excluded.

6.2.3 Administrative database frailty indices

Two administrative database frailty indices, the Johns Hopkins Adjusted Clinical Group (ACG) frailty indicator and the Hospital Frailty Risk Score (HFRS), were used to assign frailty status, based on preprocedural patient characteristics. Both the Johns Hopkins ACG frailty indicator and the HFRS have been used to identify frail patients in previous research.[17,18,19] The Johns Hopkins ACG frailty indicator is a proprietary index. Thus, specific diagnostic codes are not publicly available (example of diagnostic codes is shown in **Appendix B**). Diagnostic codes of the HFRS is shown in the **Appendix C**.

6.2.4 Healthcare costs

The primary outcome was healthcare costs incurred by the MOHLTC over a one-year period from the first day of the index hospitalization and ending 365 days later. The secondary outcome was high-cost patients defined as those in the top 5% of one-year cost.[20] We included the cost of inpatient hospitalization, emergency visits (ED), same day surgeries (SDS) and other ambulatory treatments such as dialysis and oncology, physician services and prescribed drugs. All costs were reported in 2017 Canadian dollars.

Healthcare costs from the perspective of the Ontario Ministry of Health and Long-Term Care, were calculated based on person-level healthcare utilization, captured in administrative claims and billing data.[21] Inpatient costs were estimated based on the Resource Intensity Weight (RIW), using information that includes the case mix group, age, comorbidity level, flagged intervention, intervention event and out-of-hospital intervention.[21] Emergency department visits, same day surgeries and other ambulatory

treatment (dialysis and oncology) costs were similarly estimated based on a weighting factor (i.e., the Comprehensive Ambulatory Classification System weight).[21] The cost of physician services, diagnostic services and prescribed drugs were estimated based on the amount reimbursed by the province.[21]

6.2.5 Statistical analysis

Baseline covariates include demographics, comorbidities, cardiac history and preprocedural characteristics. Baseline characteristics were compared between frail and non-frail groups. Continuous variables were presented as mean (standard deviation [SD]) and compared using the t-test. Categorical variables were presented as proportions and compared using the chi-square test. Less sensitive to large sample sizes, standardized differences were calculated.[22] Standardized differences greater than 0.1 were considered meaningful differences.[22] Both mean and median healthcare costs were presented. Difference in arithmetic mean cost was compared between frail and non-frail groups using a generalized linear model.[23,24]

For the primary outcome, we fitted a hierarchical generalized linear model with a logarithmic link and gamma distribution to examine the significance of frailty indices in predicting one-year costs adjusting for demographics, baseline comorbidities, cardiac history and preprocedural characteristics, and account for clustering by cardiac insitituion.[23,24] The model addresses the heavily right-skewed cost distribution and allows for straightforward interpretation.[23,24] The exponential of the coefficient represents the rate ratio (RR). The RR is interpreted as the percentage increase in one-year costs when changing one unit in the predictor.

For the secondary outcome, we fitted a hierarchical logistic regression model adjusting covariates, as the reference model. Frailty indices were added to the model individually to test the significance of frailty. We compared adverse outcomes between high-cost and non-high cost patients using chi-square analysis. Predictive accuracy was compared between the reference model and each model with frailty indices. Predictive performance statistics, including c-statistic, Akaike information criteria (AIC), Bayesian information

criteria (BIC), integrated discrimination improvement (IDI) and net reclassification index (NRI), were reported.[25,26,27]

SAS Enterprise 7.1 was used for all analyses; p-values of <0.05 were considered significant.

6.3 Results

6.3.1 Baseline characteristics of the cohort

The cohort consisted of 3,866 patients. Demographics, procedural characteristics and clinical outcomes by frailty were shown in **S Table 5.1 S Table 5.2**, **S Table 5.3**, **S Table 5.4**, **S Table 5.5** and **S Table 5.6**). The mean and median one-year costs of the cohort were $57, 937 and $44,380 (interquartile range [IQR], $33,076-$66,666) (**S Table 6.1**).

6.3.2 Comparison of cost between frail and non-frail patients

Costs of patients undergoing TAVI by frailty are shown in **Table 6.1** and **Table 6.2**. When frailty was diagnosed using the Johns Hopkins ACG frailty indicator, the mean and median one-year costs were $66,266 and $50,105 (IQR, $36,685-$70,509) in 867 frail patients compared with $55,529 and $42,736 (IQR, $32,363-$63,673) in 2,999 non-frail patients (**Table 6.1**). When frailty was diagnosed with the HFRS, the mean and median one-year costs were $71,708 and $54,715 (IQR, $37,643-$82,681) in 870 frail patients compared with $53,938 and $42,061 (IQR, $32,193-$61,591) in 2,996 non-frail patients (**Table 6.2**).

Table 6.1 Cost outcomes of patients undergoing TAVI frail versus. non-frail diagnosed with the Johns Hopkins ACG frailty indicator

Variables (N=3,866)	**Frail (N=867)**		**Non-frail (N=2,999)**		**p-value [f]**
	Mean	Median	Mean	Median	

	(SD)	(IQR)	(SD)	(IQR)	
Total one-year cost [a]	66,266 (50,381)	50,105 (36,685-79,509)	55,529 (42,527)	42,736 (32,363–63,673)	<0.0001
Inpatient cost [b]	47,074 (41,279)	33,930 (23,358-57,710)	39,268 (36,115)	28,558 (21,046-44,226)	<0.0001
Drug cost [c]	3,109 (4,703)	2,077 (992-3,470)	2,768 (5,956)	1,678 (819-2,988)	0.0007
Physician services and diagnostic services cost [d]	12,375 (5,884)	10,976 (8,740-14,218)	11,104 (4,897)	9,726 (7,992-12,713)	<0.0001
Ambulatory care cost [e]	3,373 (13,951)	751 (151-1,693)	2,028 (9,582)	457 (0-1,222)	<0.0001

[a] One-year cost captured costs incurred by the Ontario Ministry of Health and Long-Term Care over a one-year period from the first day of the index hospitalization and ending 365 days later, including inpatient cost, drug cost, physician and diagnostic services and ambulatory care.

[b] Inpatient cost captured inpatient costs over a one-year period, including the cost of rehospitalization, from the first day of the index hospitalization and ending 365 days later.

[c] Drug cost captured costs covered by the Ontario Drug Benefit program over a one-year period from the first day of the index hospitalization and ending 365 days later.

[d] Cost of physician and diagnostic services, over a one-year period from the first day of the index hospitalization and ending 365 days later, was captured in the OHIP database.

[e] Ambulatory care costs after discharge was captured in the NACRS database.

[f] P-value for differences in cost were estimated using a generalized linear model.

ACG, adjusted clinical groups. **TAVI**, transcatheter aortic valve implantation. **N**, sample size. **ED**, emergency department. **OHIP**, Ontario Health Insurance Plan. **NACRS**, National Ambulatory Care Reporting System.

Table 6.2 Cost outcomes of patients undergoing TVAI frail versus. non-frail diagnosed with the HFRS

Variables (N=3,866)	**Frail (N=870)**		**Non-frail (N=2,996)**		**p-value** [f]
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Total one-year cost [a]	71,708 (55,930)	54,715 (37,643-82,681)	53,938 (39,893)	42,061 (32,193-61,591)	<0.0001
Inpatient cost [b]	50,458 (45,904)	36,238 (24,848-58,873)	38,278 (34,164)	28,000 (20,905-43,033)	<0.0001
Drug cost [c]	3,106 (3,761)	2,254 (1,088-3,651)	2,768 (6,148)	1,632 (807-2,916)	0.0007
Physician services and diagnostic services cost [d]	12,817 (6,127)	11,288 (8,771-15,296)	10,974 (4,766)	9,725 (7,973-12,561)	<0.0001
Ambulatory care cost [e]	4,970 (17,600)	860 (156-1,887)	1,563 (7,490)	444 (0-1,159)	<0.0001

[a] One-year cost captured costs incurred by the Ontario Ministry of Health and Long-Term Care over a one-year period from the first day of the index hospitalization and ending 365 days later, including inpatient cost, drug cost, physician and diagnostic services and ambulatory care.

[b] Inpatient cost captured inpatient costs over a one-year period, including the cost of rehospitalization, from the first day of the index hospitalization and ending 365 days later.

[c] Drug cost captured costs covered by the Ontario Drug Benefit program over a one-year period from the first day of the index hospitalization and ending 365 days later.

[d] Cost of physician and diagnostic services, over a one-year period from the first day of the index hospitalization and ending 365 days later, was captured in the OHIP database.

[e] Ambulatory care costs after discharge was captured in the NACRS database.

[f] P-value for differences in cost were estimated using a generalized linear model.

HFRS, Hospital Frailty Risk Score. **TAVI**, transcatheter aortic valve implantation. **N**, sample size. **ED**, emergency department. **OHIP**, Ontario Health Insurance Plan. **NACRS**, National Ambulatory Care Reporting System.

6.3.3 Association between frailty and one-year costs after TAVI

Adjusting for demographics and baseline comorbidities, both the Johns Hopkins ACG frailty indicator (RR, 1.131; 95% CI, 1.063-1.204) and the HFRS (RR, 1.136; 95% CI, 1.070-1.206) were significantly associated with increased one-year costs.

