Frailty Assessment Before Cardiac Surgery

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English abstract

Background: Frailty is a geriatric syndrome of impaired resistance to stressors which has been implicated in the pathogenesis and prognosis of cardiovascular disease. Our objective was to systematically explore the role of frailty in patients with cardiovascular disease, and determine the incremental prognostic value of frailty (as measured by gait speed) for predicting adverse events in elderly patients with cardiovascular disease undergoing cardiac surgery.

Methods: After performing a systematic review of the literature, a multi-center prospective cohort of elderly patients undergoing cardiac surgery was assembled. Patients were evaluated with a questionnaire and timed 5-meter gait speed test, with frailty defined as a time taken to walk 5 meters ≥6 seconds. The composite endpoint was postoperative mortality or major morbidity.

Results: Based on nine previous studies, the prevalence of frailty was found to be 2-4 fold greater in patients with cardiovascular disease. Two studies suggested that frailty was a risk factor for mortality, although none specifically addressed frailty as a risk factor for adverse events in response to a cardiac surgery. Our cohort consisted of 131 patients undergoing cardiac surgery with a mean age of 75.8±4.4 years and 34% females. Thirty patients experienced the composite endpoint and frailty (slow gait speed) was an independent predictor (odds ratio 3.05, 95% confidence interval 1.23, 7.54). Addition of frailty to traditional risk assessment models resulted in notable improvements in model performance.

Conclusion: The prevalence of frailty is increased in patients with cardiovascular disease. Frailty, as measured by 5-meter gait speed, is a simple and effective test to identify a subset of vulnerable elders who have an incrementally higher risk of adverse events after cardiac surgery. Further studies are needed to validate the optimal cut-off for slow gait speed.

French abstract

Objectif: La fragilité est un syndrome gériatrique qui signifie une diminution de la résistance au stress physiologique impliquée dans la pathogénèse et le pronostique des maladies cardiovasculaires. Notre objectif était de revoir de façon systématique le rôle de la fragilité dans les maladies cardiovasculaires et de déterminer la valeur incrémentielle de la fragilité (telle que mesurée par la vitesse de marche) pour prédire la mortalité et la morbidité chez les sujets âgés atteints de maladie cardiovasculaire subissant une chirurgie cardiaque.

Méthodes: Après avoir revu la littérature systématiquement, une cohorte multicentrique prospective de sujets âgés subissant une chirurgie cardiaque a été assemblée. Les sujets ont été évalués à l'aide d'un questionnaire et du test de vitesse de marche sur 5 mètres avec la fragilité définie comme étant un temps ≥6 secondes pour marcher 5 mètres. L'issue primaire étant un composé de la mortalité postopératoire et des complications majeures.

Résultats: Neuf études précédentes ont démontré que la prévalence de la fragilité était 2-4 fois plus élevée chez les patients avec une maladie cardiovasculaire. Deux études ont démontré que la fragilité était un facteur de risque pour la mortalité, cependant, aucune étude n'avait précisément adressé la fragilité comme facteur de risque après une chirurgie cardiaque. Notre cohorte incluait 131 sujets subissant une chirurgie cardiaque dont l'âge moyen était de 75.8±4.4 ans et 34% étaient des femmes. Trente patients ont développé l'issue primaire et la fragilité (faible vitesse de marche) était un prédicteur indépendant (odds ratio 3.05, 95% confidence interval 1.23, 7.54). L'inclusion de la fragilité au modèle de prédiction traditionnel a eu comme résultat une nette amélioration des performances du modèle.

Conclusion: La prévalence de fragilité est plus élevée chez les sujets âgés atteints de maladie cardiovasculaire. La vitesse de marche est un test simple et efficace pour identifier une sous-population de patients vulnérables ayant un risque plus élevé de mortalité et morbidité après une chirurgie cardiaque. D'autres études sont nécessaires pour valider la valeur seuil optimale de vitesse de marche.

Contribution of authors

Jonathan Afilalo, MD

Thesis candidate. Initiated and designed the cohort study and systematic review. Wrote the protocol. Put together the questionnaire and consent forms. Prepared and submitted documentation for research ethics approval. Chaired steering committee meetings and wrote detailed meeting minutes. Trained research assistants to administer the questionnaire and gait speed test. Administered the questionnaire and gait speed test to several subjects. Created an electronic database to collect and organize data. Developed the statistical approach and performed all analyses. Wrote the thesis document, cohort study manuscript, and systematic review manuscript.

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Principal collaborator at Duke University for the cohort study, overseeing all aspects of the study at that site. Reviewed and contributed to the thesis document, cohort study manuscript, and systematic review manuscript.

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CHAPTER 1: THESIS INTRODUCTION

The elderly have historically been under-represented in major trials and observational studies, leaving large evidence gaps and consequently, opportunities to advance knowledge in this rapidly growing group of patients. This is particularly true in the field of cardiac surgery where much has been said about the heightened risks of operating on elderly patients, while little is known about the underlying cause of this association and the optimal method to stratify these patients.

Elderly patients account for half of the cardiac surgeries performed in North America, and more notably, 65% of the major complications and 78% of the postoperative deaths (1). Age is the preeminent risk factor for mortality and major morbidity, reflected by its central role in nearly every prognostic model (2). Nevertheless, randomized (3;4) and observational studies (5-10) have consistently shown that elderly patients achieve sizeable benefits from cardiac surgery.

The high-risk high-benefit dichotomy, coupled with the fact that elderly patients are often more severely ill and in need of surgical interventions (10), renders the clinician's decision-making process particularly challenging. More than 19 risk scores have been developed and validated to illuminate the decision making process (13), but these risk scores perform poorly in elderly patients (as do many other risk scores commonly used in cardiology (14-16)).

Accurately predicting outcomes has been very challenging in the elderly because of the marked heterogeneity in this population. This heterogeneity extends beyond differences in comorbid conditions to subclinical impairments in multiple inter-related systems. Accumulation of these subclinical impairments results in

reduced homeostatic reserve and resiliency to stressors – a syndrome known as frailty (25-28).

Recognition of frailty may result in a more comprehensive evaluation of the patient, particularly when assessing their risk of suffering an adverse event in the face of surgery. Therapeutic strategies aimed at preventing adverse events in frail patients are being investigated, including geriatric consultation services and exercise training programs. Moreover, the emergence of minimally invasive procedures may provide a promising alternative to surgery for frail elderly patients.

The number of publications with the subject heading "frail elderly" has grown exponentially in the past 30 years, and there is a budding body of research concerning cardiovascular disease and frailty. A Scientific Statement put forth by the American Heart Association and the Society of Geriatric Cardiology in 2007 concluded that a better understanding of frailty as it pertains to coronary care in the elderly was needed.

Thus, the objective of this thesis was to first perform a systematic review of the literature to delineate the role of frailty in cardiovascular patients; and subsequently, to test whether frailty (as measured by gait speed) was incrementally predictive of mortality and major morbidity in a prospective multi-center cohort of elderly cardiovascular patients undergoing cardiac surgery.

CHAPTER 2: SYSTEMATIC REVIEW OF THE LITERATURE

Published manuscript: "Role of Frailty in Patients with Cardiovascular Disease"

Our systematic review of frailty in cardiovascular patients is presented in manuscript form below. This manuscript was published in The American Journal of Cardiology on June 1st 2009 in volume 103, issue 11, page 1616-1621.

Role of Frailty in Patients with Cardiovascular Disease

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Abstract

Background: Frailty is a geriatric syndrome of increased vulnerability to stressors which has been implicated as an etiologic and prognostic factor in patients with cardiovascular disease. The American Heart Association and the Society of Geriatric Cardiology have called for a better understanding of frailty as it pertains to cardiac care in the elderly.

Methods: We sought to systematically review studies of frailty in patients with cardiovascular disease. We searched Ovid MEDLINE, EMBASE, Cochrane Database, and unpublished sources. Inclusion criteria were assessment of frailty using systematically defined criteria and a study population with prevalent or incident cardiovascular disease.

Results: Nine studies were included encompassing 54,250 elderly patients with a mean weighted follow-up of 6.2 years. Among community-dwelling elders, cardiovascular disease was associated with an odds ratio (OR) of 2.7-4.1 for prevalent frailty, and an OR of 1.5 for incident frailty among those who were not frail at baseline. Gait speed (a measure of frailty) was associated with an OR of 1.6 for incident cardiovascular disease. Among elderly patients with documented severe coronary artery disease or heart failure, the prevalence of frailty was 50-54% and this was associated with an OR of 1.6-4.0 for all-cause mortality after adjusting for potential confounders.

Conclusion: There exists a relation between frailty and cardiovascular disease; frailty may lead to cardiovascular disease, just like cardiovascular disease may lead to frailty. The presence of frailty confers an incremental increase in mortality. The role of frailty assessment in clinical practice may be to refine estimates of cardiovascular risk which tend to be less accurate in the heterogeneous elderly patient population.

Introduction

Frailty is a geriatric syndrome of increased vulnerability to stressors due to impairments in multiple inter-related systems (1) (Figure 1). Since it is a reflection of biological rather than chronological age, frailty may explain why there remains substantial heterogeneity in clinical outcomes within the elderly patient population. The number of publications with the subject heading "frail elderly" has grown exponentially in the past 30 years (2), and there is a growing body of reports concerning cardiovascular disease and frailty which has yet to be systematically reviewed and synthesized. Furthermore, a Scientific Statement put forth by the American Heart Association and the Society of Geriatric Cardiology recently concluded that a better understanding of frailty as it pertains to acute coronary care in the elderly was needed (3). Thus, we performed a systematic review of frailty and cardiovascular disease with the primary objective of exploring the relation between these entities in the medical literature. We hypothesized that frailty was prevalent in patients with cardiovascular disease, and that the combination of frailty and cardiovascular disease was associated with a high risk of mortality.

Methods

The approach used to identify, select, and appraise relevant studies for this systematic review is outlined below, and is in accordance with the standards put forth by the Quality of Reports of Meta-Analyses and Systematic Reviews statement (4).

We searched Ovid MEDLINE from 1966 to December 2007 with a hierarchical search strategy using the following search terms: frail, frailty, elderly, Frail Elderly, Aged, Aged, 80 and over, Health Services for the Aged, and Cardiovascular Diseases. We searched EMBASE from 1980 to December 2007,

the Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews of Effects from inception to 4th Quarter 2007, and the ACP Journal Club from 1991 to November/December 2007. We also searched the Internet and abstracts from major cardiology conferences in North America and Europe. We utilized relevant references from retrieved publications and PubMed's related articles feature to identify studies not captured by our primary search strategy. In addition, we contacted leading investigators in the field to obtain insight into frailty research as it pertains to cardiovascular patients, and to inquire about ongoing or unpublished studies.

Inclusion criteria for our systematic review were: (1) assessment of frailty using systematically defined criteria, (2) patient population with prevalent or incident cardiovascular disease, (3) human subjects. Studies aimed at the biochemical mechanism of frailty were reviewed but not included in the main analysis. Two reviewers (JA, SK) screened 361 studies of which 140 were retrieved to determine if these selection criteria were met.

All qualifying studies were assessed for representativeness of study sample, homogeneity of patients with respect to prognostic risk, completeness of follow-up, reliability and validity of the frailty criteria used.

All studies were reviewed in duplicate by two investigators (JA, SK) and verified independently by one investigator (HB). Disagreements were resolved by consensus. We were able to extract overall study data. We did not obtain individual patient data.

We extracted information on name of study, year of recruitment and publication, number of patients, duration of follow-up, inclusion and exclusion criteria, age, gender, cardiovascular disease (clinical and subclinical, prevalent and incident), frailty status, frailty criteria, and all-cause mortality.

Results

We identified 9 studies meeting our selection criteria (Figure 2), encompassing 54,250 patients with a mean weighted follow-up of 6.2 years. Patients were at least 60 years of age and living in the community (with the exception of one study which had hospitalized patients). All cohorts were recruited prospectively, although 5 of 9 studies were secondary analyses of the initial cohorts. Criteria used to define frailty varied by study and are shown in Table 1. Study characteristics are shown in Table 2.

The association between frailty and cardiovascular disease was initially noted in a secondary analysis of the Zutphen Elderly Men's Study of 450 community-dwelling elders. In this study, 62% of men who were found to be frail were also found to have cardiovascular disease as compared to only 28% of men who were found to be non-frail (OR 4.1; 95% CI 1.8, 9.3) (5).

This finding was explored in the Cardiovascular Health Study of 4,735 community-dwelling elders (6). Prevalent cardiovascular disease was associated with a 3-fold increase in prevalent frailty (OR 2.79; 95% CI 2.12, 3.67). Moreover, subclinical cardiovascular abnormalities detected on noninvasive testing (echocardiographic left ventricular hypertrophy, regional wall motion abnormalities, electrocardiographic abnormalities, systolic hypertension, carotid intimal medial thickness, MRI evidence of stroke, and ankle arm index <0.8) were each associated with frailty. Cumulative survival at 7 years was 12% in frail patients as compared to 43% in non-frail patients (adjusted HR 1.63; 95% CI 1.27, 2.08).

The Beaver Dam Eye Study confirmed the association between frailty, cardiovascular disease, and mortality in 2,962 community-dwelling elders (7). Using Klein's 4-level frailty score, a one level increase in frailty was associated with a 35% increase in odds of cardiovascular disease (OR 1.43; 95% CI 1.13, 1.82 for women / OR 1.33; 95% CI 1.06, 1.67 for men), a 20% increase in odds of

hypertension (OR 1.22; 95% CI 1.02, 1.46 for women / OR 1.22; 95% CI 1.00, 1.49 for men), and a 56% increase in all-cause mortality after 4.5 years of follow-up (adjusted HR 1.56; 95% CI 1.27, 1.92).

In the Women's Health and Aging Studies I & II, frailty was similarly associated with cardiovascular disease (OR 2.72; 95% CI 1.72, 4.30) and mortality (adjusted HR 6.03; 95% CI 3.00, 12.08) in 670 community-dwelling elders (8;9). The aforementioned studies showed a cross-sectional link between frailty and cardiovascular disease (not apparent for other chronic conditions such as cancer) but did not show whether frailty temporally preceded the development of cardiovascular disease or vice versa.

The Women's Health Initiative Observational Study was the largest study and also the first to show that cardiovascular disease was a risk factor for the development of incident frailty (10). Among patients who were not frail at baseline, coronary artery disease (OR 1.47; 95% CI 1.25, 1.73), stroke (OR 1.71; 95% CI 1.24, 2.36), hypertension (OR 1.18; 95% CI 1.08, 1.29), and diabetes mellitus (OR 1.40; 95% CI 1.11, 1.76) were each predictive of incident frailty over 3 years of follow-up. Frailty, defined by Fried's criteria, was subsequently predictive of all-cause mortality over 5.9 years of follow-up (adjusted HR 1.71; 95% CI 1.48, 1.97).

The Health Aging and Body Composition Study first to show that frailty was a risk factor for the development of incident cardiovascular disease (11). Frailty, defined by long distance (400 meter) gait velocity, was found to be a risk factor for the development of incident cardiovascular disease in the cohort of 3,075 community-dwelling elders. After adjusting for potential confounders, gait velocity in the poorest quartile (>362 seconds to walk 400 meters) was predictive of incident cardiovascular events (36.0 vs. 27.7 events per 1000 person-years; adjusted HR 1.61; 95% CI 1.05, 2.45) and all-cause mortality over 4.9 years of follow-up (39.9 vs. 14.2 events per 1000 person-years; adjusted HR 3.23; 95% CI

2.11, 4.94) as compared to those in the highest quartile (<290 seconds to walk 400 meters).

Gait velocity was similarly effective in predicting mortality in a cohort of 309 hospitalized elders with multi-vessel or left-main coronary artery disease (12). When defined as a short distance (4.6 meters, 15 feet) gait velocity <0.65 m/sec, the prevalence of frailty was 50% in this patient population and the 6-month mortality was 14.1%, 4-fold greater than non-frail counterparts (adjusted OR 4.0; 95% CI 1.1, 13.8). When defined as a score of ≥3 on the composite Fried scale, the prevalence of frailty was 27% and the 6-month mortality was 11.9% (OR 1.9; 95% CI 0.6, 6.1). Grip strength ≤25 kg, chair-stand repetitions ≤7, and the composite Rockwood scale were less closely correlated to mortality.

The impact of frailty on mortality persisted after adjustment for age, sex, treatments received, cardiac risk factors, disability, comorbid conditions, cognitive function, and depression. Although not designed to test this hypothesis, there was a trend toward more medical management and less revascularization procedures in frail patients. This study brought forth the notion that the prevalence of frailty was definition-dependent, but that regardless of the definition chosen, it was quite high in elderly patients admitted to a cardiology service with severe coronary artery disease.

The prevalence and prognostic impact of frailty were equally high in elderly patients with chronic heart failure (13). Patients with heart failure were 6 to 7-fold more likely to be frail than non-frail at baseline (OR 6.16; 95% CI 4.97, 7.64 in the Women's Health Initiative Observational Study / adjusted OR 7.51; 95% CI 4.66, 12.12 in the Cardiovascular Health Study). Using Lachs' 3-level frailty score, 54% of 120 heart failure patients had a score of 2-3 and those with a score of 3 had an increased risk of death over 12 years of follow-up (adjusted HR 1.62; 95% CI 1.08, 2.45) independent of age, sex, treatments received, NYHA class, heart failure etiology, and comorbid conditions. At 9 years, the probability of death in

patients with heart failure and a frailty score of 3 was 100% whereas the probability in patients with heart failure and a lower frailty score of 1 was 55%.

Among patients with heart failure, the 6-minute walk test was found to correlate only modestly with frailty status as defined by Fried's criteria. Of 26 patients with a 6-minute walk distances of ≤300 meters, 15 (58%) were found to be frail and 11 (42%) non-frail (kappa=0.57; 95% CI 0.37, 0.77) (14). Therefore, frailty contributes additional information to the routine clinical parameters and appears to identify a subset of the elderly population that may be vulnerable to adverse outcomes (Table 3).

Discussion

Our systematic review has shown that there exists a relation between frailty and cardiovascular disease; frailty may lead to cardiovascular disease, just like cardiovascular disease may lead to frailty. The relationship may also be collinear since these entities share common biological pathways. Consensus groups have yet to agree on one universal definition of frailty from among the domains of strength, function, nutrition, mobility, and cognition. Using the most often cited construct, frailty is associated with a 2 to 3-fold increase in the prevalence of cardiovascular disease (Figure 3). This relationship is not only limited to manifest cardiovascular disease, it extends to subclinical cardiovascular abnormalities. Moreover, frailty remains a powerful predictor of mortality in cardiovascular patients independent of age, underlying disease severity, comorbid conditions, and disability. Frailty extends the field of risk assessment, potentially permitting for early recognition and therapeutic triage of the vulnerable elderly patient, and for refining estimates of cardiovascular risk which tend to be less accurate in elderly patients (15-17).

Perturbations in the hematologic, inflammatory, and endocrine-metabolic systems have been identified in frail patients and appear to be at the root of this biological syndrome and its association to cardiovascular disease. A substudy from the Cardiovascular Health Study found that, as compared to their nonfrail counterparts, frail patients had significantly higher levels of factor VIII, D-dimer, and C-reactive protein, even after adjusting for potential confounders (18). Other reports have confirmed these findings and added low hemoglobin, high leukocytes, high fibrinogen, high glucose, and low vitamin D to the list of frailty biomarkers (9;19-21). Perhaps the most consistently associated biomarker has been the inflammatory cytokine interleukin-6 (IL-6) which has been shown to correlate closely with the phenotype of frailty and with adverse outcomes in elderly patients (22-24). The robust correlation between frailty and biomarkers of inflammation and thrombosis strikingly resembles the equally robust correlation between cardiovascular disease and these same biomarkers (25-28). This common biological pathway may explain why frailty and cardiovascular disease are inter-related at the clinical level.

