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Frailty is Associated with an Increased Risk of Major Adverse Cardiac Events in Patients with Stable Claudication

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Abstract

Objective—Frailty, a syndrome characterized by decreased physiologic reserves and resistance to stressors, is associated with disability, poor surgical outcomes, and mortality. We evaluated the impact of frailty on cardiovascular disease (CVD) events in peripheral arterial disease (PAD) patients with intermittent claudication.

Methods—We conducted a retrospective review of patients with stable intermittent claudication enrolled in the OMEGA-PAD Study between 2010–2015. The modified frailty index (mFI) is a retrospectively validated index of frailty derived from the Canadian Study of Health and Aging and was used in this study to categorize frailty as low, medium, or high. Our outcome was time to occurrence of a major adverse cardiac event (MACE), defined as a composite endpoint of myocardial infarction, coronary revascularization, stroke, or CVD-related death. Cox proportional hazards models were used to calculate relative hazards (RH).

Results—There were 129 subjects with a mean age of 67 years, 97% were men, 36% were diabetic, and 33% had known coronary heart disease. When the mFI criteria were applied, 38 subjects were “low” frailty, 72 were “medium” frailty, and 19 were “high” frailty. During the median follow-up period of 34 months (IQR 25–43), 29 subjects experienced a MACE. When compared to the lowest mFI, patients with medium frailty were 2.8 times more likely to have an event (95% CI 0.95, 8.46, P=0.06), while patients with a high mFI were 4.8 times as likely (95%

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CI 1.43, 15.8, $P=0.01$). In a model adjusted for age, smoking status, and presence of diabetes, those with a medium mFI were 4.3 times more likely to have an event (95% CI 1.37, 13.7, $P=0.01$) and those with a high mFI were 9.2 times as likely (95% CI 2.6, 32.4, $P=0.001$).

Conclusion—Higher mFI category is associated with a significantly increased risk of MACE in PAD patients with stable claudication. Frailty may serve as a useful adjunct for assessment of overall cardiac risk, particularly as treatment options are being contemplated.

Keywords

peripheral artery disease; frailty; modified frailty index; major adverse cardiac events; claudication

1.1 Introduction

Peripheral arterial disease (PAD) is estimated to affect between 8 to 12 million people in the United States and up to 20% of individuals over the age of 75^{1, 2}. With an aging global population, the prevalence of PAD has increased by more than 20% over the last decade with an estimated global disease burden of over 200 million people^{3, 4}. The presence of PAD is associated with an increased risk of major adverse cardiac events (MACE), defined as myocardial infarction, coronary revascularization, stroke, or cardiovascular disease associated death^{5, 6}. Frailty, a syndrome characterized by decreased physiologic reserves and resistance to stressors, is associated with disability, poor surgical outcomes, and mortality. The prevalence of frailty increases in an aging population and is thought to be due to a decline in a combination of molecular, cellular, and physiological systems⁷; however, age itself cannot fully capture an individual's loss of reserves to stress, as chronological age and biological age can differ substantially.

In recent years, there have been multiple tools developed to assess frailty. These include phenotypic models, such as the Hopkins Frailty Score, as well as accumulation of deficits models, such as the Frailty Index (FI) and the Risk Analysis Index⁸⁻¹⁴. These models consider a combination of medical history, physical exam, and measures of physical ability. To define frailty, we employed the modified frailty index (mFI) that was derived from the FI, developed using the Canadian Study of Health and Aging (CSHA)^{10, 14, 15}. This model, which is based on the theory of accumulation of deficits and has been retrospectively validated using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database¹⁵⁻¹⁷, has been increasingly recognized as a useful tool to assess frailty in a range of populations, including those with vascular disease¹⁷⁻²⁰.

In this study, we investigated the effect of frailty on the occurrence of MACE in a cohort of 129 patients with stable intermittent claudication at baseline. We also collected scores of traditional cardiovascular risk prediction (Lee Criteria) in order to qualitatively compare how proportions of MACE differ from frailty scores. Patients with PAD are a particularly relevant population to assess regarding the association between frailty and MACE, as these individuals tend to be of advanced age with multiple cardiac comorbidities²¹. Furthermore, there is an increasing emphasis on the medical treatment of claudicants prior to surgical revascularization; tools to assess frailty may be useful in determination of overall patient

risk. We hypothesized that within this cohort the incidence of MACE would be greater in those subjects with a greater mFI score.