When frailty was diagnosed with the Johns Hopkins ACG frailty indicator, age of 86-90, age over 90, previous valve surgery, previous permanent pacemaker and year of procedure were associated with a decreased one-year cost. Johns Hopkins ACG frailty indicator, history of heart failure, COPD, cancer, atrial fibrillation, dialysis, ED visit before TAVI, creatinine ≥120 u ml/mol and a non-transfemoral approach were associated with an increased one-year cost (**Table 6.3**).

When frailty was diagnosed with the HFRS, age of 86-90, age over 90, previous permanent pacemaker and year of procedure were associated with a decreased one-year cost. HFRS, history of heart failure, cancer, atrial fibrillation, dialysis, ED visit before

TAVI, anemia and a non-transfemoral approach were associated with an increased one-year cost (**Table 6.4**).

Table 6.3 The Johns Hopkins ACG frailty indicator and one-year cost of TAVI

Parameter	Rate ratio	95% CI	p-value
Johns Hopkins ACG frailty indicator	**1.131**	**1.063-1.204**	**0.0001**
Demographics			
Age			
66-70	Referent		
71-75	0.938	0.821-1.072	0.3494
76-80	0.905	0.798-1.026	0.1198
81-85	0.898	0.794-1.014	0.0836
86-90	**0.869**	**0.768-0.983**	**0.0260**
>90	**0.837**	**0.727-0.963**	**0.0129**
Gender			
Males	Referent		
Females	0.979	0.931-1.029	0.4047
Income quintile			
1	Referent		
2	0.982	0.914-1.054	0.6087

3	0.998	0.929-1.073	0.9610
4	0.998	0.927-1.076	0.9639
5	0.983	0.913-1.057	0.6380
Rural residence	1.029	0.955-1.108	0.4586
Comorbidities			
Myocardial infarction	1.058	0.982-1.140	0.1373
Ischemic heart disease	0.971	0.918-1.028	0.3118
History of heart failure	**1.119**	**1.058-1.183**	**<0.0001**
Heart failure hospitalization within 90 days	1.059	0.984-1.141	0.1277
Previous PCI	0.956	0.906-1.008	0.0964
Previous CABG	0.981	0.922-1.044	0.5458
Previous valve surgery	**0.841**	**0.715-0.989**	**0.0365**
Previous ICD	0.832	0.684-1.011	0.0649
Valve-in-valve	1.011	0.870-1.219	0.7338
Previous permanent pacemaker	**0.915**	**0.843-0.993**	**0.0326**
COPD	**1.051**	**1.002-1.103**	**0.0429**
Cognitive impairment/ dementia	0.945	0.859-1.040	0.2483
Hypertension	0.988	0.895-1.091	0.8141

Dyslipidemia	1.007	0.957-1.059	0.8004
Cancer	**1.112**	**1.016-1.216**	**0.0207**
Cerebrovascular disease	1.055	0.953-1.167	0.3029
Atrial fibrillation	**1.100**	**1.043-1.159**	**0.0004**
Peripheral vascular disease	1.085	0.988-1.192	0.0883
Dialysis	**1.751**	**1.529-2.005**	**<0.0001**
ED visit before TAVI (within 1 year)	**1.095**	**1.036-1.157**	**0.0012**
Anemia			
Absent	Referent		
Present	0.932	0.774-1.123	0.4589
Missing	1.008	0.826-1.229	0.9378
Creatinine (u ml/mol)			
<120	Referent		
≥120	**1.110**	**1.041-1.182**	**0.0013**
Missing	1.089	0.887-1.338	0.4152
Access site			
Transfemoral	Referent		
Non-transfemoral	**1.142**	**1.062-1.228**	**0.0003**

Year of procedure			
2012	Referent		
2013	0.917	0.824-1.021	0.1146
2014	0.949	0.853-1.055	0.3325
2015	**0.882**	**0.793-0.982**	**0.0216**
2016	**0.857**	**0.772-0.951**	**0.0039**
2017	**0.825**	**0.743-0.915**	**0.0003**

ACG, adjusted clinical groups. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department.

Table 6.4 The HFRS and one-year cost of TAVI

Parameter	Rate ratio	95% CI	p-value
Frailty (HFRS)	**1.136**	**1.070-1.206**	**<0.0001**
Demographics			
Age			
66-70	Referent		
71-75	0.948	0.830-1.083	0.4324
76-80	0.917	0.809-1.039	0.1754
81-85	0.910	0.805-1.028	0.1299
86-90	**0.882**	**0.780-0.998**	**0.0459**
>90	**0.851**	**0.739-0.978**	**0.0233**
Gender			
Males	Referent		
Females	0.979	0.931-1.029	0.3964
Income quintile			
1	Referent		
2	0.981	0.914-1.052	0.5868
3	0.996	0.927-1.070	0.9032

4	0.999	0.928-1.076	0.9864
5	0.985	0.915-1.059	0.6750
Rural residence	1.031	0.957-1.111	0.4198
Comorbidities			
Myocardial infarction	1.043	0.968-1.124	0.2648
Ischemic heart disease	0.971	0.918-1.027	0.3039
History of heart failure	**1.111**	**1.051-1.175**	**0.0002**
Heart failure hospitalization within 90 days	1.044	0.970-1.124	0.2503
Previous PCI	0.952	0.903-1.004	0.0707
Previous CABG	0.982	0.923-1.045	0.5707
Previous valve surgery	0.852	0.725-1.002	0.0522
Previous ICD	0.829	0.682-1.007	0.0588
Valve-in-valve	1.013	0.856-1.199	0.8819
Previous permanent pacemaker	**0.918**	**0.846-0.996**	**0.0401**
COPD	1.046	0.997-1.098	0.0638
Cognitive impairment/ dementia	1.001	0.919-1.092	0.9749
Hypertension	0.984	0.891-1.086	0.7511
Dyslipidemia	1.002	0.953-1.054	0.9282

Cancer	**1.109**	**1.015-1.213**	**0.0227**
Cerebrovascular disease	1.038	0.938-1.149	0.4707
Atrial fibrillation	**1.090**	**1.034-1.148**	**0.0014**
Peripheral vascular disease	1.074	0.978-1.179	0.1329
Dialysis	**1.707**	**1.490-1.957**	**<0.0001**
ED visit before TAVI (within 1 year)	**1.094**	**1.036-1.156**	**0.0013**
Anemia			
Absent	Referent		
Present	**1.103**	**1.035-1.175**	**0.0024**
Missing	1.085	0.884-1.332	0.4346
Creatinine (u mil/mol)			
<120	Referent		
≥120	0.954	0.793-1.148	0.6203
Missing	1.008	0.827-1.229	0.9362
Access site			
Transfemoral	Referent		
Non-transfemoral	**1.144**	**1.064-1.229**	**0.0003**
Year of procedure			

2012	Referent		
2013	0.915	0.822-1.018	0.1016
2014	0.940	0.846-1.046	0.2575
2015	**0.878**	**0.789-0.976**	**0.0160**
2016	**0.856**	**0.772-0.951**	**0.0036**
2017	**0.827**	**0.746-0.917**	**0.0003**

HFRS, Hospital Frailty Risk Score. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department.

6.3.4 Incremental value of frailty in predicting high-cost patients

High-cost patients were defined as those in the top 5% of one-year cost, which was greater than or equal to $133,700. Of the 193 high-cost patients, a total of 61 patients (31.61%) were identified as frail using the Johns Hopkins ACG frailty indicator and 87 patients (45.08%) were identified as frail using the HFRS (**Table 6.5**). Compared with non-high-cost patients, high-cost patients had a significant association with adverse outcomes (**Table 6.5**), including procedural stroke (7.77% vs. 1.96%), bleeding (23.83% vs. 8.71%), permanent pacemaker (25.91% vs. 12.36%), length of hospitalization (43.80 days vs. 8.22 days), in-hospital death (9.33% vs. 3.97%), rehospitalization (81.14% vs. 43.24%) and death at 1 year (33.16% vs. 13.40%).

Adjusting for demographics and baseline comorbidities, the Johns Hopkins ACG frailty indicator (odds ratio [OR], 1.433; 95% CI, 0.991-2.071) was not significantly associated with high cost (**S Table 6.2**). The HFRS (OR, 1.782; 95% CI, 1.250-2.542) was significantly associated with high cost (**S Table 6.3**). Compared with the reference

model, the HFRS led to improved classification (NRI, 0.363, p<0.0001). The Johns Hopkins ACG frailty indicator did not increase the predictive accuracy (**Table 6.6**).