Primary therapeutic interventions include exercise training (29-34), social support systems (35-37), and comprehensive geriatric assessment and management consultation services which have been shown to improve physical performance and quality of life (38-40). Drugs with the potential ability to alter frailty include oral hypoglycemic agents (in diabetic patients) (41), anti-inflammatory agents, selective androgen-receptor modulators (42), Megestrol (an appetite stimulant) (43), testosterone (44), and vitamin D (45) but these have shown mixed results. Perindopril was shown to improve physical performance in a randomized trial of elders with functional impairment (without heart failure), presumably because of angiotensin II's role in modulating muscle function (46). Large-scale studies with longer follow-up periods are required to assess whether these interventions have an impact on clinically relevant endpoints such as disability, hospitalizations, and mortality (34). In the absence of proven targeted

therapies, frail elders with cardiovascular disease can be managed with medical and lifestyle interventions aimed at comorbid conditions and modifiable impairments which have been shown to predict progressive disability (47). In addition, providers should be vigilant to the increased risk from homeostatic stress accompanying acute cardiac events such as myocardial infarction or coronary artery bypass surgery (48-50).

Novel molecular pathways for frailty are beginning to be explored and promising hypotheses have been proposed, namely: free radicals and oxidative stress, cumulative DNA damage and impaired repair mechanisms, shorter telomere length and altered cell division, reduced lamin A/C expression and nuclear fragility (51;52). Clarification of these molecular pathways will be crucial to elucidate the precise pathophysiological elements at hand and develop targeted therapies. The role of frailty as a prognostic variable in cardiovascular disease needs to be explored, and clinical algorithms will likely begin to incorporate frailty status as a parameter to help guide treatment decisions in elderly patients. Randomized controlled trials of frail patients are needed and methods to conduct such trials have been outlined in a consensus report from the Interventions on Frailty Working Group (53).

In terms of limitations, given the observational nature of the studies reviewed, we cannot definitively prove a causal link between frailty and cardiovascular disease although we did provide biological rationale to support these findings. Second, 5 out of 9 studies were secondary analyses of cohort studies, implying that the datasets used were not directly designed to test the association between frailty and cardiovascular disease. As a result, these datasets may not contain all important covariates. There is a definite need for future longitudinal studies designed a priori to confirm the effect of frailty in patients with cardiovascular disease as well as the effect of cardiovascular disease on frailty status (several such studies are ongoing). Third, the number of studies in our systematic review is relatively small partly because we excluded studies that did

not systematically assess and define frailty (many studies defined “frailty” based on non-systematic arbitrary criteria such as very advanced age, living in a nursing home, or disability). We believe that this selection criterion was necessary to avoid excessive heterogeneity in the patient population studied. Finally, some studies excluded patients with Parkinson’s disease, prior stroke, and severe dementia, limiting the generalizability to these groups.

** The following reference list applies to chapter 2 only.*

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Figure legends

Figure 1

Title: Overlap between frailty, comorbidity, and disability

Caption: ADL = Activities of Daily Living (basic self-care tasks), IADL = Instrumental Activities of Daily Living (household management tasks).

Figure 2

Title: Flow diagram

Caption: CVD = cardiovascular disease.

Figure 3

Title: Prevalence of cardiovascular disease stratified by frailty status

Caption: ADL = Depicted studies used the same definition of frailty based on Fried's criteria, with 3/5 criteria required for a diagnosis of frailty and 1-2/5 for pre-frailty.

Figure 1: Overlap between frailty, comorbidity, and disability

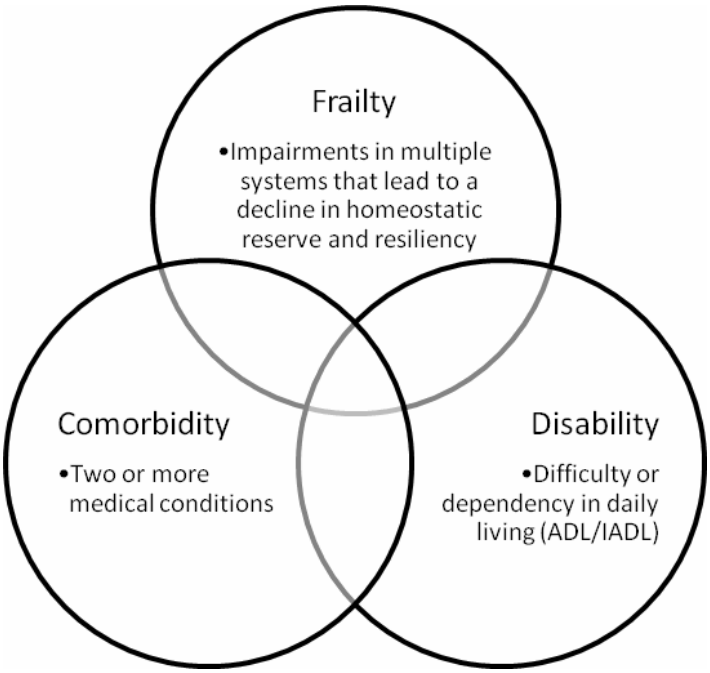

Figure 2: Flow diagram

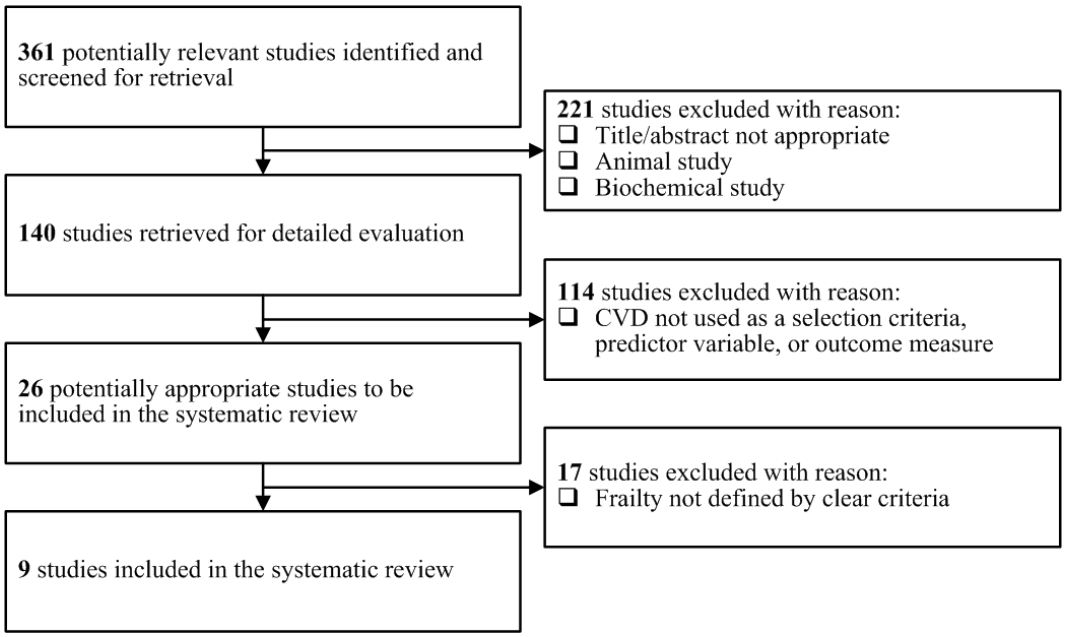

Figure 3: Prevalence of cardiovascular disease stratified by frailty status

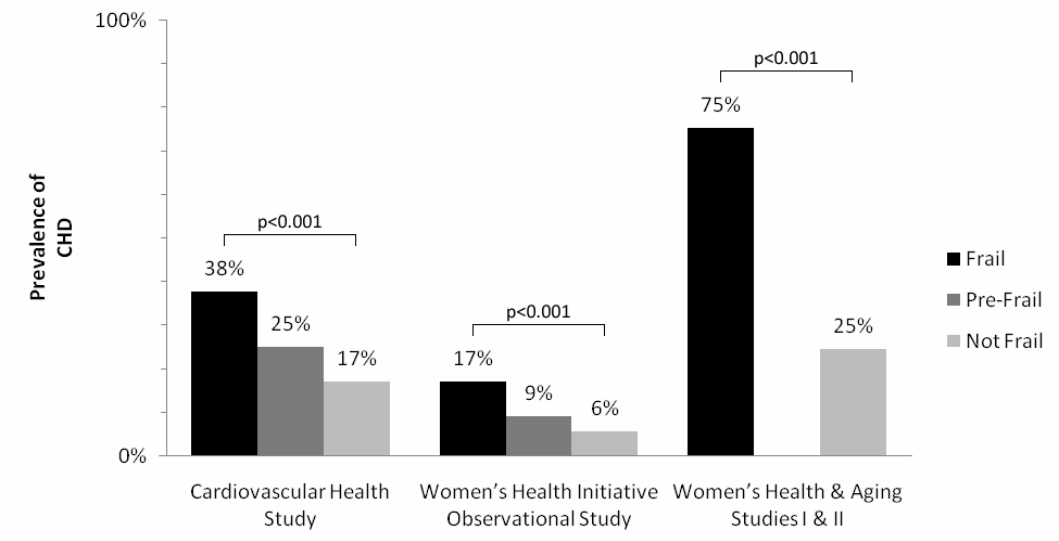

Table 1: Frailty criteria

	Gait speed	Grip strength	Exhaustion	Inactivity	Weight loss	Cognitive impairment	Visual impairment	Incontinence	Other
Chin [5]	□	□	■	■	■	□	□	□	-Low body mass index
Fried [54]	■	■	■	■	■	□	□	□	
Klein [7]	■	■	□	□	□	□	■	□	-Unable to stand without help -Low peak expiratory flow rate
Lachs [55]	□	□	□	□	□	■	■	■	-Mobility impairment -Hearing impairment -Lack of social support -Disability
Rockwood [56]	□	□	□	□	□	■	□	■	-Unable to walk without help -Unable to perform activities of daily living

* Black boxes indicate that the criteria is present in that definition of frailty, white boxes indicate that it is not present in that definition of frailty. Frailty defined as: Chin, Inactivity + 1 other criteria; Fried, 3 or more criteria (pre-frailty defined as 1-2 criteria); Klein, 4-5 criteria (mild-moderate frailty defined as 1-3 criteria); Lachs, 1 or more criteria; Rockwood, 1 or more criteria. Of note, gait speed is commonly used as a single measure of frailty.

Table 2: Study characteristics

Study	Design §	N	Age	Male	Population	Key Variables
Zutphen Elderly Men's Study [5], 1999	Secondary cross-sectional analysis of cohort study	450	65-84	100%	Community dwellers	Frailty (Chin) Prevalent CVD 3-year mortality
Cardiovascular Health Study [6], 2001	Secondary cross-sectional analysis of cohort study	4,735	73	43%	Community-dwellers	Frailty (Fried) Prevalent CVD Subclinical CVD 7-year mortality
Beaver Dam Eye Study [7], 2005	Secondary cross-sectional analysis of cohort study	2,962	53-96	43%	Community-dwellers	Frailty (Klein) Prevalent CVD 10-year mortality
WHI-OS [10], 2005	Secondary longitudinal analysis of cohort study	40,657	65-79	0%	Community-dwellers	Prevalent frailty (Fried) Incident frailty (Fried) Prevalent CVD 5.9-year mortality
WHAS I & II [8,9], 2005	Secondary cross-sectional analysis of cohort study	670	74	0%	Community-dwellers	Frailty (Fried) Prevalent CVD 3-year mortality
Cacciatore et al. [13], 2005	Prospective cohort study	1,332	76	40%	Outpatients with chronic heart failure	Frailty (Lachs) 12-year mortality
Purser et al. [12], 2006	Prospective cohort study	309	77	70%	Inpatients with severe coronary artery disease	Frailty (Fried, Rockwood, gait speed) 6-month mortality
Health ABC Study [11], 2006	Prospective cohort study	3,075	74	48%	Community-dwellers	Frailty (gait speed) Incident CVD 4.9-year mortality
Boxer et al. [14], 2008	Cross-sectional study	60	77	72%	Outpatients with chronic heart failure	Frailty (Fried) 6-minute walk test

* CVD defined as: Zutphen Elderly Men's Study, not specified; Cardiovascular Health Study, myocardial infarction (MI), angina, heart failure, revascularization, transient ischemic attack, claudication; Beaver Dam Eye Study, MI, angina, stroke; WHI-OS, any form of coronary artery disease; WHAS I & II, MI, angina, heart failure, revascularization; Health ABC Study, MI, angina, coronary heart disease death, stroke. Of note, CVD was consistently driven by MI and angina regardless of the different definitions used.

§ Design refers to the analytical approach used to describe the relationship between frailty and cardiovascular disease. In the case of a "secondary analysis", describing this relationship was not central to the main manuscript.

Abbreviations: WHI-OS, Women's Health Initiative Observational Study; WHAS, Women's Health and Aging Study; ABC, Aging and Body Composition; CVD, cardiovascular disease.

The following modifications have been made to the published version of this table: modification of design column, addition of legend §, addition of age and male columns.

Table 3: Association between cardiovascular disease and frailty

	OR (95% CI)
Prevalent frailty in elders with CVD	
Zutphen Elderly Men's Study [5], 1999	OR 4.1 (95% CI 1.8, 9.3)
Cardiovascular Health Study [6], 2001	OR 2.79 (95% CI 2.12, 3.67)
Beaver Dam Eye Study [7], 2005	OR 2.67 (95% CI 1.33, 5.41)
WHI-OS [10], 2005	OR 3.36 (95% CI 3.09, 3.66)
WHAS I & II [8,9], 2005	OR 2.72 (95% CI 1.72, 4.30)
Incident frailty in elders with CVD	
WHI-OS [10], 2005	OR 1.47 (95% CI 1.25, 1.73)
Incident CVD in frail elders	
Health ABC Study [11], 2006	HR 1.61 (95% CI 1.05, 2.45)
Mortality in frail elders with severe CVD	
Cacciatore et al. [13], 2005	HR 1.62 (95% CI 1.08, 2.45)
Purser et al. [12], 2006	OR 4.0 (95% CI 1.1, 13.8)

Abbreviations: WHI-OS, Women's Health Initiative Observational Study; WHAS, Women's Health and Aging Study; ABC, Aging and Body Composition; CVD, cardiovascular disease; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

CHAPTER 3: COMMENTARY ON SYSTEMATIC REVIEW

Since little was known about the role of frailty in cardiovascular disease, the scope of this systematic review was quite broad. The initial objective was to explore the relationship between frailty and cardiovascular disease. Given the exploratory nature of the objective, the inclusion and exclusion criteria were designed to capture any and all studies touching upon both of these entities (with the proviso that frailty had to be defined according to objective criteria). After reviewing the literature, the objective evolved into three more specific questions: (1) what is the prevalence or incidence of frailty in patients with cardiovascular disease, (2) what is the prevalence or incidence of cardiovascular disease in patients with frailty, and (3) is frailty a risk factor for adverse outcomes in patients with cardiovascular disease? Although it is somewhat atypical to begin a study without knowing the exact research questions being asked, there was insufficient prior knowledge to permit this. Therefore, a wide net was cast to review the entire body of literature, and the pertinent research questions then became apparent.

Five of the nine studies identified by the literature search were not primarily aimed at defining the role of frailty in patients with cardiovascular disease. Instead, they were cohort studies of elderly patients which happened to describe an association between these entities. This association was not necessarily central to the main analysis (therefore we refer to it as a secondary analysis), and may have been included as part of the main manuscript or a subsequent manuscript. For example, there were a number of secondary cross-sectional analyses from large cohort studies showing that elderly patients who were frail at baseline were more likely to have cardiovascular disease at baseline. The other four studies identified were primarily aimed at defining the prevalence or prognostic impact of frailty in patients with cardiovascular disease.

As a result of the heterogeneity in included studies, the extracted data could not be pooled as a meta-analysis, and it was challenging to find a structured framework for reporting and a quality assessment tool for critically appraising these studies. The QUOROM framework for reporting meta-analyses of clinical trials was used, although the MOOSE framework for reporting meta-analyses of observational studies would have been more appropriate (Stroup et al. JAMA 2000; 293: 2008). A formal quality assessment was not performed, although the Newcastle-Ottawa Quality Assessment Scale could have been applicable (Wells et al. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm, Accessed Feb 1 2010). The Newcastle-Ottawa Quality Assessment Scale has the advantage of being specifically designed and validated for rating observational studies, and being adaptable to different types of studies. Three domains are represented and each contains subdomains which are awarded a star if they meet the criteria: selection (4 subdomains), comparability (2 subdomains), and outcome (3 subdomains). Since there are 9 subdomains and each can be awarded a star, the maximum overall score is 9 stars. No formal cut-offs are provided for defining poor, intermediate, and good quality studies.

The Newcastle-Ottawa Quality Assessment Scale was applied to the nine studies in our systematic review. All of the studies had between 4 and 8 stars (which would appear to be in the intermediate-to-good quality range). Of note, five of the analyses were cross-sectional and therefore two subdomains were not pertinent and could not be judged (demonstration that the outcome was not present at start of study, and follow-up long enough for outcomes to occur). The results of the quality assessment are shown in tabular format below.

Table: Quality assessment

	Zutphen Elderly Men's Study	Cardiovascular Health Study	Beaver Dam Eye Study	WHI-OS	WHAS I & II	Cacciatore	Purser	Health ABC Study	Boxer
Representativeness of the exposed cohort	0	1	1	0	0	1	1	1	1
Selection of the nonexposed cohort	1	1	1	1	1	1	1	1	1
Ascertainment of exposure	1	1	1	1	1	1	1	1	1
Demonstration that the outcome was not present at start of study	-	-	-	1	-	1	1	0	-
Comparability of cohorts for age/sex	0	1	1	1	1	1	1	1	1
Comparability of cohorts for additional confounders	0	0	0	1	1	1	1	1	0
Assessment of outcome	1	1	0	1	1	0	1	1	1
Was follow-up long enough for outcomes to occur	-	-	-	1	-	1	0	1	-
Adequacy of follow-up of cohorts	1	1	0	1	1	1	1	1	1
Overall score (number of stars)	4	6	4	8	6	8	8	8	6

CHAPTER 4: TRANSITION FROM SYSTEMATIC REVIEW TO COHORT STUDY

The systematic review showed that frailty was prevalent in patients with cardiovascular disease, and was associated with an increased risk of mortality. In particular, the prospective cohort study by Purser showed that 1 in 2 elderly patients with severe coronary artery disease admitted to a cardiology service was frail, and that frailty was associated with 3-4 fold increase in 6-month mortality. The treatment regimens for patients in this study were variable: 42% received medical therapy, 44% received percutaneous coronary intervention, and 15% received cardiac surgery. The high proportion of patients receiving medical therapy alone (whereas severe coronary artery disease is usually treated more aggressively) hinted to the fact that aggressive therapies were withheld from these patients perhaps because of their age or frailty status.

In clinical practice, physicians often withhold aggressive therapies from frail elders because they judge that these patients will not be able to tolerate the physiologic stress imparted on the body. This is especially true for cardiac surgery, which is among the most physiologically stressful therapies. When physicians do not withhold but instead refer frail elders for cardiac surgery, they do so with an incomplete assessment of risk. The assessment of risk is incomplete because currently available risk assessment tools and risk scores do not incorporate measures of frailty. This shortcoming is well known to physicians in the fields of cardiology and cardiac surgery, who often take it upon themselves to incorporate their own subjective impressions of frailty in assessing patients, or express a need to begin incorporating objective measures of frailty in existing risk scores.