1.2 Methods

1.2.1 Study population

This is a retrospective investigation of subjects enrolled in the OMEGA-PAD Study between 2010-2015. The goal of the OMEGA-PAD Study was to assess the effects of 1-month of fish oil supplementation on inflammation, claudication symptoms, and vascular function in a cohort of PAD patients. This cohort includes people above the age of 50 years with PAD, defined as a resting ankle-brachial index <0.9 and stable claudication symptoms. Stable claudication was defined specifically as having symptoms of claudication without current tissue loss (Rutherford classification of Stage 1-3), rest pain, critical limb ischemia, or acute limb ischemia at the time of recruitment. Patients with significant renal (creatinine >2 mg/dL) or hepatic (Child-Pugh class B) impairment were excluded. A comprehensive medical history and physical exam were performed at the time of enrollment by study staff and physicians. Variables that were included in the mFI that weren't collected at baseline were retrieved via chart review by the authors.

Subject records were retrospectively reviewed by the authors for the occurrence of MACE (myocardial infarction (MI)²², coronary revascularization, stroke, or death from a cardiac cause^{23, 24}) with enrollment in the study as time of origin. MI was defined as a detected rise in cardiac markers $>99^{\text{th}}$ percentile with at least one of the following: 1) ischemic symptoms, 2) new ST elevation or left bundle branch block, 3) development of Q waves, 4) imaging evidence of loss of viable myocardium, or 5) coronary thrombus identified by coronary angiography. Death was only included if it was deemed to be cardiac in nature. The University of California San Francisco Institutional Review Board approved this research protocol.

1.2.2 The modified frailty index (mFI)

Frailty was measured using the mFI derived from the CSHA FI (Table 1)^{10, 14, 15-17}. All of the mFI variables were collected as exactly defined by the NSQIP literature based upon OMEGA-PAD baseline visit information¹⁵ and extensive chart review. Each subject was awarded 1 point for the presence of a variable in the mFI and a frailty score was calculated as the sum of frailty variables divided by 11. Based on the frailty score, subjects were placed in low (0-1 variables, mFI 0-0.09), medium (2-3 variables, mFI 0.18-0.27), or high (4 variables, mFI >0.36) frailty categories.

1.2.3 The Lee Criteria (revised cardiac risk index)

In order to qualitatively compare the usefulness of mFI scores in predicting MACE, patients were also assigned Lee Criteria scores using baseline cohort data. Although the Lee Criteria were originally created to estimate patient's perioperative cardiovascular risk, it is also commonly used as a general predictor of cardiovascular risk²⁵. Patients were assigned one point for each of the following Lee Criteria: 1) history of ischemic heart disease defined as history of MI within 6 months or the presence of CAD, 2) history of congestive heart failure

(CHF) defined as having a CHF exacerbation within 30 days, 3) history of cerebrovascular disease defined as having a prior TIA or stroke, 4) insulin-dependent diabetes mellitus, and 5) serum Cr >2mg/dL²⁵. The Lee Criteria also assigns a point for patients undergoing high-risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular) but no patients in this cohort were preparing for surgery, therefore we excluded this criterion.

1.2.4 Statistical analysis

All statistical analyses were performed using Stata version 13.0 (StataCorp, College Station, Texas). Continuous variables are expressed as mean $\pm$ standard deviation or as medians with interquartile ranges (IQR) if they were not normally distributed. Cox proportional hazards models were used to calculate relative hazards (RH), with enrollment in study as the time of origin. An adjusted model was then derived to account for the increased risk of a MACE due to advanced age or significant comorbidities. To begin, models were constructed in which frailty category was adjusted for each covariate individually. Covariates included in the development of the model were: age, sex, race, body-mass-index, ankle-brachial index, Rutherford category, smoking status, diabetes mellitus, aspirin, beta blocker, ACE inhibitor, statin, and LDL. The covariate which most improved the likelihood ratio (LR) of the univariate model (containing only frailty category) was added to the model; each of the remaining covariates was then added individually to the model containing frailty index, and the covariate that most significantly improved the LR among these models (at the $p=0.10$ level) was retained in the model along with the frailty index. Each remaining covariate was then tested with these two covariates, with the most significant being retained in the next round of models. This was continued until no significant improvements to the model could be made. The final model adjusted frailty category by age, smoking status, and diabetes (Table 3).