Table 6.5 High-cost patients by frailty status

Adverse outcomes	**Non high-cost patients**	**High-cost patients**	**p-value***	**Johns Hopkins ACG frailty indicator [a]**	**HFRS [b]**
	N=3,673	N=193		Frail patients (n=61)	Frail patients (n=87)
Stroke	72 (1.96%)	15 (7.77%)	<0.0001	SC	6 (6.90%)
Bleeding	320 (8.71%)	46 (23.83%)	<0.0001	15 (24.59%)	19 (21.84%)
Permanent pacemaker	454 (12.36%)	50 (25.91%)	<0.0001	12 (19.67%)	18 (20.69%)
Length of index hospitalization, days	8.22 (9.30)	43.80 (61.93)	<0.0001	47.84 (62.21)	44.05 (58.96)
In-hospital death	146 (3.97%)	18 (9.33%)	0.0013	7 (11.48%)	8 (9.20%)
Death at 1 year	492 (13.40%)	64 (33.16%)	<0.0001	20 (32.79%)	23 (26.44%)

Rehospitalization	1,525 (43.24%)	142 (81.14%)	<0.0001	47 (87.04%)	66 (83.54%)

ACG, adjusted clinical group. HFRS, hospital frailty risk score. SC, small cell.

*Proportion of adverse outcomes was compared between high-cost patients and non-high-cost patients using chi-square test.

[a] The number and proportion of frail (diagnosed using the Johns Hopkins ACG frailty indicator), high-cost patients having the adverse outcome.

[b] The number and proportion of frail (diagnosed using the HFRS), high-cost patients having the adverse outcome

Table 6.6 Predictive performance of frailty in predicting high-cost patients

Models	**Adjusted OR (95% CI)**	**ΔAIC**	**ΔBIC**	**Δc statistic**	**IDI**	**NRI**
Johns Hopkins ACG frailty indicator	1.433 (0.991-2.071)	-1	-10	0.0025 (p=0.3459)	-0.001 (p=0.3094)	0.130 (p=0.0781)
HFRS	**1.782 (1.250-2.542)**	-8	-7	0.0088 (p=0.0544)	-0.004 (p=0.1040)	**0.363 (p<0.0001)**

Reference model covariates include age, gender, income quintile, rural residence, MI, ischemic heart disease, heart failure, previous CABG, previous PCI, previous valve surgery, previous ICD, valve-in-valve, previous permanent pacemaker, COPD, dementia,

hypertension, dyslipidemia, cancer, CVD, AF, PVD, dialysis, ED visit before TAVI, anemia, creatinine, access site, and year of procedure.

AIC, Akaike information criteria. BIC, Bayesian information criteria. IDI, integrated discrimination improvement.

6.4 Discussion

Analyzing data from the Ontario TAVI cohort and the linked data derived from IC/ES administrative databases, we found that frail patients, regardless of the frailty indices, incurred substantial healthcare costs over a one-year period after TAVI, including inpatient cost, drug cost, physician billing, lab and diagnostic cost and ambulatory care cost. High-cost patients were significantly associated with adverse outcomes after TAVI, including death, stroke, bleeding, permanent pacemaker, longer index hospitalization stay and rehospitalization. Comparing predictive accuracy between the reference model and each model with frailty indices, we found that HFRS was a significant predictor for high-cost patients and improved classification in predicting high-cost TAVI recipients, but not the Johns Hopkins ACG frailty indicator.

Previous literature has revealed that frailty is an important driver of healthcare costs associated with TAVI. A single-center retrospective study by Patel et al[15] tested the association of frailty with cost for 407 adult patients who underwent a TAVI procedure between December 2012 and April 2018. This study found a higher adjusted mean total cost for frail patients compared with non-frail ($78,823 vs $72,425, p=0.042, costs were adjusted to 2018 United States dollars) from the perspective of the United States healthcare system.[15] Patel et al analyzed patient-level costs, and they defined frailty using impaired mobility (defined as 5-meter walk time >6 seconds) and hypoalbuminemia (defined as serum albumin <3.5 g/dL).[15] Patients were identified as frail if both criteria were met. Further to this, using the HFRS to identify frailty, a retrospective study by Malik et al[17] evaluated the impact of frailty on resource utilization after TAVI in the

United States. Malik et al[17] enrolled 20,504 patients who underwent a TAVI procedure in 2016. Using the HFRS, Malik et al[17] categorized patients as low, intermediate and high risk of frailty. They found that cost of index hospitalization was significantly associated with frailty.[17] Different to previous studies, our research aims to examine the performance of database driven frailty indices in predicting cost outcomes after TAVI. The Johns Hopkins ACG frailty indicator and the HFRS were developed and validated using administrative databases. Both frailty indices assign weights to "deficits" identified by diagnostic codes but differ in the weights assigned to each deficit in calculating the frailty score. The Johns Hopkins ACG frailty indicator is calculated based on 12 clusters of frailty-defining diagnoses. The HFRS is calculated based on 109 International Statistical Classification of Diseases (ICD-10). Although key differences amongst the administrative database frailty algorithms may contribute to differences in performance for identifying frail patients, our study demonstrates that frailty, either diagnosed with the Johns Hopkins ACG frailty indicator or the HFRS, is associated with increased one-year healthcare costs after TAVI, after adjusting for demographic, clinical and perioperative variables.

Frailty has been recognized as a significant risk factor for increased mortality and morbidity. Emerging evidence has also demonstrated the value of frailty in predicting adverse outcomes, such as prolonged length of hospitalization, longer intensive care unit stays, and higher rates of rehospitalization, all of which can dramatically increase healthcare costs.[12] our research adds to the growing evidence that the marked cost difference between frail and non-frail patients undergoing TAVI may be related to the increased rates of postoperative complications and longer hospital stay among frail patients.

Despite a small number of cases, high-cost patients disproportionately constitute healthcare expenditures, leading to considerable costs and reimbursements. Goldfarb et al[12] conducted a retrospective study to examine the association between frailty and index hospitalization cost in patients undergoing cardiac surgery in Canada. They found that the seven extreme-cost patients represented 3% of the cohort but constituted 17% of the aggregate costs.[12] Given the financial burden associated with high-cost patients,

identifying those who are likely to incur substantial healthcare costs has great economic and clinical implications. Our study compared the performance of frailty indices in predicting high-cost patient and found an incremental value of the HFRS in predicting high-cost patients compared with the reference model. Key differences amongst the administrative database frailty algorithms may contribute to differences in performance for predicting high-cost patients.

Treatment options for patients with severe aortic stenosis have been based on safety, efficacy and cost-effectiveness. In addition to clinical outcomes, cost is considered an essential factor to inform medical decision-making.[15] Improvements in TAVI technology and increased surgical team's experience have led to a trend toward better outcomes in TAVI, including decreased rates of postoperative complications and a lower rate of readmission, substantially improving the cost-effectiveness of TAVI.[28,29,30] However, although recent evidence suggests a trend toward better outcomes in TAVI procedure, some patient factors that have been shown to predict poor outcomes lead to the futility of TAVI. Amongst these patient-level factors, frailty has been recognized as a powerful predictor for adverse outcomes, and the higher cost associated with frailty may further jeopardize the cost-effectiveness of TAVI in this population.[15] Nowadays, indications for TAVI have expanded to lower risk, younger and asymptomatic patients. Preoperative frailty assessment can inform clinical decision-making related to the treatment of aortic stenosis.

Our study has several unique strengths. We included all patients aged 66 or older who underwent a TAVI procedure from 2012 to 2018 in Ontario, Canada. The linked administrative data captured health service utilization for all TAVI recipients within Ontario. Cardiac data is systematically collected through the CorHealth registry and this is considered a good source for epidemiological studies, and monitoring of trends in utilization of specific services and procedures. On the other hand, we followed the existing methodological recommendations to comprehensively reflect the performance of the two frailty indices.

Our study has several significant limitations. First, use of linked health administrative data may include possible inaccuracies in administrative database codes. Second, we only tested the performance of frailty indices in predicting cost outcomes for up to one year. Long term outcomes were not examined. Third, restricted by the availability of cost data, we did not have case-costing data. Thus, we were unable to capture costs associated with specific interventions or episodes of care. Fourth, we did not consider societal costs such as productivity costs or out-of-pocket costs to patients as these are not available in the administrative database.

In conclusion, frailty is associated with increased one-year healthcare costs after TAVI. Preoperative frailty assessment may add predictive value for cost outcomes after TAVI.

6.5 Supplementary tables

S Table 6.1 Cost outcomes of the cohort

Variables (N=3,866)	Mean (SD)	Median (interquartile range)
Total one-year cost [a]	57,937 (44,628)	44,380 (33,076-66,666)
Inpatient cost [b]	41,019 (37,472)	29,399 (21,175-46,738)
Drug cost [c]	2,844 (5,700)	1,757 (852-3,104)
Physician services and diagnostic services cost [d]	11,389 (5,161)	9,988 (8,111-13,094)
Ambulatory care cost [e]	2,329 (10,731)	535 (0-1,310)

[a] One-year cost captured costs incurred by the Ontario Ministry of Health and Long-Term Care over a one-year period from the first day of the index hospitalization and ending 365 days later, including inpatient cost, drug cost, physician and diagnostic services and ambulatory care.

[b] Inpatient cost captured inpatient costs over a one-year period, including the cost of rehospitalization, from the first day of the index hospitalization and ending 365 days later.

[c] Drug cost captured costs covered by the Ontario Drug Benefit program over a one-year period from the first day of the index hospitalization and ending 365 days later.

[d] Cost of physician and diagnostic services, over a one-year period from the first day of the index hospitalization and ending 365 days later, was captured in the OHIP database.