Before incorporating frailty in the assessment of risk for cardiac surgery, the impact of frailty in this setting had to be established. In our systematic review, we had not identified any studies addressing frailty in the context of cardiac

surgery. Although the study by Purser had shown an increased risk of mortality in elderly patients with severe coronary artery disease, and a 15% rate of cardiac surgery, it did not evaluate whether the risk of mortality was particularly increased in elderly patients with severe coronary artery disease who underwent cardiac surgery. This knowledge gap was clinically pertinent, and inspired the idea to perform a prospective study to measure the prognostic impact of frailty in elderly patients undergoing cardiac surgery.

To perform such a study, several methodological issues were considered. First, the study design had to be a prospective cohort because frailty data was not collected in our hospitals and therefore was not available retrospectively. Second, the study population was patients undergoing cardiac surgery; however, it was not clear whether this should be restricted to the narrow group of patients undergoing coronary artery bypass surgery, or whether it should be extended to patients undergoing all types of cardiac surgery (coronary artery bypass surgery and/or valvular surgery). It was chosen not to restrict to the narrow group because all patients shared similarities in terms of their general profile, and all types of cardiac surgery shared similarities such as their approach by sternotomy. In addition, including all types of surgery would accelerate enrolment while maintaining the option to test for interactions by type of surgery in the analysis phase.

Next, the choice of frailty measure was considered. The systematic review had identified at least five frailty scales, of which Fried's scale was the most commonly used. There were limited comparisons of the different scales. Purser suggested that Fried's scale was a superior predictor to Rockwood's scale. Interestingly, slow gait speed alone (one of the components of Fried's scale) was a superior predictor to either of the composite scales. This finding of gait speed as a single measure of frailty was consistent with emerging reports. In a cohort of community dwelling elders, Hardy found that slow gait speed was superior to several composite scales in predicting 8-year mortality (29). In similar cohorts of

community-dwelling elders, Cesari found that the single measure of gait speed was predictive of mortality (32), and Montero-Odasso found that it was predictive of adverse events including hospitalizations (31). Of note, these studies were not included in our systematic review of frailty in cardiovascular disease because they did not touch upon the topic of cardiovascular disease.

In light of the evidence supporting its value as a powerful prognostic marker, as well as its simplicity and applicability in routine clinical practice, gait speed was chosen as the primary measure of frailty for the prospective study. The choice of outcome measure was considered next. Mortality was a leading candidate but would have required a very large sample size, and would have ignored the importance of major postoperative complications which tend to be devastating in this patient population. The composite outcome of mortality or major postoperative complication was chosen. Fortunately, the Society of Thoracic Surgeons adult cardiac surgery database had explicitly defined this composite outcome and provided a detailed methodology for extracting it from the medical chart (36).

With these core elements in place, a research protocol was drafted and the collaboration of four university hospitals across Canada and the United States was obtained, in large part due to the relationships forged during the preparation and presentation of the systematic review.

CHAPTER 5: COHORT STUDY

Manuscript to be submitted: "Gait Speed as an Incremental Predictor of Mortality and Major Morbidity in Elderly Patients Undergoing Cardiac Surgery"

Our multi-center prospective cohort study of gait speed in elderly cardiovascular patients undergoing cardiac surgery is presented in manuscript form below. This manuscript has not yet been submitted.

Gait Speed as an Incremental Predictor of Mortality and Major Morbidity in Elderly Patients Undergoing Cardiac Surgery

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Abstract

Background: Our objective was to test the incremental value of gait speed in addition to established risk factors for predicting mortality and major morbidity in elderly patients undergoing cardiac surgery.

Methods: A multi-center prospective cohort of elderly patients undergoing cardiac surgery was assembled at 4 tertiary care hospitals between 2008 and 2009. Patients were eligible if they were aged 70 years or older, and were scheduled for coronary artery bypass and/or valve replacement or repair. Unstable patients undergoing emergent surgery were excluded. Patients were evaluated with a standardized questionnaire and a timed 5-meter gait speed test. The gait speed test consisted of asking the patient to walk a distance of 5 meters at a comfortable pace; this was repeated three times and averaged. Slow gait speed was defined as a time taken to walk 5 meters ≥6 seconds. The primary outcome measure was a composite of in-hospital postoperative mortality or major morbidity (reoperation, stroke, renal failure, prolonged intubation, deep sternal wound infection). Established risk factors for mortality and morbidity were entered in a multivariable logistic regression model with and without gait speed. Model fit, calibration, and discrimination were measured before and after addition of gait speed to determine its incremental prognostic value.

Results: The cohort consisted of 131 patients with a mean age of 75.8 ± 4.4 (SD) years and 34% females. Sixty patients (46%) were classified as slow walkers before cardiac surgery. Slow walkers were more likely to be female (43% vs. 25%, p=0.03), have shorter height (1.65m vs. 1.69m, p=0.01), diabetes (50% vs. 28%, p=0.01), and at least one disability on Nagi's scale (82% vs. 63%, p=0.02) and on instrumental activities of daily living (48% vs. 18%, p<0.0001). Thirty patients (23%) experienced the primary composite endpoint of mortality or major morbidity after cardiac surgery. Slow gait speed was an independent

predictor of the composite endpoint after adjusting for the Society of Thoracic Surgeons risk score (odds ratio 3.05, 95% confidence interval [CI] 1.23, 7.54) and for other risk scores. Addition of gait speed to the model resulted in notable improvements in model performance. In particular, the integrated discrimination index, a novel measure of average increase in sensitivity assuming no decrease in specificity, was 5% (95% CI 1%, 8%).

Conclusion: 5-meter gait speed is a simple and effective test to identify a subset of vulnerable elderly patients who have an incrementally higher risk of mortality and major morbidity after cardiac surgery. Further studies are needed to validate the optimal cut-off for slow gait speed.

Introduction

Elderly patients account for half of the cardiac surgeries performed in North America, and more notably, 65% of the major complications and 78% of the postoperative deaths (1). Advanced age, usually defined as age ≥70 in the context of cardiac surgery, is the preeminent risk factor for mortality and major morbidity, reflected by its central role in nearly every prognostic model (2). Nevertheless, randomized (3;4) and observational studies (5-10) have consistently shown that elderly patients achieve sizeable benefits from cardiac surgery. These benefits span domains of quality of life, alleviation of symptoms, prevention of major adverse cardiovascular events, and increased survival. The number needed to treat to save one life with coronary artery bypass decreases from 23 in patients aged <70 to 6 in patients aged >80 (6). Elderly patients have a slower recovery of full functional status but they tend to return to their baseline level of functioning within 6-12 months (11;12).

The high-risk high-benefit dichotomy, coupled with the fact that elderly patients are often more severely ill and in need of surgical interventions (10), renders the clinician's decision-making process particularly challenging. More than 19 risk scores have been developed and validated to illuminate the decision making process (13), but these risk scores perform poorly in elderly patients (as do many other risk scores commonly used in cardiology (14-16)). Even the most widely used risk scores have sub-par discrimination, overestimating mortality by up to 250% (17-19). Furthermore, most risk scores were developed to predict mortality and perform poorly when used to predict major morbidity (average area under the curve [AUC] 0.75 for mortality vs. 0.65 for morbidity) (20-22). Prediction of morbidity in addition to mortality is particularly relevant to the elderly because they have less resiliency to complications, and because complications are the major driver of costs, quality of life, and long-term mortality (20;23;24).

Accurately predicting outcomes has been very challenging in the elderly because of the marked heterogeneity in this population. This heterogeneity extends beyond differences in comorbid conditions to subclinical impairments in multiple inter-related systems. Accumulation of these subclinical impairments results in reduced homeostatic reserve and resiliency to stressors – a syndrome known as frailty (25-28). Gait speed reflects many of these subclinical impairments and has been validated as a reliable measure of frailty (29-32). A growing body of literature has shown that slow gait speed is associated with an increased likelihood of cardiovascular disease and adverse outcomes (33). Purser et al showed that slow gait speed was the strongest predictor of mortality at 6 months among 399 elderly patients admitted to a cardiology service with severe coronary artery disease (odds ratio [OR] 3.8, 95% confidence interval [CI] 1.1, 13.1) (30). Cesari et al showed that gait speed was correlated with inflammatory markers such as C-reactive protein, interleukin-6, and tissue necrosis factor-alpha which are known to play a key role in the pathophysiology and prognosis of cardiovascular disease (34).

Since gait speed is a measure of frailty and resiliency to stressors, and cardiac surgery is a major physiologic stressor, gait speed is well suited to foreshadow an individual's response to cardiac surgery. A recent study of cardiac surgery in octogenarians concluded that an objective assessment of frailty should be incorporated into clinical practice and research protocols (23). Thus, our primary objective was to test the ability of gait speed to predict mortality and major morbidity in a prospective multi-center cohort of elderly patients undergoing cardiac surgery. In particular, the incremental value of gait speed above established risk factors was measured by a comprehensive analysis of model performance before and after incorporating gait speed.

Methods

Study design

A prospective multi-center cohort of elderly patients undergoing cardiac surgery between February 2008 and June 2009 was assembled. Consecutive patients scheduled to undergo cardiac surgery were screened. Eligible patients were approached and asked to complete an interviewer-administered questionnaire (questionnaire presented in Appendix A) and a battery of physical performance tests including a 5-meter gait speed test. Based on this 5-meter gait speed test, patients were classified as slow walkers or normal walkers which served as the primary predictor variable for this study. The treating physicians and patients were blinded to the gait speed test results so as not to influence their decision to proceed with the surgery or their postoperative management. All patients received routine care. After discharge or transfer, medical records were examined and pertinent data were extracted. In particular, the occurrence of death or one of five major complications in the postoperative period was extracted as the primary outcome. Data from the medical record, the questionnaire, and the physical performance tests were stored in separate data files to prevent the results of the physical performance tests and questionnaire from influencing the researcher during data extraction from the medical record. These data files were later amalgamated into a comprehensive dataset. Analysis of this dataset was principally focussed on determining the incremental value of gait speed in addition to established risk factors for predicting mortality or major morbidity after cardiac surgery. The manuscript was prepared in accordance with the standards set forth by the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement (35).

Setting

Recruitment started on February 11 2008 at the Sir Mortimer B. Davis (SMBD) Jewish General Hospital (McGill University, Montreal, Quebec), on July 22 2008 at the Hôtel-Dieu de Montréal (University of Montreal, Montreal, Quebec), on October 20 2008 at the Montreal Heart Institute (University of Montreal, Montreal, Quebec), and on February 6 2009 at the Duke University Medical Center (Duke University, Durham, North Carolina). All of these hospitals are university-affiliated tertiary care centers with high-volume cardiac surgery programs. Recruitment ended and the study was closed after up to 16 months of active enrolment on June 5 2009. Follow-up continued until the time of discharge or transfer from hospital. One-year follow-up by telephone is ongoing to ascertain vital status and administer a follow-up questionnaire. Patients were approached on the cardiology and cardiac surgery wards, and in the outpatient cardiac surgery clinics. The questionnaire and physical performance tests were administered in these locations, which had to be equipped with 5-meter markings on the wall or floor for the gait speed test (in most places, markings had been previously installed for the commonly performed 6-minute walk test).

Participants

Inclusion criteria were: (1) age ≥70 years, and (2) scheduled to undergo cardiac surgery, defined as coronary artery bypass and/or valve replacement or repair via a standard sternotomy approach. Ancillary procedures such as surgery on the thoracic aorta were included, whereas minimally-invasive procedures such as surgery via a mini-thoracotomy or transapical approach were not. If patients were scheduled to undergo cardiac surgery and were recruited into the study, but then subsequently had their surgery cancelled, they were removed from the cohort and not considered in the primary analysis. Exclusion criteria were: (1) emergent surgery, defined as a surgery for which there should be no delay due

to ongoing refractory cardiac compromise, (2) clinical instability, defined as active coronary ischemia, decompensated heart failure not yet stabilized, or any acute process causing significant symptoms or abnormal vital signs, and (3) severe neuropsychiatric condition causing inability to cooperate with the study procedures. Ethics approval was obtained from the Institutional Review Board at each of the participating centers. Patients were required to sign an informed consent to participate. The informed consent and questionnaire were available in English and French, patients not speaking either of these languages were not approached. For patients who either refused to participate or were not approached, basic data were collected and compared to the study sample to ensure that there were no differences between these two groups.

Predictor variables

The primary predictor variable was 5-meter gait speed. After completing the questionnaire, patients were accompanied to a designated area which was well-lit, unobstructed, and contained clearly indicated markings at 0 and 5 meters. They were positioned with their feet behind and just touching the 0-meter start line, and instructed to walk at a comfortable pace until a few steps past the 5-meter mark. Patients were permitted to walk with an aid such as a cane or walker, or with their intravenous pole if necessary (preferably pushed by the examiner). One (or two when available) examiners timed the patient with a standard digital stopwatch, starting the timer with the first footfall after the 0-meter line and stopping it with the first footfall after the 5-meter line; similar to the gait speed protocol used in the Health, Aging and Body Composition Study (32). This sequence was repeated 3 times allowing a short time (approximately 15 seconds) between trials for rest. The recorded times were entered into the dataset and the average of the 3 times was calculated. All examiners were

trained to measure gait speed at the beginning of the study and periodically re-trained thereafter.

Numerous slightly different protocols for gait speed testing have been proposed, and no standard definition or cut-off for slow gait speed has been accepted. To identify an optimal and practical cut-off for slow gait speed to predict mortality or major morbidity in our study population, receiver operating characteristic (ROC) curves were constructed and suggested a cut-off of ≥6 seconds (ROC curves for gait speed to predict mortality or major morbidity presented in Appendix C). Thus, an average time taken to walk 5 meters ≥6 seconds was classified as slow gait speed, whereas an average time <6 seconds was classified as normal gait speed. Sensitivity analyses were performed using different cut-offs for slow gait speed, using fastest or slowest gait speed as opposed to average gait speed, and using gait speed as a continuous variable. Although speed is typically measured in meters/second, it was elected to report it in seconds (taken to walk 5 meters) in order to facilitate subsequent bedside application and interpretation of this test in clinical practice without any calculations.

Secondary predictor variables (not presented in this analysis) were frailty score based on the Cardiovascular Health Study frailty scale (27) (frailty defined as 3 points with 1 point assigned for each of the following: exhaustion, inactivity, weight loss, slow gait speed, weak handgrip strength), handgrip strength measured by Jamar dynamometer, echocardiographic parameters, and a panel of biomarkers from blood and aortic tissue.

Outcome variables

The primary outcome variable was in-hospital postoperative mortality or major morbidity, defined by the Society for Thoracic Surgeons (STS) as a composite of

all-cause death and 5 major complications. These 5 major complications are: stroke (central neurologic deficit persisting >72 hours), renal failure (new requirement for dialysis or increase in serum creatinine >177 umol/L and >2 fold the preoperative level), prolonged ventilation (>24 hours), deep sternal wound infection (requirement for operative intervention and antibiotic therapy, with positive culture), and need for reoperation (for any reason). Patients were classified in a dichotomous fashion as having the outcome if they had one or more of these complications and/or death. These specific complications were chosen by the STS to represent major morbidity for two reasons: first, they are either life-threatening or have the potential to cause permanent functional disability, and second, they tend to be uniformly reported and reliably extracted from medical records (36). To ascertain the occurrence of mortality or major morbidity, medical records were reviewed by a physician trained in cardiology (JA). To avoid observer bias, the physician ascertaining outcomes from medical records was blinded to the questionnaire and gait speed data.

Secondary outcome variables were individual components of the primary composite endpoint, discharge to a healthcare facility (nursing home, convalescence, rehabilitation, other hospital) for ongoing medical care or rehabilitation, and prolonged postoperative length of stay (>14 days after the index surgical procedure).

Covariates and confounders

In order to measure the incremental value of gait speed in predicting mortality or major morbidity, established risk factors and risk scores for mortality and major morbidity were measured. Although the list of possible risk factors is extensive, two independent committees found that 7 core variables accounted for >75% of the observed variance in mortality and that the others were relatively marginal (37;38). These core variables were: age, female sex, prior

cardiac surgery, left ventricular ejection fraction (LVEF), stenosis of the left main coronary artery, non-elective surgery, and type of surgical procedure. Type of surgical procedure was grouped according to the EuroSCORE classification of isolated coronary artery bypass graft (CABG) surgery vs. non-isolated CABG. Non-isolated CABG is defined as a major surgical procedure such as a valve replacement or repair, or thoracic aortic surgery, either alone or in conjunction with CABG.

Risk scores integrate several risk factors and aim to predict the probability of an adverse outcome after cardiac surgery. Five of the most validated risk scores were calculated: STS Predicted Major Morbidity Mortality (1;39;40), STS Predicted Mortality (1;39;40), Additive EuroSCORE (41), Logistic EuroSCORE (42), and Revised Parsonnet Score (43). The STS Predicted Major Morbidity Mortality was selected as the main risk score since it was specifically designed to predict this study's primary outcome measure, whereas the others were designed to predict mortality and were only subsequently shown to predict morbidity.

Covariates and potentially confounding variables, including the elements necessary to calculate the aforementioned risk scores, were extracted from medical records and the questionnaire using a structured data collection instrument. This instrument was organized into baseline characteristics, comorbid conditions, laboratory results, echocardiographic results, angiographic results, cardiac surgery risk scores, preoperative details, operative details, neuropsychiatric scales, functional scales, gait speed, handgrip strength, frailty score, and outcome measures.

Questionnaire

The questionnaire was constructed to collect (1) basic demographic information, (2) measures of frailty, and (3) confounders related to frailty.

The questionnaire-based measures of frailty were exhaustion, inactivity, weight loss, dementia, and depression. Exhaustion was measured by two items from the Center for Epidemiologic Studies Depression scale (CES-D) (44). Inactivity was measured by four items from the Canadian Study of Health and Aging (45). Dementia was measured by the Folstein Mini-Mental Status Examination (MMSE) (46) and the Montreal Cognitive Assessment (MoCA) (47). Depression was measured by the Hospital Anxiety and Depression Scale (HADS) (47).

The confounders related to frailty were comorbid conditions and disability. Comorbid conditions were measured by the Functional Comorbidity Index (48). Disability was measured by the Nagi items (reflecting abilities to perform tasks that are slightly more demanding than those in the activities of daily living scales) (49), the Older Americans Resources and Services (OARS) scale for Instrumental Activities of Daily Living (IADL) (50), and the Katz scale for Activities of Daily Living (ADL) (51). Previously validated translations of the CES-D, MMSE, MoCA, HADS, Functional Comorbidity Index, Nagi items, OARS scale, and Katz scale were used to generate a French version of the questionnaire.

Interviewers were trained to administer the questionnaire. They were instructed to administer all sections of the questionnaire except the HADS which was designed to be completed by the patient. After training, interviewers were asked to administer the questionnaire to the trainer to verify that the instructions had been clearly understood and were being closely followed. Thereafter, interviewers were regularly asked if they had come across any difficulties with the questionnaire for which further clarification could be provided.

Study size

The expected incidence of our primary composite endpoint was 33% based on a chart review of 156 elderly patients undergoing cardiac surgery at the SMBD-Jewish General Hospital between 2003 and 2004 (unpublished data provided by Dr Sandra Dial). The expected proportion of patients with our primary predictor variable was 50% based on studies of gait speed in elderly cardiovascular patients (30). Assuming a two-sided alpha of 0.05 and a beta of 0.20, 136 patients were required to show a twofold increase in events. A basic statistical test of proportions was used to derive this sample size estimate; it was not specifically based on a logistic regression model nor did it take into consideration covariates.