1.3 Results

The cohort contained 129 subjects with stable intermittent claudication. Mean age was 67 ± 7 years, 97% were men, 36% were diabetic, and 33% had known coronary heart disease. Within this cohort, 38 individuals (29%) were identified as low frailty, 72 (56%) as medium frailty, and 19 (15%) as most frail. There was no significant difference in age between the frailty groups (Table II). The median length of follow-up was 34 (IQR 25-43) months, during which time a total of 29 MACE occurred. Figure 2 represents the proportion of patients who had a MACE per frailty group as well as per Lee Criteria score. Patients with a Lee Criteria score of 2 or 3 were combined into the same group to be easily comparable to the high frailty group. 4 patients (11%) had an event in the low frailty group: 1 (25%) death from a cardiac cause and 3 (75%) MIs or coronary revascularizations. 17 patients (24%) had an event in the medium frailty group: 4 (23%) deaths from a cardiac cause, 11 (65%) MIs or coronary revascularizations, and 2 (12%) strokes. 8 patients (42%) had an event in the high frailty group: 3 (38%) deaths from a cardiac cause 5 (62%) MIs or coronary revascularizations. 7 patients (10%) with a Lee Criteria score of 0 had an event, 17 patients (35%) with a Lee Criteria score of 1 had an event, and 5 patients (42%) with a Lee Criteria score of 2 or 3 had an event.

As frailty category increased, subjects were significantly more likely to experience a MACE during the follow-up period (trend test $P=0.0004$, Figure 1). Compared to the lowest frailty category, those with medium frailty were 2.8 times more likely to have an event (95% CI 0.95, 8.46, $P=0.06$), while patients with a high mFI were 4.8 times as likely to experience a MACE (95% CI 1.43, 15.8, $P=0.01$). This model was then adjusted to control for the impact of advanced age and comorbidities that were significantly associated with MACE in univariate analysis. In our final model, when compared to the low frailty category, those with a medium mFI were 4.3 times more likely to have an event (95% CI 1.37, 13.7, $P=0.01$) and those with a high mFI were 9.2 times as likely to experience a MACE (95% CI 2.6, 32.4, $P=0.001$), when age, diabetes, and tobacco use were held constant.

1.4 Discussion

We have demonstrated that in a cohort of subjects with PAD and stable intermittent claudication, those with a higher mFI had an increased risk of MACE. Frailty, a syndrome characterized by the progressive loss of mental and physical function and vigor in the presence or absence of defined concomitant disease, cannot be represented by chronological age alone. We have further demonstrated this fact, as there was no significant difference between the ages of those in each of the three frailty categories. Additionally, increasing frailty category increased the risk of MACE even after adjusting for age, again establishing that age itself cannot fully capture a patient's physiologic status. Our adjusted model also demonstrates that frailty is an independent and strong risk factor for the occurrence of cardiac events, even when the presence of diabetes and smoking status, both of which are significant risk factors for cardiac events, are held constant.

Frailty is generally defined as impaired resilience and decreased physiological reserve, commonly due to chronic multi-organ disease. Frailty was initially described in the geriatrics community but recent research has identified frailty as being independent of chronological age⁹. It is hypothesized that frailty impairs outcomes through a combination of chronic disease, decreased physical activity, and decreased strength that all contribute to a complex aggregate effect of multi-system dysregulation²⁶ that leads to a cascade of systemic neurohormonal impairment^{27, 28}. This aggregate effect makes the body more susceptible to adverse outcomes and less resilient to surgery, cardiac events, or other physiologic stressors. Fried et al characterized how these aggregate effects could be identified on a physiological level as anemia, excess inflammation, endocrine abnormalities, micronutrient deficiencies, increased adiposity, and impaired fine motor speed²⁹. Focusing specifically on how this could affect rates of MACE, it has been hypothesized that multi-system dysregulation increases the rate of atherogenesis and acute coronary syndromes through chronic low-grade inflammation³⁰⁻³², insulin resistance³³, oxidation imbalance³⁰, obesity, vitamin D deficiency^{34, 35}, and excess neurohormonal activation. Additionally, patients who are more frail are less likely to be independent or active, further reducing their ability to reduce their cardiovascular risk through day-to-day physical activity³⁶.