[e] Ambulatory care costs after discharge was captured in the NACRS database.

TAVI, transcatheter aortic valve implantation. **N**, sample size. **SD**, standard deviation. **ED**, emergency department. **OHIP**, Ontario Health Insurance Plan. **NACRS**, National Ambulatory Care Reporting System.

S Table 6.2 Prediction of high-cost patients with the Johns Hopkins ACG frailty indicator

Parameter	Odds ratio	95% CI	p-value
Johns Hopkins ACG frailty indicator	1.433	0.991-2.071	0.0559
Demographics			
Age			
66-70	Referent		
71-75	1.061	0.537-2.096	0.8654
76-80	0.517	0.262-1.019	0.0566
81-85	0.678	0.359-1.282	0.2320
86-90	0.398	0.203-0.778	0.0071
>90	**0.255**	**0.101-0.644**	**0.0039**
Gender			
Males	Referent		
Females	0.874	0.625-1.222	0.4294
Income quintile			
1	Referent		
2	0.945	0.567-1.575	0.8280

3	1.247	0.764-2.033	0.3774
4	1.261	0.766-2.077	0.3623
5	1.488	0.918-2.412	0.1068
Rural residence	1.380	0.883-2.157	0.1575
Comorbidities			
Myocardial infarction	0.883	0.551-1.413	0.6026
Ischemic heart disease	0.846	0.577-1.242	0.3937
History of heart failure	**1.555**	**1.009-2.397**	**0.0453**
Heart failure hospitalization within 90 days	1.096	0.711-1.688	0.6792
Previous PCI	0.853	0.590-1.233	0.3975
Previous CABG	**0.625**	**0.401-0.973**	**0.0373**
Previous valve surgery	0.602	0.187-1.941	0.3953
Previous ICD	0.592	0.127-2.769	0.5052
Valve-in-valve	0.681	0.192-2.415	0.5516
Previous permanent pacemaker	0.726	0.393-1.341	0.3062
COPD	1.017	0.739-1.399	0.9186
Cognitive impairment/ dementia	0.560	0.281-1.115	0.0990
Hypertension	0.997	0.509-1.951	0.9923

Dyslipidemia	0.897	0.642-1.255	0.5270
Cancer	1.227	0.718-2.097	0.4551
Cerebrovascular disease	1.305	0.735-2.316	0.3631
Atrial fibrillation	1.177	0.844-1.642	0.3357
Peripheral vascular disease	1.396	0.813-2.397	0.2270
Dialysis	**7.931**	**4.943-12.725**	**<0.0001**
ED visit before TAVI (within 1 year)	**1.918**	**1.197-3.075**	**0.0068**
Anemia			
Absent	Referent		
Present	**2.253**	**1.274-3.985**	**0.0053**
Missing	**5.820**	**1.499-22.599**	**0.0110**
Creatinine (u mil/mol)			
<120	Referent		
≥120	<0.001	<0.001 - >999.999	0.9640
Missing	0.394	0.111-1.393	0.1482
Access site			
Transfemoral	Referent		
Non-transfemoral	**1.992**	**1.323**	**0.0010**

Year of procedure			
2012	Referent		
2013	0.760	0.392-1.471	0.4150
2014	1.086	0.579-2.037	0.7979
2015	0.731	0.378-1.413	0.3512
2016	0.662	0.343-1.278	0.2190
2017	0.739	0.389-1.406	0.3567

ACG, Adjusted Clinical Groups. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department.

S Table 6.3 Prediction of high-cost patients with the HFRS

Parameter	Odds ratio	95% CI	p-value
HFRS	**1.782**	**1.250-2.542**	**0.0014**
Demographics			
Age			
66-70	Referent		
71-75	1.098	0.555-2.174	0.7876
76-80	0.544	0.275-1.073	0.0789
81-85	0.725	0.383-1.372	0.3223
86-90	**0.425**	**0.217-0.833**	**0.0126**
>90	**0.281**	**0.111-0.712**	**0.0074**
Gender			
Males	Referent		
Females	0.867	0.620-1.213	0.4058
Income quintile			
1	Referent		
2	0.937	0.562-1.562	0.8017

3	1.242	0.761-2.025	0.3858
4	1.261	0.765-2.077	0.3633
5	1.498	0.923-2.431	0.1015
Rural residence	1.426	0.912-2.229	0.1200
Comorbidities			
Myocardial infarction	0.819	0.509-1.316	0.4082
Ischemic heart disease	0.849	0.578-1.246	0.4019
History of heart failure	1.501	0.972-2.318	0.0668
Heart failure hospitalization within 90 days	1.047	0.678-1.616	0.8365
Previous PCI	0.845	0.584-1.221	0.3687
Previous CABG	0.644	0.413-1.004	0.0523
Previous valve surgery	0.649	0.198-2.121	0.4738
Previous ICD	0.605	0.128-2.854	0.5254
Valve-in-valve	0.625	0.174-2.250	0.4723
Previous permanent pacemaker	0.731	0.396-1.348	0.3156
COPD	0.992	0.720-1.366	0.9615
Cognitive impairment/ dementia	0.634	0.330-1.219	0.1720
Hypertension	0.990	0.507-1.935	0.9768

Dyslipidemia	0.875	0.625-1.224	0.4359
Cancer	1.162	0.677-1.994	0.5869
Cerebrovascular disease	1.168	0.654-2.086	0.6003
Atrial fibrillation	1.110	0.794-1.553	0.5421
Peripheral vascular disease	1.342	0.781-2.305	0.2861
Dialysis	**6.920**	**4.265-11.228**	**<0.0001**
ED visit before TAVI (within 1 year)	**1.842**	**1.147-2.959**	**0.0115**
Anemia			
Absent	Referent		
Present	**2.158**	**1.217-3.825**	**0.0085**
Missing	**6.091**	**1.561-23.759**	**0.0093**
Creatinine (u mil/mol)			
<120	Referent		
≥120	<0.001	<0.001->999.999	0.9693
Missing	0.371	0.104-1.317	0.1249
Access site			
Transfemoral	Referent		
Non-transfemoral	**1.999**	**1.325-3.010**	**0.0010**
Year of procedure			

2012	Referent		
2013	0.763	0.394-1.480	0.4242
2014	1.073	0.571-2.018	0.8259
2015	0.738	0.380-1.432	0.3689
2016	0.676	0.350-1.307	0.2441
2017	0.763	0.400-1.455	0.4108

HFRS, Hospital Frailty Risk Score. **CI**, confidence interval. **TAVI**, transcatheter aortic valve implantation. **PCI**, percutaneous coronary intervention. **CABG**, coronary artery bypass grafting. **ICD**, implantable cardiac defibrillator. **COPD**, chronic obstructive pulmonary disease. **ED**, emergency department

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Chapter 7

7 Integrated discussion

This last chapter reviews key findings of this research derived from the chapters 3-6, the implications of these findings for preoperative frailty assessment in patients undergoing TAVI, and highlights future research.

7.1 Summary of key findings

Systematically reviewing the measurement of frailty in patients undergoing TAVI, we found that multi-dimensional frailty measures are more commonly used than single-dimensional measures (Chapter 3 and 4). Even with the same frailty measure, different definitions or cut-off points were utilized, leading to a wide range of frailty prevalence across the literature. The most frequently used frailty measure in TAVI recipients we identified was the modified Fried phenotype, in which disability, muscle strength, mobility, and nutrition were assessed (Chapter 3 and 4). Pooling prognosis of frail patients undergoing TAVI, we found a wide range and substantial heterogeneity of patient outcomes after TAVI, even when we focused only on studies using the Fried frailty phenotype. (Chapter 3 and 4). Using GRADE to assess confidence in prognosis estimates from the meta-analyses, we found low or very low confidence in the overall estimates, due to inconsistency as influenced by the heterogeneity of estimates and indirectness of frailty measures identified in the studies (Chapter 3 and 4).

Drawing on data from the Ontario TAVI cohort and the linked data derived from administrative databases at the IC/ES, we found poor agreement between the two database driven frailty indices (Johns Hopkins ACG frailty indicator and HFRS), despite similar proportions of frail patients diagnosed (Chapter 5). Adjusting for demographics and baseline comorbidities, hierarchical cluster regression analysis showed that both the Johns Hopkins ACG frailty indicator and the HFRS were significantly associated with one-year mortality and rehospitalization following TAVI (but not in-hospital mortality) (Chapter 5). Comparing predictive performance between the pre-specified reference model and each model with frailty indices, we found that both the Johns Hopkins ACG

frailty indicator and HFRS improved performance of the model with frailty indices in predicting one-year mortality and rehospitalization (but not in-hospital mortality) (Chapter 5).

Analysis cost data from the Ontario TAVI cohort showed that frail patients incurred significantly increased one-year healthcare costs (including inpatient cost and costs of drugs, physician billing, lab, diagnostic test and ambulatory care) after TAVI (Chapter 6). The HFRS was a significant predictor for high-cost patients. Comparing predictive performance between the pre-specified reference model and each model with frailty indices, we found that the HFRS improved the performance of the model in predicting high-cost patients undergoing TAVI (Chapter 6).