Statistical methods

Basic descriptive statistics (number of observations, number of missing values, minimum value, maximum value, mean) were examined to identify errors in the recorded data. Summary statistics and graphs were plotted to explore the distribution and outliers for each variable. Variables with skewed distributions or marked outliers were log or inverse transformed to assume a more normal distribution (distribution of non-transformed and transformed gait speed is graphically presented in Appendix B). Although both transformed variables and nonparametric tests are acceptable methods of dealing with non-normally distributed variables, the former was chosen in order to maintain consistency with the rest of the analyses which were parametric in nature. Univariate comparisons were performed with the t-test for continuous variables, chi-square test for categorical variables, chi-square test for trend for ordered categorical variables, and Fisher's exact test for categorical variables with fewer than 5 expected observations per cell. The confounders of interest were pre-specified based on prior knowledge (7 core risk factors), although additional confounders

were identified based on univariate testing and explored in sensitivity analyses. An additional confounder was defined as a variable that was significantly associated with the predictor and outcome in univariate testing, with a clinically meaningful difference between the exposed and non-exposed groups, and a biologically plausible mechanism to justify its confounding effect.

Multivariable analyses were performed with logistic regression modelling and reported as OR's with their 95% CI's. Logistic regression was chosen (instead of survival analysis) for two reasons. First, the in-hospital follow-up time was relatively short for all patients and therefore the time-to-event was not clinically meaningful (for example, a death or stroke suffered on day 3 would be equivalent to one suffered on day 13). Second, censoring due to incomplete follow-up was anticipated to be low given the confined in-hospital follow-up time and lack of competing risks. Logistic regression models to predict the outcome measure were first built without gait speed, and then with gait speed added to the model. Since the number of risk factors in patients undergoing cardiac surgery is very large (STS score, 77 variables; Parsonnet score, 37 variables; EuroSCORE, 17 variables), entering all of the variables in our model would have resulted in model instability and overfitting (52). Since our sample size was a limiting factor, three approaches were taken to overcome this issue. Firstly, the calculated risk estimates produced by the five risk scores were each entered in a separate model with and without gait speed. This resulted in parsimonious 1-2 covariate models. The limitation of this approach was that the calculated risk score estimates would not be expected to fully adjust for the individual variables within risk scores. Secondly, the 7 core risk factors were entered in a model with and without slow gait speed. This resulted in a 7-8 covariate model. Thirdly, all potentially significant covariates were entered in a comprehensive model with and without slow gait speed. The number of covariates in this model surpassed the recommended limit but this was still

explored as a sensitivity analysis to ensure that significant confounding had not been missed.

Missing data were listwise deleted, a conservative approach which implies that patients with missing data are removed from models containing that variable. In the case of our primary predictor variable (gait speed), listwise deletion would have resulted in a disproportionate loss of statistical efficiency. Therefore, missing values were inferred from our interrelated secondary predictor variable (frailty score) and patients with missing gait speed (n=12) were inferred to have slow gait speed if their frailty score was positive for frailty (n=2/12). The frailty score has previously been shown to be closely correlated with gait speed in cardiovascular patients (AUC 0.89) (30). This approach was felt to be more direct and transparent for the general readership in comparison to multiple imputation techniques. Although multiple imputation is a valid approach, the specific variables used to generate the missing data are unknown and multiple. Sensitivity analysis excluding patients with missing gait speed was also performed.

Interactions were evaluated by successively adding an interaction term for gait speed and the covariate of interest in the logistic regression model and, as suggested by Hosmer and Lemeshow (52), testing the change in model deviance before and after addition of the interaction term. The change in model deviance was compared to the chi-square distribution with 1 degree of freedom and yielded a p-value for the change. If this p-value was <0.05, the interaction term was considered statistically significant. Interactions were further verified by calculating stratum-specific OR's. The OR for slow gait speed on mortality or major morbidity was calculated for men and women, for ages ≥ 80 and <80, and so forth for other covariates.

The fit of the various models was calculated before and after addition of gait speed in order to determine its incremental value on model performance.

Specifically, global model fit was measured with the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). Both the AIC and BIC are statistics that reflect the tradeoff between model precision and complexity, whereby a lower value is favourable and indicates higher precision and/or lower complexity. A large number of covariates will unfavourably increase the AIC and BIC; whereas the BIC adds an additional penalty for large sample sizes (since very large sample sizes can introduce random noise). As a result, BIC tends to have smaller underfit models and AIC tends to have larger overfit models. Given these potential differences between BIC and AIC, both were measured and reported.

Model calibration, which reflects the agreement between predicted and observed risks, was measured with the Hosmer-Lemeshow goodness-of-fit chi-square test and with visual inspection of calibration plots. The Hosmer-Lemeshow test is a standard chi-square test comparing the number of events predicted by the model (usually grouped by deciles of risk) against the number of events observed. The calibration plot represents this graphically.

Model discrimination, which reflects the ability to assign a higher predicted risk to those who will have the observed outcome, was measured with the AUC (also known as the c-statistic) and the integrated discrimination improvement (IDI) statistic described by Pencina (53). The AUC reflects, when considering two subjects – one who will have the event and one who will not, the probability that the model will assign a higher risk estimate to the subject who will have the event. To compare the discrimination of a model with and without an added covariate, the difference in AUC between the two models is calculated. Although this is a commonly used method in the medical literature, it has been criticized for several reasons (54). First, the AUC is not sensitive or responsive, and important covariates may result in minimal changes in AUC. Second, the change in AUC between two models is a statistic which does not translate easily into a clinically meaningful statement, making it difficult to gauge for the clinician. The IDI overcomes both of these limitations by being more sensitive to change and

more clinically relevant. For a given model, the mean predicted probability of having the event is calculated for cases and controls. The difference between the mean predicted probability for cases and the mean predicted probability for controls is calculated, known as the Yates slope, with higher values indicating increased model discrimination. The IDI reflects the difference between the Yates slope for the first model and the Yates slope for the second model. Otherwise said, the IDI reflects the average increase in sensitivity of the model (integrated across all possible values) without incurring a decrease in specificity after addition of a new covariate (detailed statistical output and instructions on how to calculate the IDI are presented in Appendix D). All analyses were performed with the STATA 10 statistical software package (College Station, Texas).

Results

Three-hundred sixty eight patients met the inclusion criteria and were eligible to participate in the study, of which 140 were included (Figure 1). The most common reason for not being included was not being reached by a member of the research team before the time of surgery (usually patients presenting after-hours and taken to the operating room early the next morning). A comparison of eligible patients who were included and eligible patients who were not included is shown in Table 1. There were no statistically significant differences in mean age (difference +0.9, 95% CI -0.04, 1.8), female sex (difference +8%, 95% CI -2%, 18%), proportion undergoing aortic valve replacement (AVR) (difference -3%, 95% CI -7%, 13%), proportion undergoing mitral valve replacement (MVR) (difference +4%, 95% CI -3%, 11%), proportion undergoing CABG (difference -6%, 95% CI -14%, 3%), and number of coronary artery bypasses per patient (difference -0.1, 95% CI -0.4, 0.2). Nine patients were included but subsequently had their surgeries cancelled and were removed from the cohort. No patients

were lost to follow-up. Patient interviews were conducted in the inpatient cardiology and cardiac surgery wards in 99% of cases (only one patient interview was conducted in the outpatient clinic). The mean duration of the interview was 31.7 ± 16.0 minutes, and the questionnaire comprehension was very good or good in 92% of cases (Table 2).

The final cohort consisted of 131 patients with a mean age of 75.8 ± 4.4 years, 23% octogenarians, and 34% females. Baseline characteristics, predictor variables, and outcome variables stratified by slow and normal gait speed are shown in Tables 3, 4, and 5, respectively. Sixty patients (46%) were classified as slow walkers before cardiac surgery. Slow and normal walkers were similar with respect to age, weight, comorbidities (with the exception of diabetes), ADL's, dementia, anxiety, depression, reason for hospitalization, type of surgery, urgency of surgery, hemoglobin, baseline creatinine, angiographic findings, and echocardiographic findings including a nearly identical LVEF in both groups (53% vs. 54%, p=0.73). However, slow walkers were more likely to be female (43% vs. 25%, p=0.03), have shorter height (1.65m vs. 1.69m, p=0.01), diabetes (50% vs. 28%, p=0.01), and at least one disability on Nagi's scale (82% vs. 63%, p=0.02) and on the OARS IADL's scale (48% vs. 18%, p<0.0001). The cardiac surgery risk scores predicted higher risks of major morbidity and/or mortality in slow walkers.

Thirty patients (23%) experienced the primary composite endpoint of mortality or major morbidity after cardiac surgery which was well balanced across study centers (Table 6). Univariate predictors were (in descending order of magnitude): prior cardiac surgery (OR 6.53, 95% CI 1.46, 29.20), anxiety as measured by the Hospital Anxiety and Depression Scale (OR 5.81, 95% CI 1.52, 22.25), slow gait speed (OR 3.23, 95% 1.28, 8.13), age ≥80 (OR 3.07, 95% CI 1.26, 7.49), non-isolated CABG (OR 2.83, 95% CI 1.22, 6.54), female sex (OR 2.48, 95% CI 1.08, 5.72), pulmonary hypertension (OR 2.43, 95% CI 1.05, 5.63), and disability on Nagi's scale (OR 1.28, 95% CI 1.05, 1.56) (Table 7).

A multivariable logistic regression model containing the 7 core risk factors and slow gait speed showed that only prior cardiac surgery (adjusted OR 7.93, 95% CI 1.34, 47.02), age ≥80 (adjusted OR 3.98, 95% CI 1.43, 11.12), and slow gait speed (adjusted OR 3.17, 95% CI 1.17, 8.59) were independent predictors of mortality or major morbidity. The overall fit, calibration, and discrimination of the model improved when gait speed was added to the model (Table 8). Reflecting improved overall fit, the AIC decreased from 137 to 133. Reflecting improved calibration, the Hosmer-Lemeshow goodness-of-fit chi-square decreased from 6.78 (p=0.56) to 5.70 (p=0.68), and the calibration plots showed tighter agreement between predicted and observed rates. Reflecting improved discrimination, the AUC increased from 0.78 (95% CI 0.69, 0.87) to 0.81 (95% CI 0.73, 0.89), and the IDI was 4% (95% CI 0%, 7%) with an absolute change of integrated sensitivity of 3% and a relative change of 7%.

Another multivariable logistic regression model containing the STS risk score and slow gait speed similarly showed that slow gait speed was an independent predictor of mortality or major morbidity and that the performance of the model improved after addition of gait speed to the model. Reflecting improved overall fit, the BIC decreased from -496 to -497, and the AIC decreased from 137 to 133. Reflecting improved calibration, the Hosmer-Lemeshow goodness-of-fit chi-square decreased from 11.53 (p=0.17) to 10.29 (p=0.25), and the calibration plots showed tighter agreement between predicted and observed rates. Reflecting improved discrimination, the AUC increased from 0.70 (95% CI 0.60, 0.80) to 0.74 (95% CI 0.64, 0.84), and the IDI was 5% (95% CI 1%, 8%) with an absolute change of integrated sensitivity of 4% and a relative change of 14%. For a given STS predicted risk of mortality or major morbidity, the projected risk based on our regression model was 2-3 fold greater in patients with slow gait speed as compared to patients with normal gait speed (Figure 2).

Slow gait speed was the strongest independent predictor of discharge to a healthcare facility (adjusted OR 3.19, 95% CI 1.40, 8.41) along with age ≥80

(adjusted OR 3.19, 95% CI 1.19, 8.60). Only age was an independent predictor of prolonged postoperative length of stay (adjusted OR 2.95, 95% CI 1.15, 7.59) along with a trend for slow gait speed (adjusted OR 2.32, 95% CI 0.95, 5.67). Length of stay was highly variable (often not related to patient factors but rather to administrative issues or hospital practice) and models did not perform particularly well with this outcome measure. No individual risk factors were independent predictors of mortality. The additive EuroSCORE was predictive of mortality (OR 1.35, 95% 1.14, 1.65) as was the logistic EuroSCORE (OR 1.05, 95% CI 1.004, 1.10) and the revised Parsonnet score (OR 1.09, 95% CI 1.05, 1.14) but not the STS risk score (OR 1.06, 95% CI 0.84, 1.35). Table 9 shows the improvement in model performance with the addition of slow gait speed to these risk scores for the primary and secondary outcome measures.

Addition of interaction terms to the model did not result in statistically significant increases in model deviance. No statistically significant interactions were found. For example, addition an interaction term for sex and gait speed resulted in a change of 2.203 in model deviance which, when compared to the chi-square distribution with 1 degree of freedom, yielded a nonsignificant p-value of 0.14. For this reason, the model without the interaction term was preferred. Despite this, there was a signal suggesting that the effect of slow gait speed may be modified by female sex. The OR for mortality or major morbidity was 1.9 in males and 8.0 in females, with this difference in stratum-specific OR's suggesting a trend towards interaction. Therefore, females with slow gait speed may be a particularly high-risk subgroup.

In sensitivity analyses, the variables found to be associated with gait speed and mortality or major morbidity in univariate analyses were added to the 7 core risk factor model to check for residual confounding. This expanded model did not reveal any confounding nor did the added variables achieve statistical significance, with the exception of anxiety as measured by the Hospital Anxiety and Depression Scale (OR 12.59, 95% CI 2.55, 62.08). Patients with missing gait

speed data were excluded and this did not change the results, with slow gait speed remaining an independent predictor of mortality or major morbidity (adjusted OR 2.67, 95% CI 1.03, 6.93). Gait speed was entered in the model as a continuous variable and as a dichotomous variable with different cut-offs (≥5, ≥6, ≥7, ≥7.7 seconds). The dichotomous cut-off of ≥6 seconds to walk 5-meters was consistently more robust, achieving superior discrimination to predict the outcomes of interest.

Discussion

Our study found that 5-meter gait speed was a powerful predictor of mortality or major morbidity in elderly patients undergoing cardiac surgery, conferring a 2-3 fold increase in risk. This simple, rapid, and inexpensive test effectively stratified patients beyond traditional estimates of risk which tend to be inaccurate in the elderly. Addition of gait speed to existing cardiac surgery risk models resulted in a net improvement in model discrimination and a modest improvement in calibration and overall fit. This improvement in discrimination translated into more accurately predicting who will suffer a major complication or death, and who will need to be discharged to a healthcare facility for ongoing medical care or rehabilitation.

There are no previous studies evaluating gait speed or frailty in patients undergoing cardiac surgery. Two studies evaluated disabilities in ADL's as a predictor of outcomes after cardiac surgery and entitled this "frailty" (55;56). Although there is no universally accepted definition for frailty, it is generally agreed upon that disability and frailty are different entities (26). One study evaluated frailty, as measured by the Edmonton frailty scale, as a predictor of outcomes after elective non-cardiac surgery (57). Those who were frail had higher rates of complications, higher rates of discharge to a healthcare facility, and longer lengths of stay. In other studies, the 2-minute walk test (a measure

of cardiopulmonary endurance only modestly correlated with frailty (58)) did not predict higher rates of complications after cardiac surgery whereas the SF-36 physical performance questionnaire predicted 6-month mortality (59) and 1-year functional status (60). The SF-36 had only modest predictive ability and improvement in model performance (calibration, discrimination) was not addressed.

The analytic approach for this study was focused on demonstrating the incremental prognostic value of slow gait speed rather than simply showing that it was a significant predictor. Statistical significance of a new marker does not imply clinical significance or improvement in model performance. Pencina and Cook have emphasized the importance of evaluating model performance before and after addition of a new marker (53;54). This is usually achieved by statistical tests such as the AIC and BIC for overall fit, the Hosmer-Lemeshow goodness-of-fit chi-square for calibration, and the AUC for discrimination (61). Moreover, novel reclassification statistics such as the IDI have been developed and are being increasingly used in epidemiologic studies (62-66) because they provide a more sensitive and intuitive estimate of change in model performance. The net reclassification index (NRI) is similar to the IDI but requires prespecified grouping of patients into risk categories in order to measure the probability of being correctly reclassified into another risk group. The NRI was not calculated in this study because of the lack of meaningful risk categories for the primary outcome measure of mortality or major morbidity.

Several metrics of model performance were measured and compared before and after incorporating gait speed. The IDI was found to be the most sensitive indicator of improvement in model performance after additing gait speed to traditional risk factors (IDI 5%, 95% CI 1%, 8%). Moreover, the IDI was more intuitive than other statistical tests; whereas the change in AUC from 0.78 to 0.81 is difficult to gauge, the IDI of 5% is essentially the average increase in sensitivity after incorporating gait speed assuming no decrease in specificity.

The clinical impact of measuring gait speed before cardiac surgery is twofold. First, by refining risk predictions in this challenging group, clinicians can have a more comprehensive assessment of their patient and provide and more accurate estimate of risk to the patient. Risk predictions should not be used to determine operability since no level of predicted risk is unequivocally associated with adverse outcomes (24). Second, frail patients with slow gait speed may benefit from therapeutic interventions in the pre-, peri-, or post-operative period. These interventions may include: comprehensive geriatric assessment and management (67;68), intensive monitoring, early mobilization (69), planned discharge to a specialized physical rehabilitation facility, and low-intensity exercise training (70-73). Perindopril may be an attractive option for future study, with one randomized trial showing improved physical performance in elderly patients (presumably through angiotensin II's role in modulating muscle function) (74). Other targeted therapies are under investigation.

There are a number of limitations with this study. The cut-off used to define slow gait speed was derived from a single dataset, and was not confirmed by a resampling method (cross-validation, bootstrapping) or a validation cohort. Validation is critical to ensure that the optimal cut-off has been identified, that the observed associations are not idiosyncratic to the patients or physicians in the study center, and that the instrument can be applied in various centers. This is somewhat mitigated by our multi-center design and the fact that our 0.83 m/s cut-off used was within the range of previously used cut-offs (0.65-1.00 m/s).

The primary outcome was measured in-hospital as opposed to at 30 days, and events occurring after discharge or transfer were not captured. This is particularly true for deep sternal wound infections which typically occur weeks after surgery, once patients have been discharged. There were only 3 deep sternal wound infections in our cohort, which is likely an underestimate. Nevertheless, the other components of the primary outcome measure (stroke, renal failure, prolonged ventilation, reoperation, and death) typically occur very

early after surgery and should not have been significantly underestimated. The STS and other committees have debated this issue and continue to recommend using in-hospital measures (1;37). Only 15 (11%) of our patients were transferred to other hospitals; when patients were transferred, medical records were requested from the second hospital.

Systematic differences between non-enrolled and enrolled patients may have introduced bias. To examine this bias, basic data on non-enrolled patients was collected and did not suggest any such differences. Furthermore, the main reason for non-enrolment was logistical in nature and did not, to the best of our knowledge, reflect patient-related factors. The questionnaire and gait speed test were designed to be brief and non-obtrusive in order to maximize enrolment and minimize non-response bias. As a result, the proportion of patients who were approached and agreed to participate was high. Patients who were not referred to surgery were not eligible and therefore not included in this study. Since elderly patients who are more likely to have slow gait speed (the very frail) and more likely to have mortality or major morbidity (the very ill) are less likely to be referred to surgery, referral bias was identified as an unavoidable issue which may have led to an underestimation of the effect.

Since there were a total of 30 patients who experienced the primary outcome, the number of covariates which could be entered in the regression model was limited. Classical teaching suggests that no more than 1 covariate per 10 events be entered (75-77), although more recent simulations have liberalized this rule especially when performing sensitivity analyses to rule out additional confounding (78). We performed such sensitivity analyses with expanded models. Moreover, the number of patients in this study was modest and the CI's surrounding the effect estimates were wide. Definitive recommendations for interpretation and widespread implementation of gait speed testing should be tempered by this limitation pending further confirmatory evidence.