7.2 Measurement of frailty in TAVI recipients

As described, multi-dimensional measures were found to be used more commonly than single-dimensional measures in patients undergoing TAVI (Chapter 4). A wide range of frailty prevalence was found in patients undergoing TAVI, primarily owing to the variety of frailty concepts. Due to the variety of frailty definitions and the diversity of TAVI populations, a substantial heterogeneity of patent outcomes after TAVI was found, lowering the confidence in the overall prognosis estimates from the meta-analyses. These findings highlight challenges associated with frailty measurement in research and clinical practice: a lack of a perfect frailty measure and difficulties in choosing which frailty measure to use. Challenges associated with frailty measurement have been pointed out across previous literature, not only in TAVI research [1] but also in community-based studies.[2] Efforts to address these challenges may include deciding on one frailty measure from the existing measures, developing a new standard frailty measure, or using one measure for frailty screening and a second one for a full frailty assessment.[3,4] Although current TAVI research continues on the impacts of frailty on post-TAVI outcomes,[5] consensus on the best approach to assess frailty for patients undergoing TAVI remains unclear. The recently developed Frailty-AVR measure, developed specifically for use in patients with aortic stenosis using a large sample size, may yet emerge as a consensus,

but the novelty of the measure and its use in only one publication meant we were unable to include the Frailty-AVR data in our systematic review.[6]

Since both the Fried frailty phenotype and Rockwood frailty index demonstrated high validity and reliability, the two frailty measures are often reported as the two most commonly used frailty measures in research and clinical practice.[3] However, the most commonly used frailty measure in TAVI recipients we identified was the modified Fried phenotype, in which disability, muscle strength, mobility and nutrition were assessed. Approaches to modify the Fried frailty phenotype we identified included measuring fewer domains than the Fried frailty phenotype measures (i.e. exhaustion, weight loss, lower level of physical activity, slowness and weakness), using different cut-off points, or using different tools to assess the same domain. Previous literature [3] has revealed that many frailty measures were modified from the original, validated version, and many of these frailty measures had not been validated. A systematic review [7] conducted by Theou and colleagues found that among the 264 studies evaluating frailty using the phenotype criteria, only 24 studies assessed all criteria proposed in the original Fried frailty phenotype. The great majority of studies modifying the Fried frailty phenotype led to substantial differences in frailty prevalence, the performance of identifying frailty and the ability to predict patient outcomes.[7] Future studies should consider the impacts of modifying the original frailty measure if the original frailty criteria will be modified.

Patients referred for TAVI typically have advanced age and multiple comorbidities, and the prevalence of frailty can be as high as 90% (Chapter 4). TAVI is associated with a unique set of complications, such as stroke, bleeding, conduction disturbances and acute kidney injury, all of which may increase the risk of death following TAVI.[8,9] The decision to perform TAVI has been primarily based on preoperative risk assessment using risk scoring systems, such as the STS risk score and the EuroSCORE.[10,11,12,13,14] However, neither the STS risk score nor the EuroSCORE measures frailty preoperatively. As a missing parameter not captured by traditional risk scores for cardiac surgery, frailty has been recognized as a powerful predictor for post-TAVI outcomes, such as mortality, morbidity and functional decline.[15,16,1] In order to better reflect a patient's actual biological status and inform clinical decision-making related to the treatment of severe

aortic stenosis, current guidelines have recommended assessing frailty preoperatively in patients who are candidates for TAVI. [17,18,15] Although there have been a large number of frailty measures, only some of these measures are suited for clinical preoperative frailty assessment. Dent and colleagues [3] suggested that frailty measures suited for population-level frailty screening and those used for clinical assessment are different. Martin and colleagues [19] also highlighted that clinical decision-makers should focus on improving prediction of benefit and risk through a quantitative assessment of frailty, and a frailty measure's reliability and predictive performance are of importance. Moreover, for the purpose of designing population-level interventions, frailty assessment should help identify those at increased risk of adverse outcomes, enabling more effective use of healthcare resources.[19] Future studies should consider using the most effective measure to identify frailty in patients undergoing TAVI based on their purposes.

Frailty indices that were derived and validated using health administrative data have unique advantages. For instance, these frailty indices can be used wherever electronic health data are available and encoded, reducing inter-operator variability and operationalization burden associated with manual scoring systems.[20,21] Our systematic review included articles published between January 2006 and October 10, 2018 (Chapter 3). The systematic review did not include any study assessing frailty using the Johns Hopkins ACG frailty indicator or the HFRS (Chapter 4). Both the Johns Hopkins ACG frailty indicator and HFRS are administrative database driven frailty indices.[20,22,23] The Johns Hopkins ACG frailty indicator has been validated against a clinical frailty measure (the Vulnerable Elderly Scale[23]) in patients aged 65 years or older who underwent an elective noncardiac surgery.[22] The HFRS was developed and validated in patients aged 75 years or older with elective, non-elective and day-case admissions to hospitals.[20] Further to this, McIsaac and colleagues [21] recently developed and validated a Preoperative Frailty Index using linked administrative data of patients aged 65 years or older who had major elective or emergency surgery in Canada. The new frailty indices represent recent efforts to develop frailty algorithms for use with health administrative databases or electronic medical records.[20,21,24,25,26] However, none of these frailty indices was developed or validated in TAVI populations. Future research may consider

developing a frailty algorithm for a TAVI population's use with health administrative data.

7.3 Prognosis of frail patients undergoing TAVI

Systematically reviewing the frailty measures in TAVI patients and pooling clinical outcomes of frail TAVI recipients, our research can help better understand how frailty is assessed among TAVI patients, provide information on the prognosis of frail patients after TAVI, and ultimately inform clinical decision-making related to treatment of severe aortic stenosis. Previous studies have demonstrated that frail patients were associated with worse prognosis after TAVI. Our research also suggested that frailty was associated with one-year mortality and rehospitalization (Chapter 5). However, with different frailty measures and substantial heterogeneity in TAVI populations, studies evaluating the same patient outcomes may show conflicting results. For example, a prospective observational study by Bureau et al[27] assessed frailty using a multidimensional prognostic index based on comprehensive geriatric assessment, and found there was no significant difference in the 30-day mortality following TAVI between frail and non-frail groups. In contrast, a study by Alfredsson et al [28] showed a significantly higher 30-day mortality after TAVI in the frail group (defined by slow gait speed) (8.4%) than that in the non-frail group (6.6%). Furthermore, with different frailty definitions, the prognosis of frail patients can vary widely. For example, our research found one-year mortality after TAVI ranging from 14.8% to 37.5% (Chapter 4). These findings suggest that key differences amongst frailty measures may result in different prognosis of frail patients undergoing TAVI. Therefore, if preoperative frailty assessment is incorporated into clinical practice as part of preoperative risk assessment in patients referred for TAVI, the striking impacts of different frailty measures on predictive performance should be considered.

In addition to mortality and morbidity, quality of life after TAVI is also of clinical importance to clinicians, patients and policy decision makers. Our systematic review found few studies reporting frail patients' quality of life following TAVI. Only two studies[29, 30] measured quality of life in frail patients undergoing TAVI. Kobe et al[29]

assessed quality of life before and 30 days after TAVI using the Short Form-36 questionnaire, and found that the mean scores of all but role physical and social functioning were significantly lower in frail patients (diagnosed with a comprehensive frailty score [31] that assessed chair risk, weakness, stairs, clinical frailty scale and serum creatinine). Okoh et al[30] assessed quality of life using the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ), and found that at 30 days, frail patients (diagnosed by the Fried frailty phenotype) reported worse scores in two domains (i.e. KCCQ-symptoms and KCCQ physical limitation), but the quality of life improved overall. Future research may need to measure the quality of life before and after TAVI using standardized quality of life measurement tools to understand the prognosis of frail patients undergoing TAVI more comprehensively.

7.4 Performance of frailty indices in predicting post-TAVI outcomes

Our study found similar proportions of frail patients diagnosed and a fair agreement (kappa statistic: 0.3236; 95% CI, 0.2888-0.3582) between the Johns Hopkins ACG frailty indicator and the HFRS (Chapter 5). Although frail and non-frail groups demonstrated marked differences in their demographics and procedural characteristics, differences in patient characteristics were found more dramatic when frailty was diagnosed using the HFRS (Chapter 5). In the original validation study of the HFRS,[20] the authors compared the HFRS with dichotomized Fried and Rockwood scales. The authors found fair agreement between the HFRS and dichotomized Fried (kappa statistic, 0.22; 95% CI, 0.15-0.30) and Rockwood scales (kappa statistic, 0.30; 0.22-0.38).[20] Further to this, Aguayo and colleagues [32] assessed the agreement between 35 frailty scores using the kappa score. The authors found a wide range of agreement amongst the frailty scores, with the kappa score ranging from 0.10 to 0.83.[32] In the study by Aguayo and colleagues,[32] the highest degree of agreement was found among frailty scores based on the accumulated deficits framework. In our research, both the Johns Hopkins ACG frailty indicator and the HFRS were developed and validated based on the accumulated deficits model. The principle of the accumulated deficits model is to count deficits in health. The more deficits a patient has, the more likely the patient is to be frail.[33,34,35] However, the

Johns Hopkins ACG frailty indicator and the HFRS included different health deficits. The Johns Hopkins ACG frailty indicator assessed malnutrition, dementia, impaired vision, decubitus ulcer, incontinence of urine, loss of weight, poverty, barriers to access to care, difficulty in walking and falls,[22] whereas the HFRS assessed a total of 109 health deficits.[20] Moreover, the weights assigned to each deficit in calculating the frailty score might differ. Of the 109 health deficits in the HFRS, dementia in Alzheimer's disease, hemiplegia, Alzheimer's disease, sequelae of cerebrovascular disease and other symptoms and signs involving the nervous and musculoskeletal systems are the five deficits assigned with highest weights.[20] Due to the proprietary nature of the Johns Hopkins ACG system, specific codes are not publicly available and thus it is not possible to compare the weighting between the two codes.[22] Our findings suggest that differences amongst the frailty indices may result in substantial differences in the ability to identify frailty. Even though developed based on the same frailty concept, the frailty indices should not be considered interchangeable.