Future studies stemming from this cohort of patients will include 1-year follow-up of patients to assess the effect of preoperative gait speed on long-term vital status, functional capacity, and adverse events. Other clinical markers of frailty such as the Cardiovascular Heath Study frailty scale and handgrip strength will be explored in detail to determine whether they are predictive and additive to gait speed. Interesting findings from this study such as the impact of preoperative anxiety on adverse events will be evaluated further. Finally, blood and aortic tissue samples provided by patients will be analyzed for novel biochemical markers of frailty. These biomarkers, including lamin A/C expression and telomere length, may be a promising method to detect frailty.

To our knowledge, this is the first study to test the value of gait speed in patients undergoing cardiac surgery. The results of this study may be generalizable to other centers given the multi-center design and the non-restrictive inclusion criteria intended to reflect real-world practice. Gait speed has the advantage of being applicable in daily practice with minimal investment. Beyond its role as a predictor of outcomes, gait speed demonstrated an incremental value to improve the performance of existing risk models and help overcome some of their relative shortcomings when applied to the elderly patient population. Future efforts should be directed towards validation and ultimately implementation of models incorporating gait speed, and developing targeted interventions for vulnerable elderly patients with slow gait speed.

Conflict of interest

None declared.

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** The following reference list applies to chapters 1, 4, and 5.*

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Legend for figures, tables, and appendices

Figures

Tables

Appendices

Figure 1: Flow diagram

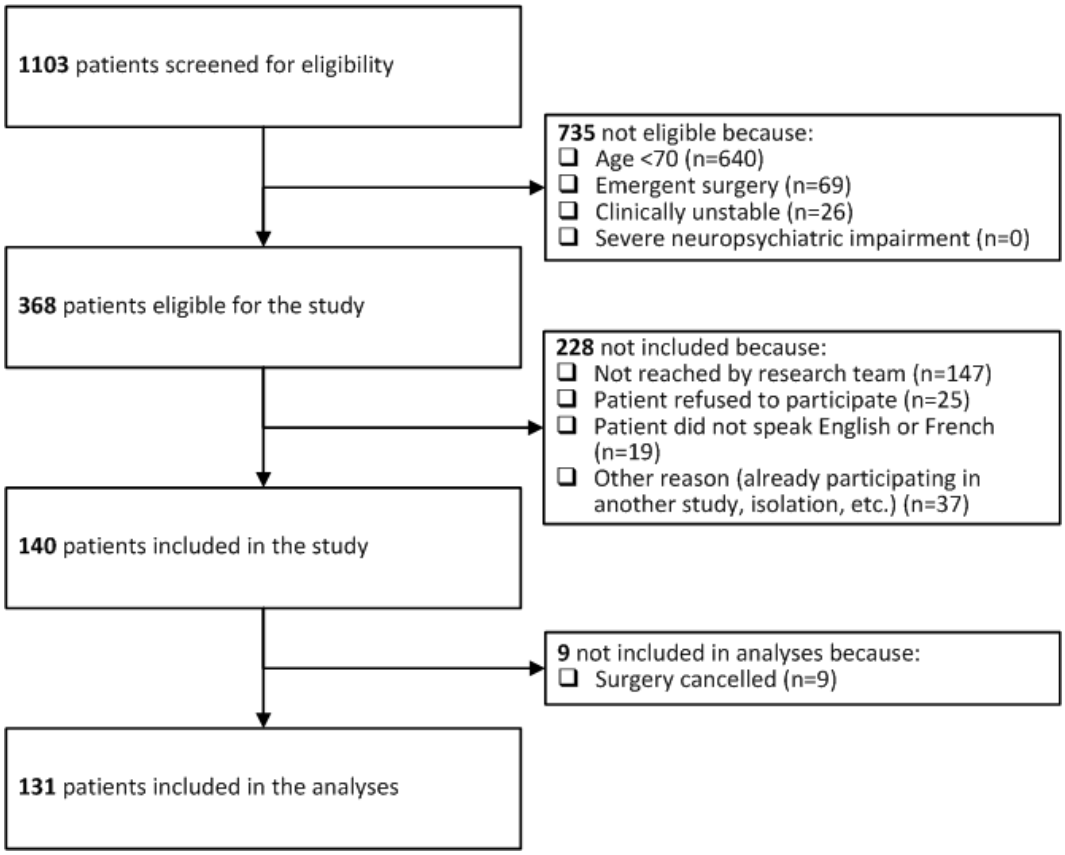
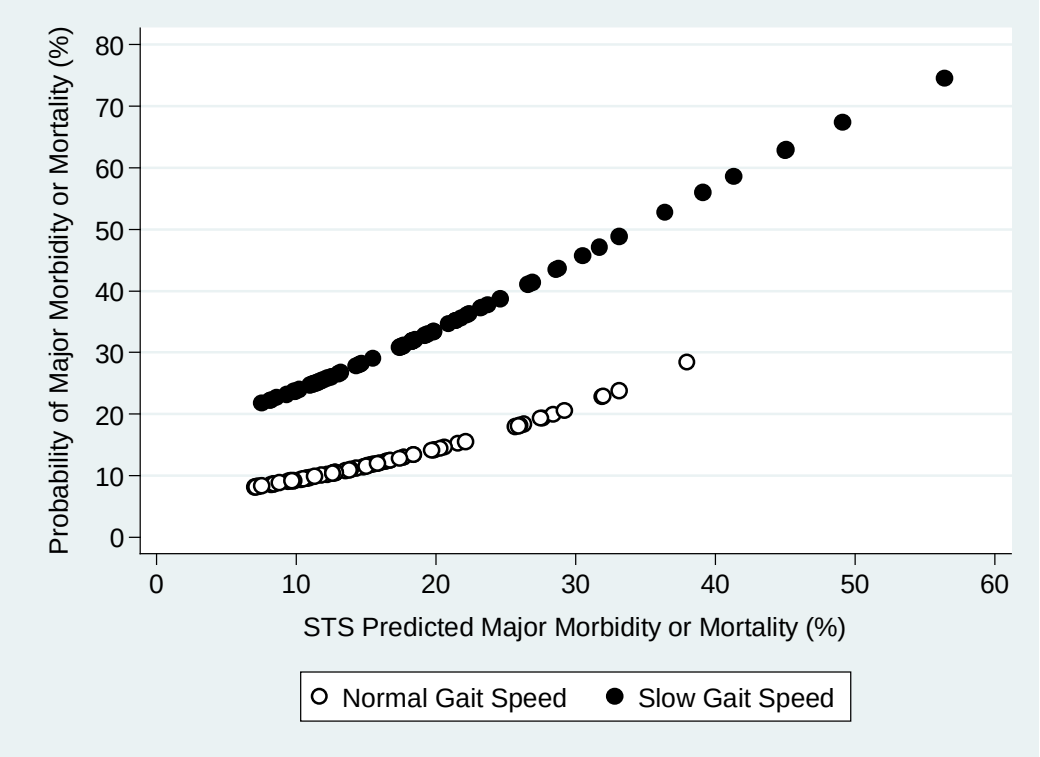


Figure 2: Projected probability of mortality or major morbidity according to the STS predicted risk and gait speed



* The data points shown in the figure represent the projected probabilities of mortality or major morbidity (y-axis) for a given level of STS risk (x-axis) according to the study's logistic regression model

Table 1: Comparison of eligible patients who were included vs. not included

	Included n=140	Not included n=228	Mean difference (95% CI)
Age, years ± SD	75.8 ± 4.4	76.7 ± 4.3	+0.9 (-0.04, 1.8)
Female sex	34%	42%	+8% (-2%, 18%)
Type of surgery			
Coronary artery bypass	82%	76%	-6% (-14%, 3%)
Number of bypasses, ± SD	3.4 ± 1.2	3.3 ± 1.3	-0.1 (-0.4, 0.2)
Aortic valve replacement	35%	38%	+3% (-7%, 13%)
Mitral valve replacement/repair	10%	14%	+4% (-3%, 11%)

Table 2: Patient enrolment and interview, stratified by gait speed

	Overall	Normal gait speed n=71 (54%)	Slow gait speed n=60 (46%)	Missing
Center				0
Hospital A	63 (48)	33 (46)	30 (50)	
Hospital B	35 (27)	17 (24)	18 (30)	
Hospital C	19 (14)	13 (18)	6 (10)	
Hospital D	14 (11)	11 (15)	6 (10)	
Location of interview				0
Outpatient clinic	1 (1)	1 (1)	0 (0)	
Cardiology ward	38 (29)	21 (30)	17 (28)	
Cardiac surgery ward	92 (70)	49 (69)	43 (72)	
Comprehension of questionnaire				11
Very good	92 (77)	49 (78)	43 (75)	
Good	18 (15)	8 (13)	10 (18)	
Fair	7 (6)	3 (5)	4 (7)	
Poor	3 (3)	3 (5)	0 (0)	
Very poor	0 (0)	0 (0)	0 (0)	
Duration of interview, minutes ± SD	31.7 ± 16.0	30.8 ± 16.2	32.7 ± 15.9	7

Table 3: Baseline covariates, stratified by gait speed

	Overall	Normal gait speed n=71 (54%)	Slow gait speed n=60 (46%)	Missing
General characteristics				
Age, years ± SD	75.8 ± 4.4	75.4 ± 4.5	76.2 ± 4.2	0
Age				0
70-74	60 (46)	38 (54)	22 (37)	
75-79	41 (31)	18 (25)	23 (38)	
80-84	25 (19)	12 (17)	13 (22)	
85-90	5 (4)	3 (4)	2 (3)	
Female sex	44 (34)	18 (25)	26 (43)	0
Height, m ± SD	1.67 ± 0.08	1.69 ± 0.08	1.65 ± 0.08	0
Weight, kg ± SD	75.4 ± 13.2	75.4 ± 12.6	75.6 ± 13.9	0
Body mass index, kg/m^2 ± SD	27.1 ± 4.6	26.5 ± 4.0	27.8 ± 5.1	0
Living in nursing home	11 (9)	2 (3)	9 (15)	2
Living alone	35 (27)	16 (24)	19 (32)	3
Married	85 (66)	51 (74)	34 (57)	2
University-level education	34 (26)	22 (32)	12 (20)	2
General perception of health				2
Very good	28 (22)	23 (33)	5 (8)	
Good	55 (43)	25 (36)	30 (50)	
Fair	37 (29)	18 (26)	19 (32)	
Poor	9 (7)	3 (4)	6 (10)	
Very poor	0 (0)	0 (0)	0 (0)	
Comorbid conditions				
Obesity	30 (23)	13 (18)	17 (28)	0
Diabetes	50 (38)	20 (28)	30 (50)	0
Hypertension	95 (73)	51 (72)	44 (73)	0
Dyslipidemia	87 (66)	49 (69)	38 (63)	0
Active smoking	12 (9)	6 (8)	6 (10)	0
Angina	65 (50)	37 (52)	28 (47)	0
Myocardial infarction	50 (38)	25 (35)	25 (42)	0
Chronic heart failure	38 (29)	21 (30)	17 (28)	0
Atrial fibrillation	24 (18)	11 (15)	13 (22)	0
Prior cardiac surgery	8 (6)	3 (4)	5 (8)	0
Chronic renal failure	21 (16)	9 (13)	12 (20)	0
Dialysis	1 (1)	0 (0)	1 (2)	0
Cirrhosis	0 (0)	0 (0)	0 (0)	0

COPD	35 (27)	18 (25)	17 (28)	0
Stroke	14 (11)	5 (7)	9 (15)	0
Peripheral arterial disease	13 (10)	8 (11)	5 (8)	0
Cancer (non-skin)	17 (13)	7 (10)	10 (17)	0
Dementia	0 (0)	0 (0)	0 (0)	0
Depression	13 (10)	8 (11)	5 (8)	0
Hip fracture	3 (2)	2 (3)	1 (2)	0
Osteoporosis	13 (10)	9 (13)	4 (7)	0
Osteoarthritis	13 (10)	5 (7)	8 (13)	0
Index hospitalization				
Reason for admission				0
No symptoms	8 (6)	7 (10)	1 (2)	
Stable angina	18 (14)	10 (14)	8 (13)	
Unstable angina	29 (22)	19 (27)	10 (17)	
NSTEMI	37 (28)	16 (23)	21 (35)	
STEMI	4 (3)	2 (3)	2 (3)	
Heart failure	35 (27)	17 (24)	18 (30)	
MI within 7 days	12 (9)	8 (11)	4 (7)	0
MI within 90 days	39 (30)	17 (24)	22 (37)	0
Critical preoperative state	2 (2)	0 (0)	2 (3)	0
Endocarditis	3 (2)	2 (3)	1 (2)	0
Geriatric instruments				
MMSE, score out of 30 ± SD	26.1 ± 3.7	26.4 ± 4.0	25.7 ± 3.4	3
MMSE, score <24	35 (27)	16 (24)	19 (32)	3
MoCA, score out of 30 ±SD	25.2 ± 3.6	25.0 ± 3.0	25.4 ± 4.3	78
MOCA, score ≤25	24 (45)	13 (43)	11 (48)	78
HADS anxiety score >11	10 (8)	3 (4)	7 (12)	4
HADS depression score >11	6 (5)	1 (1)	5 (8)	4
Nagi items, number of disabilities out of 7 ± SD	2.3 ± 2.1	1.6 ± 1.7	3.2 ± 2.1	4
IADL's (OARS), number of disabilities out of 7 ± SD	0.7 ± 1.3	0.3 ± 0.9	1.2 ± 1.5	4
ADL's (Katz), number of disabilities out of 6 ± SD	0.1 ± 0.6	0.1 ± 0.7	0.03 ± 0.2	4
Laboratory data				
Hemoglobin, g/L ± SD	124 ± 23	126 ± 22	123 ± 24	0
Platelets, $x10^9$/L ± SD	227 ± 76	218 ± 70	239 ± 83	0
Creatinine, umol/L ± SD	98 ± 62	92 ± 25	105 ± 88	0
Creatinine >200	2 (2)	0 (0)	2 (3)	0
Creatinine clearance ≤60 mL/min	58 (44)	29 (41)	20 (48)	0

Echocardiographic data				
LVEF, % ± SD	53.6 ± 13.9	54.0 ± 13.4	53.1 ± 14.5	0
LVEF				0
>50%	93 (71)	51 (72)	42 (70)	
30-50%	28 (21)	14 (20)	14 (23)	
<30%	10 (8)	6 (8)	4 (7)	
Diastolic dysfunction (≥moderate)	18 (18)	13 (23)	5 (12)	33
Right ventricular dysfunction	16 (15)	7 (12)	9 (18)	24
Pulmonary hypertension (PAPs ≥30 mmHg)	61 (47)	30 (42)	31 (52)	0
Angiographic data				
Number of major epicardial vessels ≥70%, ± SD	2.2 ± 1.1	2.2 ± 1.1	2.2 ± 1.1	0
Left main stenosis ≥50%	38 (29)	25 (35)	13 (22)	0
Proximal LAD stenosis ≥70%	49 (37)	25 (35)	24 (40)	0
Risk scores				
STS mortality or major morbidity, predicted % ± SD	18.3 ± 9.3	16.3 ± 7.2	20.7 ± 11.0	0
STS mortality, predicted % ± SD	3.1 ± 2.6	2.6 ± 1.9	3.7 ± 3.2	0
EuroSCORE (Additive), points ± SD	7.2 ± 2.5	6.8 ± 2.5	7.7 ± 2.5	0
EuroSCORE (Logistic,) predicted % ± SD	10.2 ± 9.9	9.0 ± 8.4	11.7 ± 11.3	0
Revised Parsonnet score, points ± SD	20.8 ± 10.7	18.7 ± 10.1	23.3 ± 10.8	0
Surgery				
Type of surgery				0
Isolated CABG	78 (60)	42 (59)	36 (60)	
Isolated valve	24 (18)	12 (17)	12 (20)	
Combined CABG + valve	20 (22)	17 (24)	12 (20)	
Number of bypasses, ± SD	3.4 ± 1.2	3.5 ± 1.2	3.3 ± 1.1	0 *
Internal mammary artery	98 (92)	54 (92)	44 (92)	0 *
Urgent surgery	70 (53)	36 (51)	34 (57)	0
Off-pump	14 (18)	7 (17)	7 (19)	0 *
Thoracic aortic intervention	8 (6)	6 (8)	2 (3)	0
Aortic valve replacement	46 (35)	25 (35)	21 (35)	0
Mitral valve replacement	7 (5)	0 (0)	7 (12)	0
Mitral valve repair	6 (5)	6 (8)	0 (0)	0
Tricuspid valve repair	2 (2)	1 (1)	1 (2)	0
Non-isolated CABG	53 (40)	29 (41)	24 (40)	0

* Number of bypasses and internal mammary artery not applicable to 24 patients who did not have CABG; Off-pump not applicable to 53 patients who did not have isolated CABG.

Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; MI, myocardial infarction; MMSE, mini-mental status examination; MoCA, Montreal cognitive assessment; HADS, hospital anxiety and depression scale; IADL, instrumental activities of daily living; OARS, older Americans resources and services; ADL, activities of daily living; LVEF; left ventricular ejection fraction; PAPs, systolic pulmonary artery pressure; LAD, left anterior descending coronary artery; STS, Society of Thoracic Surgeons; CABG, coronary artery bypass graft surgery.

Table 4: 5-meter gait speed and frailty score

	Overall	Normal gait speed n=71 (54%)	Slow gait speed n=60 (46%)	Missing
5-meter gait speed				
Walking aid used	26 (22)	9 (15)	17 (29)	12
Average time taken to walk 5 meters, sec ± SD	6.6 ± 2.9	5.0 ± 0.6	8.2 ± 3.3	12
Average time				12
<4 sec	3 (3)	3 (5)	0 (0)	
4-4.9 sec	24 (20)	24 (39)	0 (0)	
5-5.9 sec	34 (29)	34 (56)	0 (0)	
6-6.9 sec	27 (23)	0 (0)	27 (47)	
7-7.9 sec	18 (15)	0 (0)	18 (31)	
8-8.9 sec	3 (3)	0 (0)	3 (5)	
≥9 sec	10 (7)	0 (0)	10 (18)	
Fastest time, sec ± SD	6.3 ± 2.7	4.8 ± 0.6	7.9 ± 3.1	12
Slowest time, sec ± SD	6.8 ± 3.0	5.2 ± 0.6	8.6 ± 3.6	12
Average speed, m/sec ± SD	0.85 ± 0.24	1.02 ± 0.16	0.66 ± 0.15	0
Cut-offs for slow gait speed				
≥5 sec (≤1 m/sec)	92 (77)	34 (56)	58 (100)	12
≥6 sec (≤0.8 m/sec)	58 (49)	0 (0)	58 (100)	12
≥7 sec (≤0.7 m/sec)	31 (26)	0 (0)	31 (53)	12
≥7.7 sec (≤0.65 m/sec)	18 (15)	0 (0)	18 (31)	12
Frailty scale				
Frailty score, /5 ± SD	1.5 ± 1.1	0.9 ± 0.8	2.1 ± 1.1	0
Frailty score				0
0	28 (21)	24 (34)	4 (7)	
1	46 (35)	30 (42)	16 (27)	
2	33 (25)	15 (21)	18 (30)	
3	19 (15)	2 (3)	17 (28)	
4	4 (3)	0 (0)	4 (7)	
5	1 (1)	0 (0)	1 (2)	
Frailty score ≥3	24 (18)	2 (8)	22 (92)	0
Inactivity	63 (50)	28 (42)	35 (59)	6
Exhaustion	26 (20)	11 (16)	15 (25)	4
Weight loss	15 (12)	5 (7)	10 (17)	3
Gait speed <frailty limit	26 (22)	0 (0)	26 (45)	12
Grip strength <frailty limit	60 (47)	22 (33)	38 (63)	4

Table 5: Outcome variables, stratified by gait speed

	Overall	Normal gait speed n=71 (54%)	Slow gait speed n=60 (46%)	Missing
Mortality or major morbidity	30 (23)	9 (13)	21 (35)	0
Mortality	7 (5)	1 (1)	6 (10)	0
Renal failure	9 (7)	2 (3)	7 (12)	0
Stroke	5 (4)	1 (1)	4 (7)	0
Deep sternal wound infection	3 (2)	1 (1)	2 (3)	0
Prolonged ventilation	13 (10)	4 (6)	9 (15)	0
Reoperation	12 (9)	3 (4)	9 (15)	0
Reason for reoperation				
Bleeding or tamponade	7 (5)	2 (3)	5 (8)	0
Graft dysfunction	1 (1)	0 (0)	1 (2)	0
Valve dysfunction	1 (1)	0 (0)	1 (2)	0
Other cardiac cause	2 (2)	0 (0)	2 (3)	0
Noncardiac cause	3 (2)	1 (1)	2 (3)	0
Postoperative length of stay, days ± SD	13.5 ± 14.2	11.5 ± 10.2	15.8 ± 17.6	0
Prolonged postoperative length of stay (>14 days)	34 (26)	13 (18)	21 (35)	0
Discharge to a healthcare facility	39 (31)	14 (20)	25 (46)	0 *

* Discharge to a healthcare facility not applicable to 7 patients who were deceased.

Table 6: Outcome variables, stratified by study center

	Hospital A n=63 (48%)	Hospital B n=35 (27%)	Hospital C n=19 (14%)	Hospital D n=14 (11%)
Mortality or major morbidity	15 (24)	9 (26)	3 (16)	3 (21)
Mortality	2 (3)	5 (14)	0 (0)	0 (0)
Renal failure	5 (8)	2 (6)	1 (5)	1 (7)
Stroke	1 (2)	2 (6)	2 (11)	0 (0)
Deep sternal wound infection	3 (5)	0 (0)	0 (0)	0 (0)
Prolonged ventilation	8 (13)	3 (9)	0 (0)	2 (14)
Reoperation	7 (11)	4 (11)	1 (5)	0 (0)
Reason for reoperation				
Bleeding or tamponade	5 (8)	1 (3)	1 (5)	0 (0)
Graft dysfunction	1 (2)	0 (0)	0 (0)	0 (0)
Valve dysfunction	1 (2)	0 (0)	0 (0)	0 (0)
Other cardiac cause	0 (0)	2 (6)	0 (0)	0 (0)
Noncardiac cause	2 (3)	1 (3)	0 (0)	0 (0)
Postoperative length of stay, days ± SD	16.9 ± 17.7	11.5 ± 11.2	8.6 ± 4.4	9.5 ± 7.1
Prolonged postoperative length of stay (>14 days)	21 (33)	8 (23)	3 (16)	2 (14)
Discharge to a healthcare facility	25 (41)	8 (27)	6 (32)	0 (0)

Table 7: Univariate predictors of mortality or major morbidity

	Odds Ratio	95% CI
General characteristics		
Age, per year	1.08	(0.98, 1.18)
Age		
70-74	1	Referent
75-79	0.92	(0.32, 2.60)
80-84	4.11	(1.48, 11.42)
≥85	∞	n/a
Age ≥80	3.07	(1.26, 7.49)
Female sex	2.48	(1.08, 5.72)
Height, per m	0.01	(0.00, 1.35)
Weight, per kg	0.99	(0.96, 1.02)
Body mass index, per kg/m^2	1.03	(0.94, 1.12)
Comorbid conditions		
Obesity	1.31	(0.51, 3.33)
Diabetes	1.11	(0.48, 2.54)
Hypertension	3.01	(0.97, 9.36)
Dyslipidemia	1.24	(0.51, 2.99)
Active smoking	0.98	(0.64, 1.50)
Angina	1.02	(0.45, 2.30)
Myocardial infarction	0.64	(0.22, 1.86)
Chronic heart failure	2.32	(0.99, 5.45)
Atrial fibrillation	1.93	(0.73, 5.09)
Prior cardiac surgery	6.53	(1.46, 29.2)
Chronic renal failure	2.46	(0.91, 6.67)
Dialysis	-	-
Cirrhosis	-	-
COPD	1.86	(0.78, 4.44)
Stroke	0.91	(0.24, 3.50)
Peripheral arterial disease	0.58	(0.12, 2.8)
Cancer (non-skin)	1.04	(0.31, 3.47)
Osteoporosis	0.58	(0.12, 2.80)
Osteoarthritis	0.58	(0.12, 2.80)
Index hospitalization		
MI within 7 days	-	-
MI within 90 days	1.01	(0.42, 2.47)
Critical preoperative state	-	-

Endocarditis	-	-
Geriatric instruments		
MMSE score <24	0.96	(0.38, 2.41)
MOCA score ≤25	1.28	(0.35, 4.64)
HADS anxiety score >11	5.81	(1.52, 22.25)
HADS depression score >11	3.48	(0.66, 18.25)
Nagi items, per disability	1.28	(1.05, 1.56)
IADL's (OARS), per disability	1.28	(0.96, 1.72)
ADL's (Katz), per disability	0.74	(0.19, 2.82)
Laboratory data		
Hemoglobin, per g/L	0.99	(0.97, 1.01)
Platelets, per 10^9/L	1.00	(0.99, 1.00)
Creatinine, per umol/L	1.01	(1.00, 1.02)
Creatinine >200	3.45	(0.21, 56.85)
Creatinine clearance ≤60 mL/min	2.75	(1.18, 6.38)
Echocardiographic data		
LVEF, per %	0.99	(0.96, 1.02)
LVEF		
<35%	2.78	(0.80, 9.65)
35-49%	1.32	(0.42, 4.16)
50-69%	1	Referent
≥70%	4.38	(1.35, 14.18)
LVEF <40%	2.06	(0.74, 5.75)
Diastolic dysfunction (≥moderate)	0.87	(0.47, 1.63)
Right ventricular dysfunction	1.05	(0.55, 2.00)
Pulmonary hypertension (PAPs ≥30 mmHg)	2.43	(1.05, 5.63)
Angiographic data		
Number of major epicardial vessels ≥70%, per vessel	0.66	(0.47, 0.92)
Left main stenosis ≥50%	0.41	(0.14, 1.17)
Proximal LAD stenosis ≥70%	0.65	(0.27, 1.57)
5-meter gait speed		
Walking aid used	0.77	(0.26, 2.28)
Average time, per sec	1.12	(0.98, 1.28)
Fastest time, per sec	1.13	(0.98, 1.30)
Slowest time, per sec	1.12	(0.98, 1.27)
Average speed, per m/sec	0.06	(0.01, 0.49)
Average time ≥5 sec (1 m/sec)	4.66	(1.03, 21.15)
Average time ≥6 sec (0.83 m/sec)	3.23	(1.28, 8.13)

Average time ≥7 sec (0.71 m/sec)	3.07	(1.24, 7.65)
Average time ≥7.7 sec (0.65 m/sec)	2.58	(0.89, 7.49)

Frailty scale

Frailty score, per point	1.59	(1.10, 2.30)
Frailty score ≥3	3.92	(1.53, 10.07)
Inactivity	1.42	(0.61, 3.31)
Exhaustion	1.60	(0.61, 4.16)
Weight loss	1.76	(0.55, 5.62)
Gait speed <frailty limit	2.79	(1.08, 7.22)
Grip strength <frailty limit	2.18	(0.93, 5.11)
Grip strength, per kg	0.94	(0.90, 0.99)

Risk scores

STS mortality or major morbidity, per predicted %	1.06	(1.02, 1.11)
STS mortality, per predicted %	1.19	(1.03, 1.38)
EuroSCORE (Additive) per point	1.37	(1.14, 1.65)
EuroSCORE (Logistic), per %	1.07	(1.02, 1.12)
Revised Parsonnet score, per point	1.09	(1.05, 1.14)

Surgery

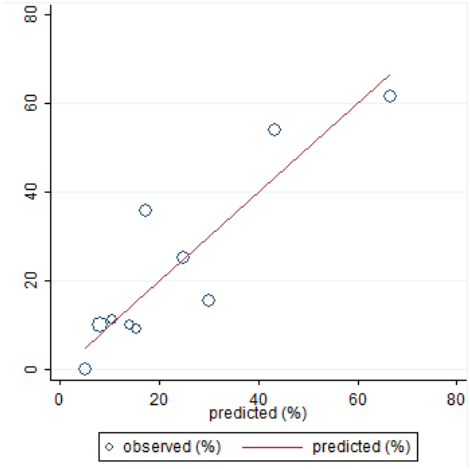
Type of surgery		
Isolated CABG	1	Referent
Isolated valve	3.30	(1.18, 9.25)
Combined CABG + valve	2.48	(0.91, 6.72)
Number of bypasses, per bypass	0.72	(0.47, 1.09)
Internal mammary artery	0.70	(0.16, 2.98)
Urgent surgery	0.70	(0.31, 1.59)
Off-pump	0.90	(0.17, 4.65)
Thoracic aortic intervention	2.13	(0.48, 9.50)
Aortic valve replacement	2.70	(1.17, 6.23)
Mitral valve replacement	5.03	(1.06, 23.87)
Mitral valve repair	-	-
Tricuspid valve repair	3.45	(0.21, 56.85)
Non-isolated CABG	2.83	(1.22, 6.54)

* Odds ration and 95% CI's indicated as "-" when there were too few events and the regression model could not predict or perfectly predicted the outcome and therefore did not provide an estimate

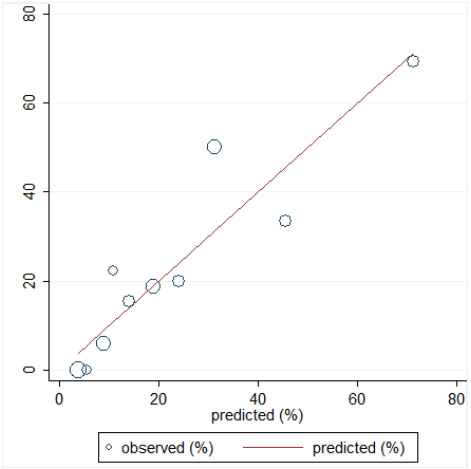
Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; MMSE, mini-mental status examination; MoCA, Montreal cognitive assessment; HADS, hospital anxiety and depression scale; IADL, instrumental activities of daily living; OARS, older Americans resources and services; ADL, activities of daily living; LVEF; left ventricular ejection fraction; PAPs, systolic pulmonary artery pressure; LAD, left anterior descending coronary artery; STS, Society of Thoracic Surgeons; CABG, coronary artery bypass graft surgery.

Table 8: Comparison of two models to predict mortality or major morbidity

	Model without gait speed	Model with gait speed
Variables entered in model	*OR (95% CI)*	*OR (95% CI)*
Age ≥80	4.22 (1.55, 11.47)	3.98 (1.43, 11.12)
Female sex	2.25 (0.89, 5.71)	1.90 (0.72, 5.01)
Prior cardiac surgery	8.1 (1.49, 44.09)	7.93 (1.34, 47.02)
LVEF <40%	2.17 (0.67, 7.05)	1.81 (0.54, 6.03)
Left main stenosis ≥50%	0.60 (0.18, 1.99)	0.75 (0.22, 2.56)
Urgent surgery	1.11 (0.41, 3.01)	0.91 (0.33, 2.55)
Non-isolated CABG	1.99 (0.70, 5.63)	2.15 (0.76, 6.07)
Slow gait speed	Not entered	3.17 (1.17, 8.59)
Model performance		
AIC	133	129
BIC	-483	-483
Hosmer-Lemeshow χ^2 (P)	6.78 (0.56)	5.70 (0.68)
AUC (95% CI)	0.78 (0.69, 0.87)	0.81 (0.73, 0.89)
IDI (95% CI)	4% (95% CI 0%, 7%)	
Calibration plots		



	1	2	3	4	5	6	7	8	9	10
obs	0	2	1	1	1	5	3	2	7	8
pred	0.8	1.6	0.9	1.4	1.7	2.4	3.0	3.9	5.6	8.6



	1	2	3	4	5	6	7	8	9	10
obs	0	0	1	2	2	3	2	7	4	9
pred	0.7	0.4	1.5	1.0	1.8	3.0	2.4	4.4	5.5	9.2

Abbreviations: OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft surgery; AIC, Akaike information criterion; BIC, Bayesian information criterion; IDI, integrated discrimination index; obs, observed number of events; pred, predicted number of events.

Table 9: Performance of various models to predict outcome measures

	AIC	BIC	Hosmer-Lemeshow χ2 (P)	AUC (95% CI)	IDI (95% CI)	ΔIS
Mortality or major morbidity						
7 risk factors	133	-483	6.78 (0.56)	0.78 (0.69, 0.87)	0.037	0.075
7 risk factors + gait speed	129	-483	5.70 (0.68)	0.81 (0.73, 0.89)	(-0.001, 0.074)	
STS score	137	-496	11.53 (0.17)	0.70 (0.60, 0.80)	0.049	0.135
STS score + gait speed	133	-497	10.29 (0.25)	0.74 (0.64, 0.84)	(0.013, 0.084)	
EuroSCORE	131	-502	9.45 (0.15)	0.70 (0.60, 0.80)	0.048	0.118
EuroSCORE + gait speed	127	-503	5.96 (0.65)	0.75 (0.66, 0.85)	(0.007, 0.088)	
Parsonnet	126	-507	5.88 (0.66)	0.75 (0.66, 0.85)	0.043	0.097
Parsonnet + gait speed	123	-507	7.31 (0.50)	0.77 (0.68, 0.87)	(0.006, 0.080)	
Mortality						
7 risk factors	61	-555	7.10 (0.53)	0.84 (0.71, 0.96)	0.008	0.060
7 risk factors + gait speed	60	-553	1.97 (0.98)	0.88 (0.80, 0.97)	(-0.013, 0.029)	
STS score	58	-575	11.34 (0.18)	0.67 (0.50, 0.83)	0.022	0.301
STS score + gait speed	56	-575	7.04 (0.53)	0.76 (0.64, 0.88)	(0.006, 0.038)	
EuroSCORE	54	-579	3.30 (0.77)	0.70 (0.52, 0.88)	0.017	0.158
EuroSCORE + gait speed	52	-578	4.45 (0.81)	0.82 (0.73, 0.91)	(-0.007, 0.040)	
Parsonnet	53	-580	3.73 (0.88)	0.75 (0.57, 0.93)	0.021	0.178
Parsonnet + gait speed	51	-579	6.94 (0.54)	0.84 (0.75, 0.93)	(-0.001, 0.042)	
Discharge to a healthcare facility						
7 risk factors	154	-421	2.90 (0.94)	0.71 (0.62, 0.81)	0.066	0.144
7 risk factors + gait speed	148	-424	6.79 (0.56)	0.77 (0.67, 0.86)	(0.023, 0.109)	
STS score	157	-435	10.28 (0.25)	0.60 (0.50, 0.71)	0.062	0.157
STS score + gait speed	150	-439	7.46 (0.49)	0.68 (0.57, 0.78)	(0.014, 0.110)	
EuroSCORE	157	-435	12.44 (0.05)	0.57 (0.47, 0.67)	0.059	0.142
EuroSCORE + gait speed	150	-439	11.72 (0.16)	0.67 (0.57, 0.77)	(0.008, 0.110)	
Parsonnet	155	-437	10.22 (0.25)	0.61 (0.51, 0.71)	0.053	0.120
Parsonnet + gait speed	149	-440	8.14 (0.42)	0.68 (0.58, 0.79)	(0.005, 0.101)	
Prolonged length of stay						
7 risk factors	150	-465	4.13 (0.85)	0.71 (0.60, 0.81)	0.031	0.063
7 risk factors + gait speed	149	-464	3.76 (0.88)	0.73 (0.62, 0.83)	(0.000, 0.061)	
STS score	151	-482	14.01 (0.08)	0.66 (0.56, 0.76)	0.035	0.092
STS score + gait speed	150	-480	7.69 (0.46)	0.67 (0.57, 0.78)	(0.009, 0.062)	
EuroSCORE	149	-484	13.87 (0.03)	0.61 (0.50, 0.71)	0.035	0.085
EuroSCORE + gait speed	147	-483	8.03 (0.43)	0.66 (0.56, 0.76)	(0.005, 0.064)	
Parsonnet	142	-491	11.80 (0.16)	0.68 (0.58, 0.78)	0.028	0.062
Parsonnet + gait speed	142	-489	12.87 (0.12)	0.70 (0.60, 0.81)	(0.004, 0.053)	

Abbreviations: CI, confidence interval; AIC, Akaike information criterion; BIC, Bayesian information criterion; IDI, integrated discrimination index; ΔIS, relative change in integrated sensitivity; STS, Society of Thoracic Surgeons.

CHAPTER 4: THESIS CONCLUSION

The topic of frailty as it pertains to older adults with cardiovascular disease has been explored in depth in this thesis. Frailty and cardiovascular disease appear to be closely connected at the biological and clinical levels, with frail elders having a greater risk of mortality and morbidity. Given the high prevalence of frailty in cardiovascular patients, clinicians should be sensitized to this issue.

In our review of the literature, the prevalence of frailty was 2-4 fold greater in patients with cardiovascular disease. The association between frailty and cardiovascular disease was bidirectional; some studies suggested that cardiovascular disease led to incident frailty, whereas others suggested that frailty led to incident cardiovascular disease.

The prognostic value of frailty in patients with cardiovascular disease was evaluated in a limited number of studies. These studies showed that frailty was a significant risk factor for mortality in patients with severe coronary artery disease and chronic heart failure. However, no previous studies had evaluated whether frailty was a risk factor for adverse events in response to therapeutic interventions.

This is relevant since evidence-based therapies are often withheld from elderly patients because chronological age and comorbid conditions are equated with their health status, even though these are rough proxies. Disentangling chronological age from physiological age would enable the delivery of safe and effective cardiovascular care for older adults to compress morbidity and optimize quality of life.

Incorporating frailty into clinical decision making could help refine risk predictions in this challenging group and allow clinicians to have a more comprehensive assessment of their patient and tailor therapy accordingly. In the

context of cardiac surgery, caution should be taken not to overemphasize risk predictions since no level of predicted risk is unequivocally associated with adverse outcomes.

In our prospective multi-center study, 131 elderly patients with cardiovascular disease requiring surgical intervention were enrolled. Frailty was measured by a 5-meter gait speed test, which is among the most validated markers for frailty. Patients were followed until their respective discharge from hospital for the occurrence of major postoperative complications or death.

The risk of death or major complications after cardiac surgery was found to be 2-3 fold greater in patients with frailty defined as slow gait speed before cardiac surgery. When slow gait speed was added to traditional risk prediction models commonly used to predict risk in patients undergoing cardiac surgery, there was a net improvement in model performance.

Particular attention was placed on the evaluation of model performance; encompassing measures of global model fit, calibration, and discrimination. These measures consistently showed that slow gait speed was an incremental predictor which could be incorporated into traditional risk prediction models and risk scores.

To our knowledge, the cohort study performed is the first to test the prognostic value of gait speed in patients undergoing cardiac surgery. Our findings may be generalizable to other centers given the multi-center design and the non-restrictive inclusion criteria intended to reflect real-world practice. Moreover, gait speed can be applied in daily practice with minimal investment.

It should be noted that our results represent a derivation cohort and should be confirmed in a large validation cohort before being implemented in routine clinical practice. This is important to ensure that the optimal cut-off for slow gait speed has been identified in this patient population.