Frail and non-frail groups demonstrated significant differences in in-hospital mortality, 1-year mortality and rehospitalization following TAVI (Chapter 5). Adjusting for demographics and baseline comorbidities, our research found that both the Johns Hopkins ACG frailty indicator and the HFRS were significantly associated with 1-year mortality and rehospitalization, but not in-hospital mortality (Chapter 5). Our findings demonstrate the predictive value of frailty in predicting mortality and rehospitalization 1 year after TAVI, further highlighting the significance of preoperative frailty assessment. Current guidelines recommend assessing frailty preoperatively to inform better clinical decision-making.[17,18] Moreover, existing research examining the association of frailty and post-TAVI outcomes also recognizes frailty as a powerful predictor for adverse outcomes after TAVI. A study by Afilalo and colleagues[6] examining whether frailty measures add incremental value to existing risk scores in predicting adverse outcomes following TAVI or SAVR. The study[6] compared c-statistic, BIC and IDI, and found that frailty, regardless of the measure, adds incremental value above existing risk prediction models. Our research compared the AIC, BIC, IDI, c-statistic and NRI, suggesting that the inclusion of either the Johns Hopkins ACG frailty indicator or the HFRS adds incremental value

above a pre-specified reference model to predict mortality and rehospitalization 1 year after TAVI (but not in-hospital mortality). Restricted by the availability of data housed at the IC/ES, our research was unable to adjust for all variables that have been demonstrated to impact on outcome variables, such as New York Heart Association classification and left ventricular ejection fraction. Future research could examine the performance of the frailty indices in predicting post-TAVI outcomes compared to other existing risk models.

Although differences in patient characteristics were more dramatic when frailty was diagnosed using the HFRS, the Johns Hopkins ACG frailty indicator outperformed the HFRS to predict mortality and rehospitalization 1-year after TAVI. In addition to more negative values of AIC and BIC (i.e., more negative values indicating improved prediction[36]), more positive values of IDI and NRI (i.e., more positive values indicating improved prediction[37,38]) were observed when the Johns Hopkins ACG frailty indicator was added to a pre-specified reference model (Chapter 5). The NRI is considered the sum of differences in proportions of patients 'moving up' (i.e., the probability of the event increases) minus the proportion 'moving down' (i.e., the probability of the event decreases) for patients with the outcome, and the proportion of patients moving down minus the proportion moving up for patient without the outcome.[38] For patients with outcomes (i.e., 1-year mortality and rehospitalization), the NRIs were negative. The negative NRIs for patients with the outcomes were offset by the more positive NRIs for patients without the outcomes, leading to positive NRIs overall (Chapter 5). Our findings indicated that with a frailty assessment, clinicians might be able to screen out robust patients who are likely to benefit from TAVI more accurately. However, the risk of patients who are likely to experience adverse outcomes may be underestimated. The NRIs our research calculated was category-free NRI, which is considered the best metric to assess a new predictor's true discriminatory ability compared to other predictors.[39] Category-free NRI does not rely on pre-defined risk thresholds and has been criticized for lacking a clinically meaningful interpretation in the literautre.[40,41,42,39] However, category-free NRI has unique advantages. For example, since category-free NRI depends mainly on the effect size of a new predictor, it is not affected by the baseline model.[37,39] The category-free NRI is considered to capture the marginal strength of the new predictor,

representing a summary measure of quantifying the correct upward versus downward movement in model-based predicted probabilities for patients with outcomes and those without outcomes.[37,39] To better explore the improved prediction offered by adding a frailty measure, future research could compare category-free NRI and the NRI based on pre-defined risk categories.

The lack of consensus surrounding frailty measures limits their use in clinical practice. Although there is no one perfect frailty measure, Clegg et al [43] proposed several criteria for a frailty measure, including identifying frailty reliably, predicting adverse health outcomes accurately and being simple to apply.[3,43,44] Developed and validated with health administrative data, both the Johns Hopkins ACG frailty indicator and the HFRS have unique advantages over frailty measures that may be subject to inter-operator variability and operationalization burden. Our research suggests that preoperative frailty assessment, using either the Johns Hopkins ACG frailty indicator or the HFRS, may add predictive value for clinical outcomes after TAVI. These findings add to the growing evidence that database driven frailty indices can be utilized for preoperative frailty assessment. As discussed, neither the Johns Hopkins ACG frailty indicator nor the HFRS was developed or validated in TAVI populations. Future research could improve accuracy by further examining the role of the included variables or adding additional variables. Additional studies could compare the performance of other database driven frailty indices (i.e., preoperative frailty index developed by McIsaac et al[21]) in predicting post-TAVI outcomes. Future research could also compare the performance of database driven frailty indices with frailty measures based on different frailty concepts (i.e., Fried frailty phenotype).

7.5 Performance of frailty indices in predicting costs of TAVI

The incorporation of preoperative frailty assessment into clinical practice for patients undergoing TAVI may provide important information about risk and prognosis, to assist with shared decision making.[45,46] Existing research has revealed that frailty is associated

with prolonged hospitalization length, longer intensive care unity stays and a higher rate of rehospitalization, all of which can dramatically increase healthcare costs.[47] Given the clear connection between frailty and adverse outcomes and between adverse outcomes and healthcare costs, the link between frailty and costs after TAVI has been suggested to be considered. In addition to clinical outcomes, healthcare cost is considered an essential factor to inform medical decision-making.[48] Our research demonstrated that frail patients, defined using either the Johns Hopkins ACG frailty indicator or the HFRS, incurred increased one-year healthcare costs after TAVI (Chapter 6). The marked cost difference between frail and non-frail patients may largely be related to the increased rates of postoperative complications and longer hospital stay among frail patients. Our findings contribute to the emerging literature that frail patients incurred increased healthcare costs in the year following TAVI. Given the higher cost associated with frailty, the cost-effectiveness of TAVI might be jeopardized in this population. Further research could examine the cost-effectiveness of TAVI in frail patients to inform medical decision-making related to the treatment of aortic stenosis.

Although frail patients, defined using either the Johns Hopkins ACG frailty indicator or the HFRS, incurred increased healthcare costs after TAVI, only the HFRS was significantly associated with increased healthcare costs after adjusting for patient and procedure characteristics (Chapter 6). Although frail and non-frail groups demonstrated marked differences in their clinical outcomes (i.e., one-year mortality, in-hospital mortality, rehospitalization and length of hospitalization), differences in patient outcomes were more dramatic when frailty was diagnosed using the HFRS (Chapter 5). These findings suggest that the association of frailty and healthcare costs might be largely determined by rates of adverse outcomes. Additional studies could further explore the impacts of frailty on healthcare costs

Despite a small number of cases, high-cost patients disproportionately constitute healthcare expenditures, leading to considerable costs and reimbursements. Given the financial burden associated with high-cost patients, identifying those who are likely to incur substantial healthcare costs has great economic and clinical importance. Compared with the pre-specified reference model, the HFRS improved performance in predicting

high-cost patients (Chapter 6). These findings suggest that preoperative frailty assessment may add predictive value for high-cost patients after TAVI. The HFRS demonstrated improved prediction for high-cost patients, whereas the Johns Hopkins ACG frailty indicator outperformed the HFRS in predicting one-year mortality and rehospitalization. Our findings may also suggest that the performance of frailty indices might vary when predicting different outcomes. Preoperative frailty assessment should carefully consider the type of outcomes, and use the most reliable, accurate frailty measure.

Preoperative frailty assessment provides additional information not captured by traditional surgical risk assessment, and may help clinicians make more informed decisions so as to optimize care and resources utilization. Previous research [3, 4] has recommended a 2-step frailty assessment, in which a rapid, user-friendly tool would be used to screen out robust patients, and those flagged as potentially frail would be referred for comprehensive geriatric assessment. Using a health-economic model, we evaluated the cost-effectiveness analysis of a frailty assessment initiative in patients undergoing coronary artery bypass graft (CABG) surgery. The study[49] suggested that in the Canadian setting, preoperative frailty screening may lead to improved survival after CABG, with reduced healthcare costs. Further research could estimate the cost-effectiveness of preoperative frailty assessment in patients undergoing TAVI to better understand the incorporation of frailty assessment into clinical practice for TAVI.