Future efforts should be directed towards validation and implementation of models incorporating gait speed, and developing targeted interventions for vulnerable elderly patients with slow gait speed. The knowledge gained with this thesis suggests that frailty may become a core component of cardiovascular care and a “geriatric vital sign” in our rapidly aging patient population.

Appendix A: Study questionnaire

Patient's initials: _____	Patient's study ID#: _____	Date: ___ / ___ / ___ y m d

Section I: Interviewer Start Notes

I. A. Approach results:

1. Agrees to participate (Go to question 1. C.)
2. Hospitalized
3. Unreachable
4. Deceased
5. Refuses to participate (Go to question 1. B.)

I. B. If refuses to participate, indicate the reason(s) [check all that apply]:

1. Cognitive problems
2. Mental problems
3. Physical problems
4. Not interested/motivated
5. No refusal reason mentioned
6. Other (specify): _____

I. D. Start time of interview: _____h / _____min

I. E. Date of interview: _____d / _____m / _____y

I. F. Place of interview:

1. Clinic
2. Cardiology ward
3. Cardiac surgery ward
4. Other (specify):_____

I. G. Study center:

1. SMBD-Jewish General Hospital
2. CHUM-Hotel Dieu de Montreal
3. Montreal Heart Institute
4. Duke University Medical Center

Section II: Socio-demographic Data

II. A. Where were you born?

1. Canada
2. China
3. France
4. Germany
5. Greece
6. Guyana
7. Hong Kong
8. Hungary
9. India
10. Italy
11. Jamaica
12. Netherlands
13. Philippines
14. Poland
15. Portugal
16. United Kingdom
17. United States
18. Vietnam
19. Sri Lanka
20. Other (specify): _____

II. B. Where do you currently live?

1. At home
2. Nursing home
3. Other (specify): _____

II. C. Does anyone live with you?

1. No
2. Spouse
3. Child(ren)
4. Spouse and child(ren)
5. Other (specify): _____

II. D. What is your current marital status?

1. Married or living in common law
2. Widow/widower
3. Separated or divorced
4. Single (never married)
5. Other (specify): _____

II. E. What is your highest level of education completed?

1. Elementary school (or less)
2. High school
3. College / University (or higher)

I1. F. What is your household income per year (before taxes)?

1. < $10,000
2. $10,000 – $24,999
3. $25,000 – $49,999
4. $50,000 – $75,000
5. $75.000 – $100,000
6. $100,000
7. Refuse to answer
8. Does not know

Section III: Health Status

III. A. In general, would you say that your health is?

1. Very good
2. Good
3. Fair
4. Poor
5. Very poor

III. B. Compared to one year ago, how would you rate your health in general now?

1. Much better now than a year ago
2. Somewhat better now than one year ago
3. About the same as one year ago
4. Somewhat worse now than one year ago
5. Much worse now than one year ago

III. C. Functional Comorbidity Index: "Has your doctor ever told you that you have …"

		Yes	No
1.	Arthritis (rheumatoid and osteoarthritis)	1	2
2.	Osteoporosis	1	2
3.	Asthma	1	2
4.	Chronic obstructive pulmonary disease (COPD), acquired respiratory distress syndrome (ARDS), or emphysema	1	2
5.	Angina	1	2
6.	Congestive heart failure (or heart disease)	1	2
7.	Heart attack (myocardial infarct)	1	2
8.	Neurological disease (such as multiple sclerosis or Parkinson's)	1	2
9.	Stroke or TIA	1	2
10.	Peripheral vascular disease	1	2
11.	Diabetes types I and II	1	2
12.	Upper gastrointestinal disease (ulcer, hiatal hernia, reflux)	1	2
13.	Depression	1	2
14.	Anxiety or panic disorders	1	2
15.	Visual impairment (such as cataracts, glaucoma, macular degeneration) "unable to see ordinary newsprint or recognize a friend on the other side of the street even with glasses or contact lenses"	1	2
16.	Hearing impairment (very hard of hearing, even with hearing aids) "unable to hear a conservation in a group or in a quite room, even with a hearing aid"	1	2
17.	Degenerative disc disease (back disease, spinal stenosis, or severe chronic back pain)	1	2
18.	Obesity and/or BMI>30kg/m^2 (will be calculated with measured weight and height)	1	2

Nutrition

III. D. Measured height: _____cm

III. E. Measured weight: _____kg

III. F. Have you unintentionally lost weight in the last 12 months (not due to dieting or exercise)?

1. Yes
2. No
3. Does not know

III. G. If yes, how much weight have you lost in the last 12 months?

Specify: _____lbs / kg (circle one)

Physical activity

III. H. Do you exercise regularly?

1. Yes
2. No

If yes, please answer the following two questions:

III. I. How often do you exercise?

1. Three or more times a week
2. One-two times a week
3. Less than weekly

III. J. What type of exercise do you do?

1. More vigorous than walking
2. Walking (does not include walking around the house)
3. Less vigorous than walking

III. K. During the past year, did you do any physical activities or exercise such as walking, swimming, sports or working in the yard? For each named activity, how often did you do this?

	Name of activity	Frequency (e.g. less than once a month, two times a week)
1.		
2.		
3.		
4.		
5.		

III. M.MMSE

Orientation

1. What year is this? ___/1
2. What season is this? ___/1
3. What month of the year is this? ___/1
4. What is today' s date? ___/1
5. What day of the week is this? ___/1
6. What country are we in? ___/1
7. What province are we in? ___/1
8. What city are we in? ___/1
9. What is the name of this hospital? ___/1
10. What floor of the building are we on? ___/1

Registration

11. I am going to name 3 objects. After I have said all 3 objects, I want you to repeat them.
    Remember what they are because I am going to ask you to name them again in a few minutes:
    Ball *Car* *Man*
    Please repeat the 3 items for me ___/3

Attention and Calculation

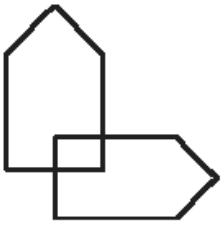
12. Subtract 7 from 100 and keep subtracting seven from what's left until I tell you to stop
    or spell the word "world" backward ___/5

Recall

13. Now what were the three objects that I asked you to remember? ___/3

Language

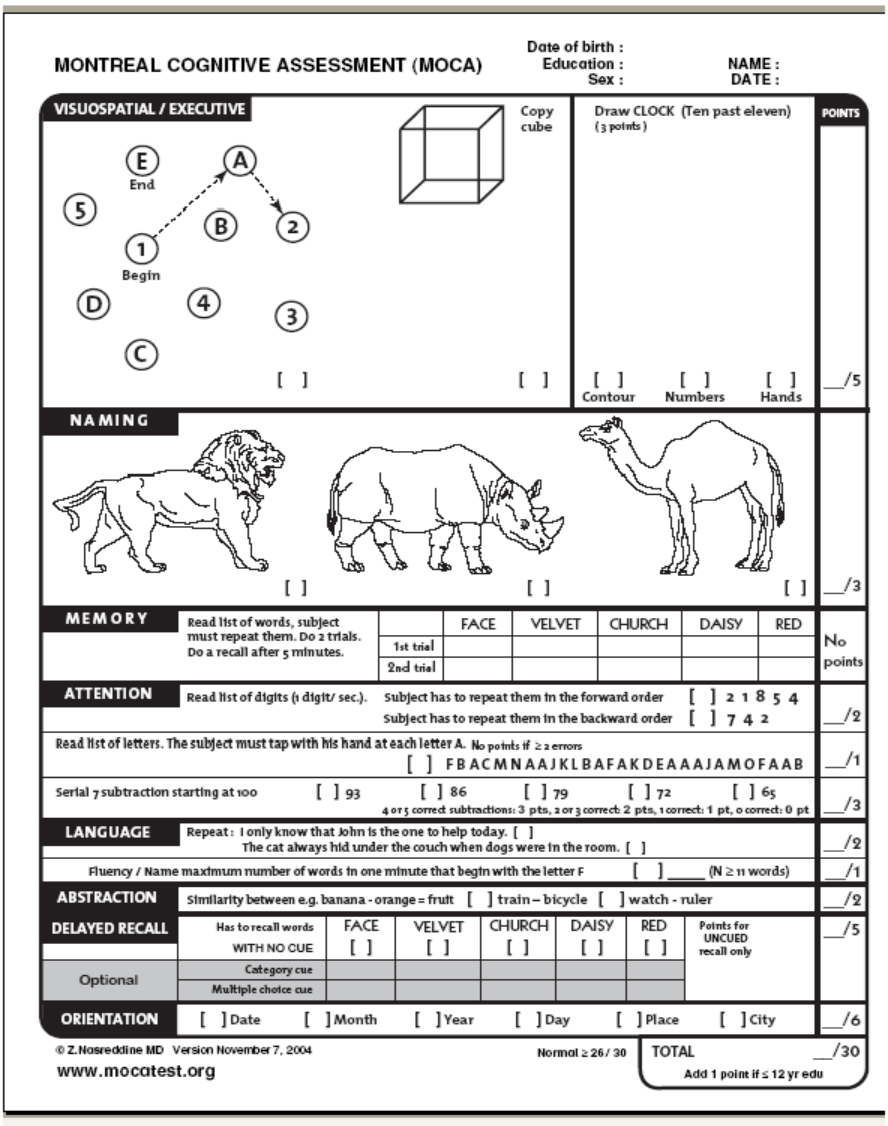
14. What is this called (a watch) ___/1
15. What is this called (a pencil) ___/1
16. Repeat the following phrase; "No ifs, ands, or buts" ___/1
17. Follow a 3-stage command: "Take a paper in your right hand, fold it in half, and put it on the floor" ___/3
18. Read the words on this paper and do what it says: Close your eyes ___/1
19. Write a complete sentence on this piece of paper ___/1
20. Copy the design shown ___/1



CLOSE YOUR EYES

MMSE Total Score: _____

III. N. MoCa (skip this step if the MMSE total score is ≤25)



MONTREAL COGNITIVE ASSESSMENT (MOCA)

Date of birth :
Education :
Sex :

NAME :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

__/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Mood

III. O. HADS Scale

**** For this section only, the patient must read the questions and circle his/her own choices ****

A1 I feel tense or "wound up":

3 Most of the time
2 A lot of time
1 From time to time, occasionally
0 Not at all

D2 I still enjoy the things I used to enjoy:

0 Definitely as much
1 Not quite so much
2 Only a little
3 Hardly at all

A3 I get a sort of frightened feeling as if something awful is about to happen:

3 Very definitely and quite badly
2 Yes, but not too badly
1 A little, but it doesn't worry me not at all
0 Not at all

D4 I can laugh and see the funny side of things:

0 As much as I always could
1 Not quite so much now
2 Definitely not so/ much now
3 Not at all

A5 Worrying thoughts go through my mind:

3 A great deal of the time
2 A lot of the time
1 Not too often
0 Very little

D6 I feel cheerful:

3 Never
2 Not often
1 Sometimes
0 Most of the time

A7 I can sit down feeling relaxed and at ease:

0 Definitely
1 Usually
2 Not often
3 Not at all

D8 I feel as if I am slowed down:

3 Nearly all the time
2 Very often
1 Sometimes
0 Not at all

A9 I get a sort of frightened feeling like "butterflies" in the stomach:

0 Not at all
1 Occasionally
2 Quiet often
3 Very often

D10 I have lost interest in my appearance:

3 Definitely
2 I don't take as much care as I should
1 I may not take quite as much care
0 I take just as much care as ever

A11 I feel restless as if I have to be on the move:

3 Very much
2 Quite a lot
1 Not very much
0 Not at all

D12 I look forward with enjoyment to things:

0 As much as ever I did
1 Rather less than I used to
2 Definitely less than I used to
3 Hardly at all

A13 I get sudden feelings of panic:

3 Very often
2 Quite often
1 Not very often
0 Not at all

D14 I can enjoy a good book or radio or television programme:

0 Often
1 Sometimes
2 Not often
3 Very seldom

IV. P. CES-D Scale

1. "I felt that everything I did was an effort"

How often in the last week before you were hospitalized did you feel this way?

3 Most of the time
2 A moderate amount of the time (3-4 days)
1 Some or a little of the time (1-2 days)
0 Rarely or non of the time (<1 day)

2. "I could not get going"

How often in the last week before you were hospitalized did you feel this way?

3 Most of the time
2 A moderate amount of the time (3-4 days)
1 Some or a little of the time (1-2 days)
0 Rarely or non of the time (<1 day)

Section IV: Functional Status

IV. A. Nagi items: "How much difficulty do you have …"

	None	Some	A lot	Unable
1. Pulling or pushing a large object like a living room chair?	1	2	3	4
2. Bending over, crouching or kneeling?	1	2	3	4
3. Raising your arms over your head?	1	2	3	4
4. Picking up or handling small objects with your fingers?	1	2	3	4
5. Lifting something that weights over 5 kilos (10 pounds)?	1	2	3	4
6. Walking up or down a flight of stairs?	1	2	3	4
7. Walking one mile (1.5 kilometres)?	1	2	3	4

IV. B. OARS instrumental activities of daily living

	Without help	With some help	Completely unable	Not applicable
1. Can you use the telephone (look up and dial the number?	1	2	3	4
2. Can you get to places out of walking distance? (taking the bus, the train, the taxi, driving a car)	1	2	3	4
3. Can you go shopping for groceries or clothes?	1	2	3	4
4. Can you prepare your own meals?	1	2	3	4
5. Can you do your housework?	1	2	3	4
6. Can you take your own medicine?	1	2	3	4
7. Can you handle your own money? (write cheques, pay bills)	1	2	3	4

IV. C. Katz activities of daily living

	Yes	No
1. Can you bath yourself completely? (or needs help only a single part of the body)	1	0
2. Can you dress yourself? (gets clothes from drawers, puts them on, may have help tying shoes)	1	0
3. Can you go to toilet by yourself? (goes to toilet, gets on and off, arranges clothes)	1	0
4. Can you move from one place to another without help? (moves in and out a chair or bed unassisted)	1	0
5. Can you exercises complete self control over urination and defecation?	1	0
6. Can you eat without help? (preparation may be done by somebody else)	1	0

IV. D. Do you receive services at home (personal care, house work)?

1. Yes, for personal care
2. Yes, for house work
3. Yes, for personal care and housework
4. No

IV. E. If you answered yes to the previous question, how many hours per week do you receive these services?

Specify: _____hours per week

Section V: Interviewer End Notes

V. A. End time of interview: _____h / _____min

V. B. Did somebody else answer for the participant?

1. Yes, help with the majority of questions
2. Yes, help with the minority of questions
3. No

V. C. Comprehension of questions:

1. Very Good
2. Good
3. Fair
4. Poor
5. Very poor

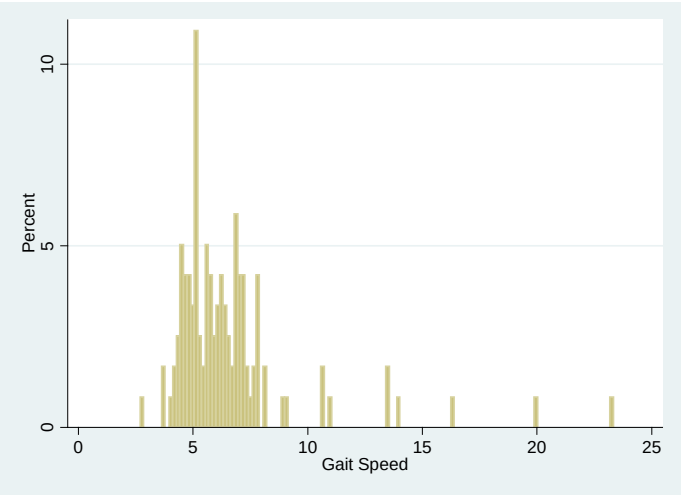
V. D. Indicate the questions or sections that were difficult to understand:

_____
_____
_____

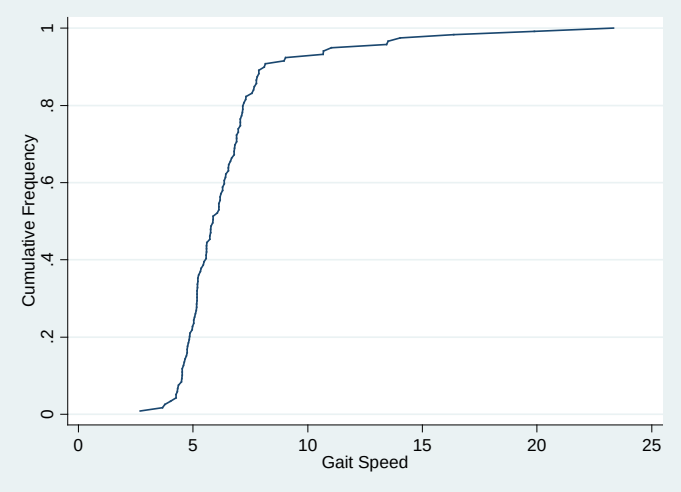
V. E. Other comments:

_____
_____
_____

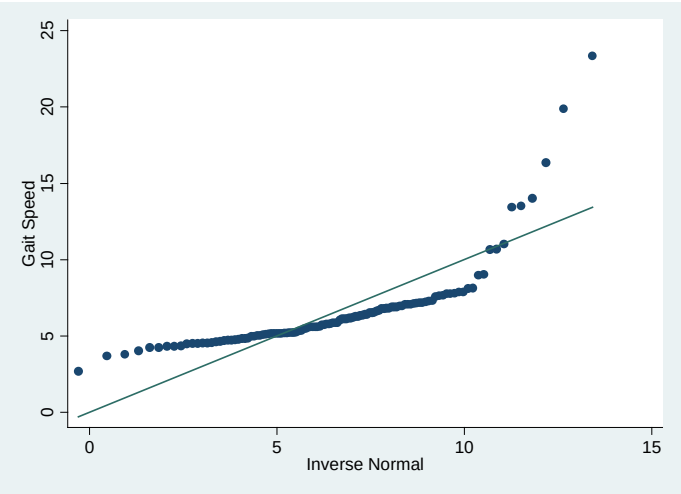
Appendix B: Distribution of gait speed



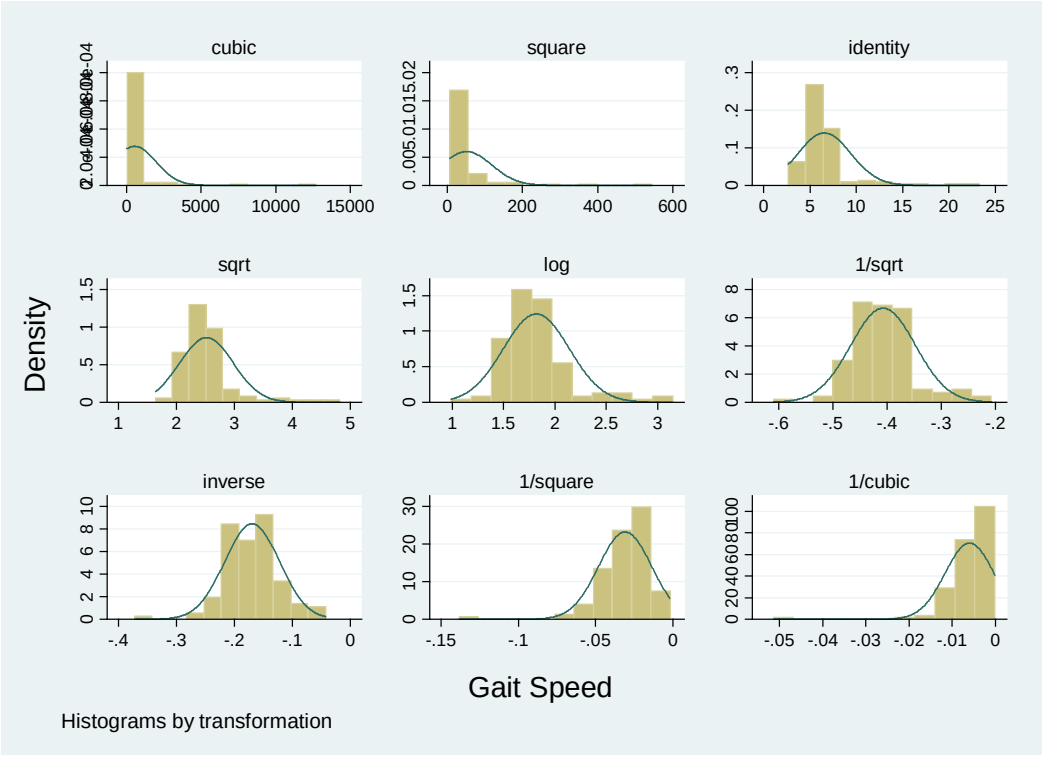
Graph 1: Histogram showing the distribution of gait speed expressed in seconds (time taken to walk 5 meters) which has several outliers.



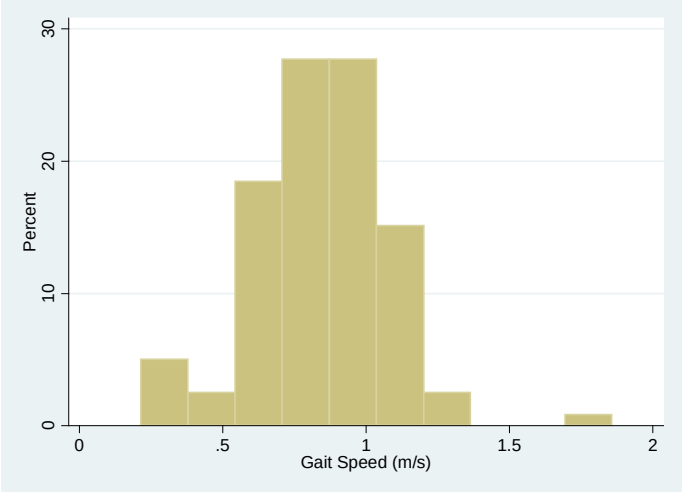
Graph 2: Cumulative frequency plot which has a sigmoidal start but then plateaus due to outliers.



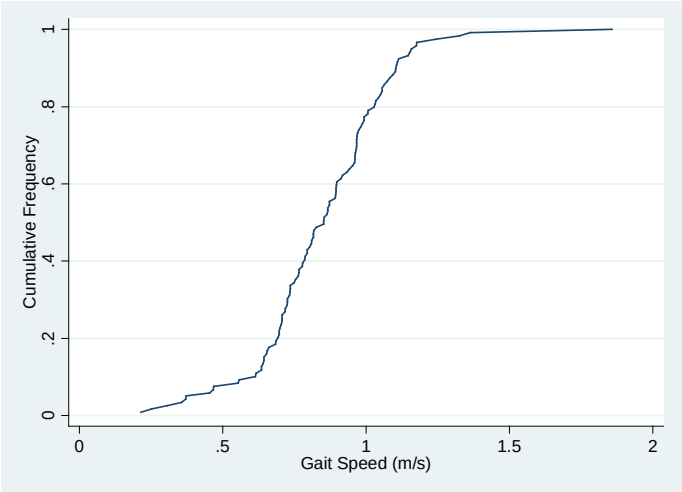
Graph 3: Normal quantile plot suggesting that, as a result of outliers, the distribution is not normal.



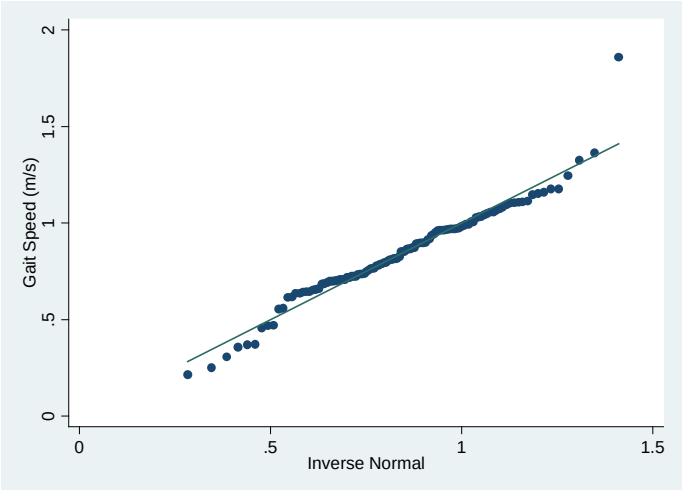
Graph 4: Ladder-of-powers histograms showing the distribution of gait speed expressed in seconds (time taken to walk 5 meters) transformed in multiple ways. Interestingly, the inverse transformation expressed in 1/seconds appears to be among the most normally distributed. This suggests that gait speed expressed in meters/second should be a normally distributed variable, as confirmed in Figures 5-7.



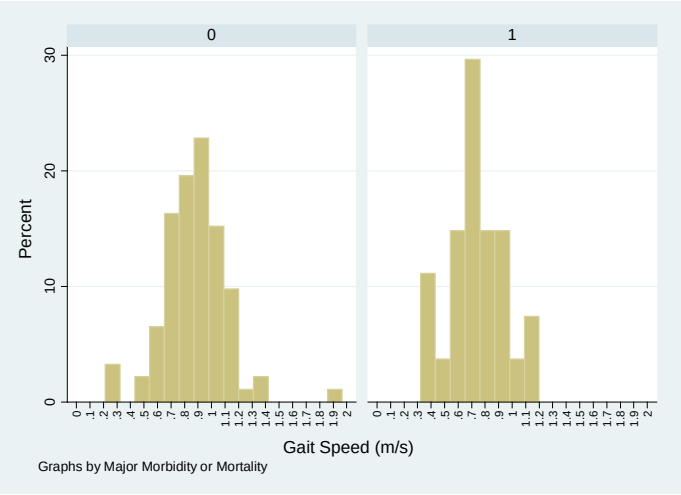
Graph 5: Histogram showing normal distribution of gait speed expressed in meters/sec without very many outliers.



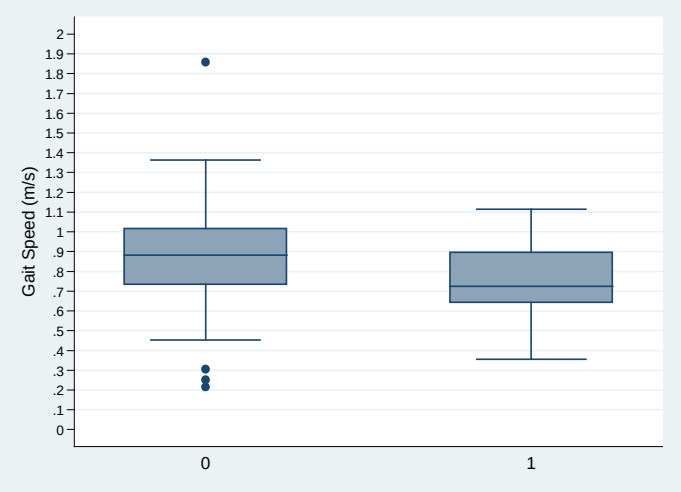
Graph 6: Cumulative frequency plot for gait speed expressed in meters/sec which is sigmoidal reflecting its normal distribution.



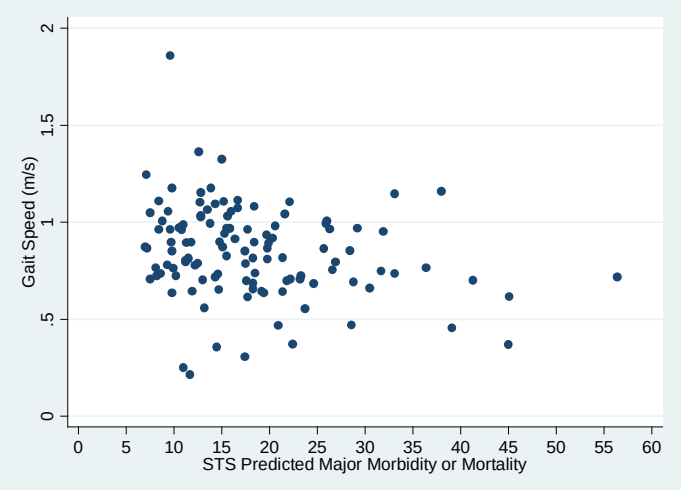
Graph 7: Normal quantile plot confirming that the distribution of gait speed expressed in meters/sec is normal. Recall that the distribution of gait speed expressed in seconds was not normal (Figure 3).



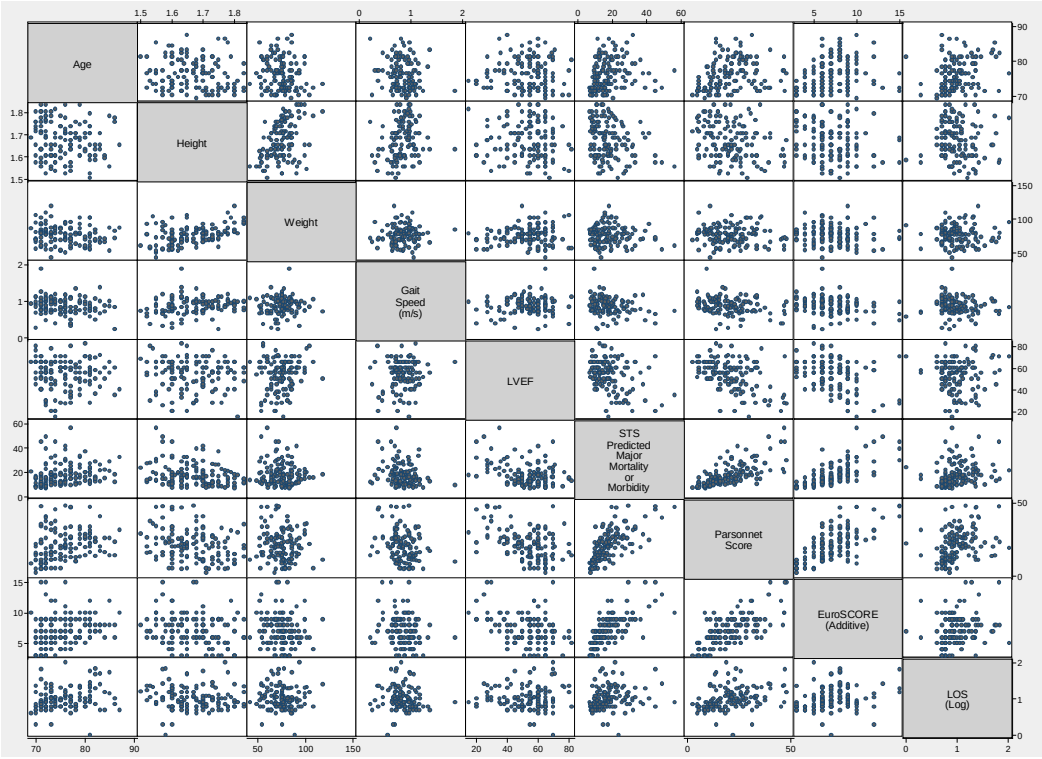
Graph 8: Histograms for gait speed, grouped by those who had a mortality or major morbidity (right) and those who did not (left). Average gait speed was slower for those who had an event.



Graph 9: Boxplot for gait speed, grouped by those who had a mortality or major morbidity (right) and those who did not (left). Average gait speed was slower for those who had an event.

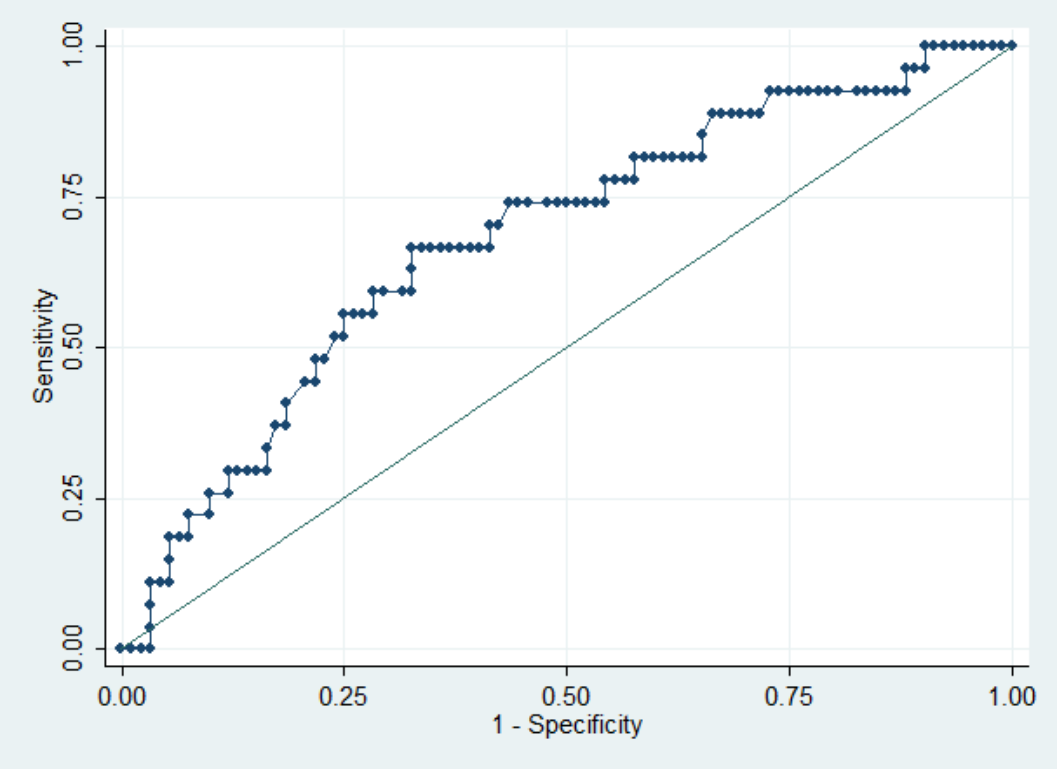


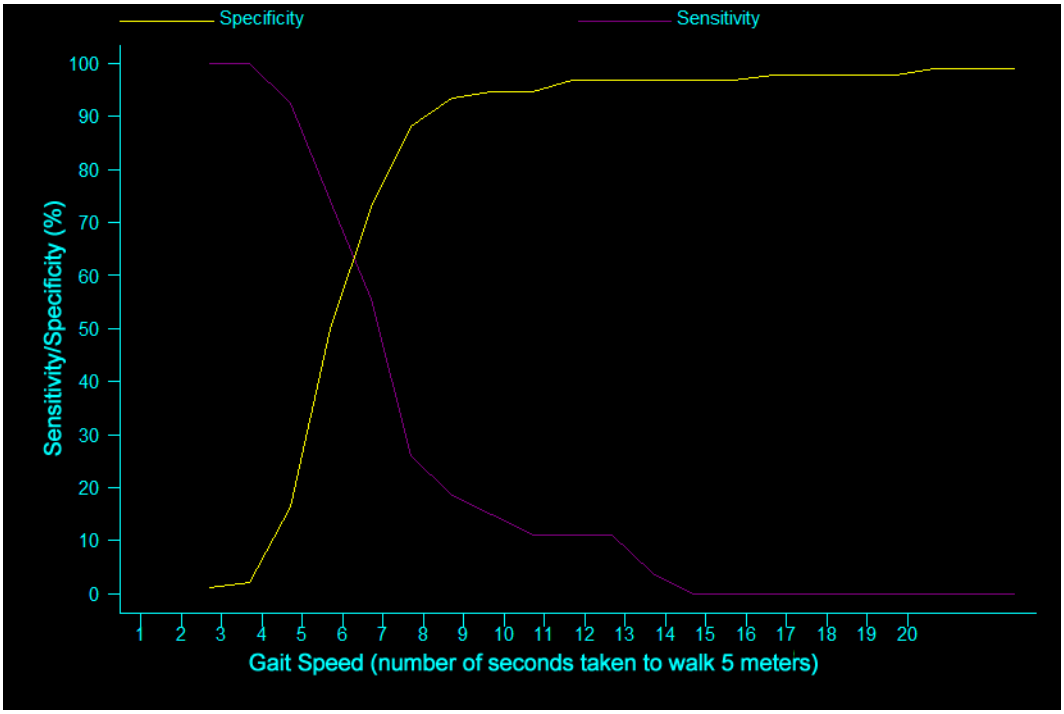
Graph 10: Scatterplot showing the lack of (or weak) correlation between gait speed and STS risk score.



Graph 11: Scatterplot matrix showing the correlations between key variables. In particular, gait speed does not appear to be correlated with other covariates suggesting that it is offering unique information.

Appendix C: ROC curves for gait speed to predict mortality or major morbidity





Appendix D: Calculating the integrated discrimination index (IDI)

Step 1: Calculate the probability of observing an event ("event=1") and probability of not observing an event i.e. nonevents ("event=0") under the new model which includes gait speed ("pSTSnew") and the old model which does not include gait speed ("pSTSold").

```
-> event = 0

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 pSTSnew |     101    .2037535    .0126884    .1275164    .1785802    .2289269
 pSTSold |     101    .2148582    .0100197    .1006964    .1949795    .2347369
---------+--------------------------------------------------------------------
    diff |     101   -.0111047    .0087348    .0877836   -.0284342    .0062249
------------------------------------------------------------------------------

-> event = 1

Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
 pSTSnew |      30    .3140298    .0285871    .1565782    .2555625     .372497
 pSTSold |      30    .2766441    .0230373    .1261804    .2295275    .3237606
---------+--------------------------------------------------------------------
    diff |      30    .0373857    .0158275    .0866906    .0050149    .0697565
------------------------------------------------------------------------------
```

Results from step 1

$P_{\text{new model,events}}$ = 0.3140298

$P_{\text{new model,nonevents}}$ = 0.2037535

$P_{\text{old model,events}}$ = 0.2766441

$P_{\text{old model,nonevents}}$ = 0.2148582

SE_{events} = 0.0158275

$SE_{\text{nonevents}}$ = 0.0087348

Step 2: Calculate the IDI with its 95% CI, and calculate the absolute and relative change in integrated sensitivity (IS) which represent the average increase in model sensitivity across all possible values.

$IDI = (P_{new\ model,events} - P_{new\ model,nonevents}) - (P_{old\ model,events} - P_{old\ model,nonevents})$

IDI = (0.3140298 - 0.2037535) - (0.2766441 - 0.2148582)

IDI = 0.0484904

$SE = sqrt(SE_{events}^2 + SE_{nonevents}^2)$

$SE = sqrt(0.0158275^2 + 0.0087348^2)$

SE = 0.0180777899

95% CI = IDI ± 1.96(SE)

95% CI = 0.0484904 ± 1.96(0.0180777899)

95% CI = 0.0130579318, 0.0839228682

$Absolute\ change\ in\ IS = P_{new\ model,events} - P_{old\ model,events}$

Absolute change in IS = 0.3140298 - 0.2766441

Absolute change in IS = 0.0373857

$Relative\ change\ in\ IS = Absolute\ change\ in\ IS / P_{old\ model,events}$

Relative change in IS = 0.0373857 / 0.2766441

Relative change in IS = 0.135140059

Results from step 2 (final output)

IDI	**= 5%**
95% CI	**= 1%, 8%**
Absolute Δ IS	**= 4%**
Relative Δ IS	**= 14%**