7.6 Future research and directions

In summary, further research should 1) focus on the reliability and accuracy of frailty measures in patients undergoing TAVI with different clinical characteristics and examine how these frailty measures contribute to the prediction of post-TAVI outcomes as well as health-related quality of life, 2) compare the two frailty indices (i.e., Johns Hopkins ACG frailty indicator and the HFRS) with other frailty measures (i.e., existing database driven frailty indices, frailty measures derived from other frailty concepts), 3) examine the cost-effectiveness of TAVI in frail patients, 4) estimate the cost-effectiveness of preoperative frailty assessment in patients undergoing TAVI, and 5) explore how to incorporate the

preoperative frailty assessment into clinical practice for TAVI patients in the Canadian setting.

7.7 References

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Appendices

Appendix A: Purpose of the database and key parameters taken from the database

Database	**Purpose of the database**	**Key parameters taken from the database**
Discharged Abstract Database (DAD)	Captures administrative, clinical and demographics information on hospital discharges, including deaths and transfers.	- Death - Demographics - Readmission - Cost - Myocardial infarction - Ischemic heart disease - Previous coronary artery bypass grafting - Previous Aortic valve replacement - Previous mitral valve replacement or repair - Previous tricuspid valve replacement or repair - Previous percutaneous coronary intervention - Previous implantable cardiac defibrillator - Permanent pacemaker - Dyslipidemia - Past atrial fibrillation - Peripheral vascular disease

		- Cerebrovascular disease - History of cancer - Cognitive impairment/ dementia - Dementia - Dialysis - Bleeding - Stroke after TAVI
National Ambulatory Care Reporting System (NACRS)	Contains data for all hospital-based and community-based ambulatory care, including day surgery, outpatient and community-based clinics and emergency departments	- ED visit
Ontario Drug Benefit Claims (ODB)	Contains drug prescriptions for patients aged 65 years and older in Ontario	- Dementia - Cost
Home Care Database (HCD)	Captures services provided by or coordinated by Ontario's Community Care Access Centres. Community Care Access Centres are organizations established by the Ministry of Health and Long-Term Care.	- Cost
Continuing Care Reporting System (CCRS)	Contains demographic, administrative, clinical and resource utilization	- Cost

	information on individuals who receive continuing care services in hospitals or long-term care homes in Canada	
National Rehabilitation Reporting System (NRS)	Captures information from participating adult inpatient rehabilitation facilities and programs across Canada	- Cost
Ontario Health Insurance Plan Claims Database (OHIP)	Captures all claims made by physicians for insured services provided to Ontario residents.	- Frailty indices - Cost - Previous coronary artery bypass grafting - Previous Aortic valve replacement - Previous mitral valve replacement or repair - Previous tricuspid valve replacement or repair - Previous percutaneous coronary intervention - Previous implantable cardiac defibrillator - Permanent pacemaker - Dyslipidemia - Dementia - Dialysis
Same Day Surgery Database (SDS)	Summarizes same day surgery information about residents in Ontario	- Cost

Congestive Heart Failure (CHF)	Contains all identified prevalent cases since 1991.	- Heart failure
Chronic Obstructive Pulmonary Disease (COPD)	Contains all identified prevalent cases (age 35 yrs.+) since 1991.	- COPD
Ontario Hypertension Dataset (HYPER)	Contains all Ontario hypertension patients identified since 1988.	- Hypertension
Ontario Census Area Profiles (CENSUS)	Contains information from the Census of population in Ontario	- Income quintile
Registered Persons Database (RPDB)	Contains information on persons registered under the OHIP	- Death
Assistive Devices Program (ADP)	Covers the cost of specialized supplies for people with long-term physical disability	- Cost
Client Agency Program Enrolment (CAPE)	Contains information on primary care organizations that a patient registered	- Cost
Ontario Case Costing Initiative (OCCI)	Captures the costs of acute inpatient, day surgery, ambulatory care cases, mental health, rehabilitation and complex continuing care.	- Cost

Appendix B: Frailty-Defining Diagnoses in Johns Hopkins ACG Frailty Indicator

Frailty Concept Diagnoses (Examples)	
Malnutrition	Nutritional marasmus Other severe protein-calorie malnutrition
Dementia	Senile dementia with delusional or depressive features Senile dementia with delirium
Impaired Vision	Profound impairment, both eyes Moderate or severe impairment, better eye/lesser eye: profound
Decubitus Ulcer	Decubitus ulcer
Incontinence of Urine	Incontinence without sensory awareness Continuous leakage
Loss of Weight	Abnormal loss of weight and underweight Feeding difficulties and mismanagement Incontinence of feces Obesity (morbid)
Poverty	Lack of housing Inadequate housing Inadequate material resources

Barriers to Access of Care	No medical facility for care No medical facilities necessary
Difficulty in Walking	Difficulty in walking Abnormality of gait
Fall	Fall on stairs or steps Fall from wheelchair

Appendix C: List of 109 ICD-10 codes included and number of points for each to create the hospital frailty risk score (HFRS)

ICD Code	ICD Description	Points awarded
F00	Dementia in Alzheimer's disease	7.1
G81	Hemiplegia	4.4
G30	Alzheimer's disease	4.0
I69	Sequelae of cerebrovascular disease (secondary codes)	3.7
R29	Other symptoms and signs involving the nervous and musculoskeletal systems (R29.6 Tendency to fall)	3.6
N39	Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	3.2
F05	Delirium, not induced by alcohol and other psychoactive substances	3.2
W19	Unspecified fall	3.2
S00	Superficial injury of head	3.2
R31	Unspecified haematuria	3.0
B96	Other bacterial agents as the cause of diseases classified to other chapters (secondary code)	2.9

R41	Other symptoms and signs involving cognitive functions and awareness	2.7
R26	Abnormalities of gait and mobility	2.6
I67	Other cerebrovascular diseases	2.6
R56	Convulsions, not elsewhere classified	2.6
R40	Somnolence, stupor and coma	2.5
T83	Complications for genitourinary prosthetic devices implants grafts	2.4
S06	Intracranial injury	2.4
S42	Fracture of shoulder and upper arm	2.3
E87	Other disorders of fluid, electrolyte and acid base balance	2.3
M25	Other joint disorders, not elsewhere classified	2.3
E86	Volume depletion	2.3
R54	Senility	2.2
Z50	Care involving use of rehabilitation procedures	2.1
F03	Unspecified dementia	2.1
W18	Other fall on same level	2.1
Z75	Problems related to medical facilities and other health care	2.0
F01	Vascular dementia	2.0

S80	Superficial injury of lower leg	2.0
L03	Cellulitis	2.0
H54	Blindness and low vision	1.9
E53	Deficiency of other B group vitamins	1.9
Z60	Problems related to social environment	1.8
G20	Parkinson's disease	1.8
R55	Syncope and collapse	1.8
S22	Fracture of rib(s), sternum and thoracic spine	1.8
K59	Other functional intestinal disorders	1.8
N17	Acute renal failure	1.8
L89	Decubitus ulcer	1.7
Z22	Carrier of infectious disease	1.7
B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	1.7
L97	Ulcer of lower limb, not elsewhere classified	1.6
R44	Other symptoms and signs involving general sensations and perceptions	1.6
K26	Duodenal ulcer	1.6
I95	Hypotension	1.6
N19	Unspecified renal failure	1.6

A41	Other septicaemia	1.6
Z87	Personal history of other diseases and conditions	1.5
J96	Respiratory failure, not elsewhere classified	1.5
X59	Exposure to unspecified factor	1.5
M19	Other arthrosis	1.5
G40	Epilepsy	1.5
M81	Osteoporosis without pathological fracture	1.4
S72	Fracture of femur	1.4
S32	Fracture of lumbar spine and pelvis	1.4
E16	Other disorders of pancreatic internal secretion	1.4
R94	Abnormal results of function studies	1.4
N18	Chronic renal failure	1.4
R33	Retention of urine	1.3
R69	Unknown and unspecified causes of morbidity	1.3
N28	Other disorders of kidney and ureter, not elsewhere classified	1.3
R32	Unspecified urinary incontinence	1.2
G31	Other degenerative disease of nervous system, not elsewhere classified	1.2
Y95	Nosocomial condition	1.2

S09	Other and unspecified injuries of head	1.2
R45	Symptoms and signs involving emotional state	1.2
G45	Transient cerebral ischaemic attacks and related syndromes	1.2
Z74	Problems related to care-provider dependency	1.1
M79	Other soft tissue disorders, not elsewhere classified	1.1
W06	Fall involving bed	1.1
S01	Open wound of head	1.1
A04	Other bacterial intestinal infections	1.1
A09	Diarrhoea and gastroenteritis of presumed infectious origin	1.1
J18	Pneumonia, organism unspecified	1.1
J69	Pneumonitis due to solids and liquids	1.1
R47	Speech disturbances, not elsewhere classified	1.0
E55	Vitamin D deficiency	1.0
Z93	Artificial opening status	1.0
R02	Gangrene, not elsewhere classified	1.0
R63	Symptoms and signs concerning food and fluid intake	0.9
H91	Other hearing loss	0.9
W10	Fall on and from stairs and steps	0.9

W01	Fall on same level from slipping, tripping and stumbling	0.9
E05	Thyrotoxicosis [hyperthyroidism]	0.9
M41	Scoliosis	0.9
R13	Dysphagia	0.8
Z99	Dependence on enabling machines and devices	0.8
U80	Agent resistant to penicillin and related antibiotics	0.8
M80	Osteoporosis with pathological fracture	0.8
K92	Other diseases of digestive system	0.8
I63	Cerebral infarction	0.8
N20	Calculus of kidney and ureter	0.7
F10	Mental and behavioural disorders due to use of alcohol	0.7
Y84	Other medical procedures as the cause of abnormal reaction of the patients	0.7
R00	Abnormalities of heart beat	0.7
J22	Unspecified acute lower respiratory infection	0.7
Z73	Problems related to life-management difficulty	0.6
R79	Other abnormal findings of blood chemistry	0.6
Z91	Personal history of risk factors, not elsewhere classified	0.5

S51	Open wound of forearm	0.5
F32	Depressive episode	0.5
M48	Spinal stenosis (secondary code only)	0.5
E83	Disorders of mineral metabolism	0.4
M15	Polyarthrosis	0.4
D64	Other anaemias	0.4
L08	Other local infections of skin and subcutaneous tissue	0.4
R11	Nausea and vomiting	0.3
K52	Other noninfective gastroenteritis and colitis	0.3
R50	Fever of unknown origin	0.1

Appendix D: Key parameters and coding details

Key parameters	Database	Coding details
Myocardial infarction	CIHI-DAD	ICD-10 codes: I21, I22, I252
Ischemic heart disease	CIHI-DAD	ICD-9: 410-414 ICD-10: I20-I25
Heart failure	CHF	Use the ICES Derived Cohort (CHF) - contains all identified prevalent cases since 1991.
Previous PCI	CIHI-DAD OHIP CorHealth TAVI registry	CCP: 48.02, 48.03 CCI: 1IJ50, 1IJ54GQ-AZ,1IJ57GQ OHIP: Z434
Previous CABG	CIHI-DAD OHIP CorHealth TAVI registry	CCP: 48.1 CCI: 1IJ76 OHIP: R742, R743
Previous valve surgery	CIHI-DAD OHIP	Aortic valve surgery or replacement CCP: 47.03, 47.13, 47.24, 47.25 CCI: 1HV80, 1HV90 OHIP: R738, R863

		Mitral valve surgery or replacement CCP: 47.02, 42.12, 47.22, 47.23 CCI: 1HU80, 1HU90 OHIP: R734-735 Tricuspid valve surgery or replacement CCP: 47.04, 47.14, 47.26, 47.27 CCI: 1HS80, 1HS90 OHIP: R728
Previous ICD	CIHI-DAD OHIP	CCI: 1HZ53GRFS, 1HZZ53LAFS, 1HZ53SYFS, 1HZ53GRFU OHIP: R761, R753, Z429
Previous permanent pacemaker	CIHI-DAD OHIP	CCI: 1HZ53GRNM, 1HZ53GRNK, 1HZ53GRNL, 1HZ53LANL, 1HZ53LANM, 1HZ53LANK, 1HZ53QANK, 1HZ53QANL, 1HZ53QANM, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR OHIP: R752, Z444, Z429
COPD	COPD	Use the ICES Derived Cohort (COPD) - contains all identified prevalent cases (age 35 yrs+) since 1991.
Cognitive impairment/ dementia	CIHI-DAD ODB	ICD-10:

	OHIP	F00,F01,F02,F03,F051, G30,G311,G041,G114,G801,G802,G81,G82,G830,G831,G832,G833,G834,G839 OHIP: 290, 331, 797 ODB subclnam = 'CHOLINESTERASE INHIBITOR'
Hypertension	HYPER	Use the ICES Derived Cohort (HYPER) - contains all Ontario hypertension patients identified since 1988. The presence in Hypertension database any point before index event.
Dyslipidemia	OHIP CIHI-DAD	1)Any in-patient or same-day surgery record with a diagnosis of dyslipidemia or 2) Two OHIP records with a diagnosis of dyslipidemia within 2 years or 3) One OHIP record with a diagnosis of dyslipidemia followed by one in-patient or same-day surgery record with a diagnosis of dyslipidemia within 2 years Diagnosis codes - ICD-9: 272 or ICD-10: E78
Cancer	CIHI-DAD	Primary Cancer: ICD-9: 140-172, 174-1958, 200-208, 2386

		ICD-10: C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97 Metastatic Cancer: ICD-9: 196-199 ICD-10: C77-C80
Cerebrovascular disease	CIHI-DAD	ICD-9: 3623, 430-438 ICD-10: G45, G46, H340, I60-I69
Atrial fibrillation	CIHI-DAD	ICD-10 codes: I48
Peripheral vascular disease	CIHI-DAD	ICD-9: 441.3, 441.4 (abdominal aortic aneurysm), 440.2, 443.9, 444.2 (peripheral artery disease) CCP: 5012 (carotid endarterectomy/stent) ICD-10: I71.3, I71.4 (abdominal aortic aneurysm), I70.2, I73.9, I74.3, I74.4 (peripheral artery disease) CCI: 1JE57, 1JE50, 1JE87 (carotid endarterectomy/ stent)
Dialysis	CIHI-DAD OHIP	CCP: 51.95, 66.98 CCI: 1PZ21HQBR, 1PZ21HPD4 OHIP: R849, R850, G323, G325, G326, G330, G331, G332, G860, G333, G083, G091, G085, G295, G082, G090, G092, G093, G094, G861, G862, G863, G864, G865, G866, G294, G095, G096
Hemoglobin	CorHealth	"HEMOGLOBIN_PRE" in CorHealth

Creatinine	CorHealth	"CREATININECLEARANCEVALUE_PRE" in CorHealth
STS score	CorHealth	"STSSCOREONTHEDAYOFTAVIPROCEDURE" in CorHealth
Transvalvular gradient	CorHealth	"ECHO_MEANTRANSVALVULARGRADIENT" in CorHealth
Status of procedure	CorHealth CIHI-DAD	"STATUSOFPROCEDURECD" in CorHealth If missing, check CIHI-DAD
TAVI access site	CorHealth CIHI-DAD	Use the following CCI codes in CIHI-DAD linked data to confirm the TAVI Access Site (incode 1 to 20): 1HV90GPXXL = transfemoral 1HV90STXXL=transapical/transaorticl/axilaary (i.e. non-transfemoral) 1HV90GRXXL = other (transeptal) Cross check with CorHealth
Valve-in-valve	CIHI-DAD CorHealth	CCP: 47.24, 47.25 CCI: 1HV90 OHIP: R738, R863 (only when in combination with CCP or CCI codes) in patient with current TAVI, then valve-in-valve
Death	CIHI-DAD RPDB	Defined as DTHDATE (death date from admin + RPDB data) in RPDB database

Stroke after TAVI	CIHI-DAD	ICD-9 codes: 362.3, 430, 431, 434, 435, 436 ICD-10: I60, I61, I63 (excluding I63.6), I64, H34.0, H34.1, G45 (excluding G45.4)
Permanent pacemaker after TAVI	CIHI-DAD	CCP: 1HZ53GRNM, 1HZ53GRNK, 1HZ53GRNL, 1HZ53GRFS, 1HZ53GRFR OHIP: R752, Z444, R761, Z429
Bleeding after TAVI	CIHI-DAD	Gastrointestinal I850, K226, K250, K252, K254, K256, K 260, K 262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922 Intracranial I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I621, I629 Urological N020-029, R310, R311, R318 Pulmonary Bleeding R040, R041, R042, R048, R049 Other Bleeding R58, T810
Readmission	CIHI-DAD	Check “ADMDATE” variable in DAD database

ED visit	NACRS	Check “EDVISIT” variable in NACRS database

CIHI, Canadian Institute for Health Information. DAD, Discharge Abstract Database. ICD, implantable cardiac defibrillator. CHF, Congestive Heart Failure. OHIP, Ontario Health Insurance Plan. TAVI, transcatheter aortic valve implantation. CCP, classification of procedures. CCI, classification of health interventions. COPD, chronic obstructive pulmonary disease. ODB, Ontario Drug Benefit. HYPER, Ontario Hypertension Dataset. NACRS, National Ambulatory Care Reporting System.

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5. Publications

In preparation

Li Z, Wijeysundera HC, Bagur R, Cheng D, Martin J, Kiaii B, Qiu F, Fang J, John-Baptiste A. Performance of Frailty Indices in Predicting Clinical Outcomes of Patients Undergoing Transcatheter Aortic Valve Implantation

Li Z, Wijeysundera HC, Bagur R, Cheng D, Martin J, Kiaii B, Qiu F, Fang J, John-Baptiste A. Performance of Frailty Indices in Predicting Cost Outcomes of Patients Undergoing Transcatheter Aortic Valve Implantation.

Under revision

Li Z, Dawson E, Moodie J, Martin J, Bagur R, Cheng D, Kiaii B, John-Baptiste A. Measurement and prognosis of frail patients undergoing transcatheter aortic valve implantation: a systematic review and meta-analysis. BMJ Open.

Published

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