Since patients with PAD are already in a state of physical impairment, chronic inflammation, impaired physiologic reserve, and high cardiovascular risk, they are an especially relevant population in which to study the relationship between frailty and MACE. These individuals

tend to be elderly and are at an increased risk for cardiac events due to the fact that PAD itself is a cardiac risk equivalent³⁷. Early in the evaluation period of patients presenting with stable claudication, the identification of frailty could be advantageous in identifying a high-risk patient population. Over a five- year period, between 12-29% of patients with intermittent claudication will progress to the point of requiring a surgical intervention³⁸. Those identified to be of a higher frailty category could potentially benefit from more aggressive rehabilitation prior to reaching the point where an operation is required. For example, a recent study identified that a home-based rehabilitation program improved outcomes after cardiac surgery³⁹ and previous studies have showed that aggressive multi-domain (nutrition, exercise, cognitive) intervention improves frailty⁴⁰. Considering these options in addition to traditional medical optimization (aspirin, statin, tobacco use, etc) in frail claudicants or prior to revascularization should be considered.

Although there are several indices for evaluating frailty, the mFI is commonly used in the surgical setting given its ease of measurement. In the setting of operative interventions, frailty is an established risk factor for poor outcomes. The mFI is an effective tool for the global evaluation of patient frailty and it has been used to evaluate post-operative morbidity and mortality across several surgical subspecialties, including urology^{41, 42}, otolaryngology⁴³, neurosurgery^{44, 45}, and hepato-pancreato-biliary surgery⁴⁶. In the case of vascular surgery, a higher mFI has been associated with increased morbidity and mortality after both open and endovascular repair of abdominal aortic aneurysms (AAA)¹⁸. Additionally, the mFI has been found to be a better predictor of patient mortality than both the Lee Cardiac Risk Index and the American Society of Anesthesiologists Physical Status Classification in those undergoing AAA repair and carotid endarterectomy²⁰. However, when examining proportions of MACE in this cohort, patients stratified by Lee Criteria scores had very similar proportions of MACE as the frailty groups. This suggests that frailty accurately predicts MACE in stable claudicants, however, it is unclear if measures of frailty offer any predictive information that current risk predictors do not. Additionally, the current use of frailty is not as clear as traditional cardiovascular risk predictors and it may be inappropriate to compare frailty groups directly with traditional cardiovascular risk predictors. However, our data suggests that frailty can predict cardiac risk similarly to traditional cardiovascular risk predictors.

Hall et al. demonstrated that the implementation of a Frailty Screening Initiative (FSI), based on the Risk Analysis Index, could be used to identify patients who may benefit, prior to elective surgery, from further evaluation by their care team, including clinicians from surgery, anesthesia, and critical care⁴⁷. In that study, a significant decrease in mortality was seen in frail individuals included in the FSI. In addition to this, previous data supports intensive rehabilitation in improving an individual's measured frailty⁴⁰. Our study demonstrates that patients presenting with stable claudication can be stratified early with regard to their degree of frailty. Although, this was not largely different from risk stratified by Lee Criteria scores, it suggests that frailty may play a similar predictive role in patients with intermittent claudication. This will potentially allow for the identification of those who may benefit from medical and physical optimization prior to the point of requiring an operative intervention.

1.5 Limitations

Limitations of the study include the fact that it was a retrospective analysis of a relatively small cohort that included mostly men. This study can only establish an association between frailty and MACE and these results may not be generalizable to women. Other variables of interest for the analysis of frailty, such as measures of sarcopenia and grip strength, were not available. Additionally, the mFI has been criticized for relying heavily on comorbidities rather than somatic characteristics, and has not been prospectively validated. Although the mFI has been compared to other frailty indices with acceptable results⁴⁷ and is widely used in the operative setting¹⁵⁻¹⁷ it is possible that these results are not applicable to other assessments of frailty. Since this was a retrospective chart review of patients who participated in the OMEGA-PAD Study, there were no patients who were functionally dependent at baseline. Further research examining the relationship between frailty and outcomes in prospective community PAD cohorts is required.

1.6 Conclusion

This study is the first of its kind to establish an association between frailty and increased risk for MACE in patients with stable intermittent claudication. While frailty has been evaluated frequently in the perioperative setting, it is only recently that an increased focus has developed on the benefit of preoperative frailty stratification. Although in this study frailty did not seem to provide more predictive value than standard cardiac risk predictors (Lee Criteria scores), it supports further inquiry into the role of frailty and outcomes in PAD populations. The determination of frailty in PAD patients may serve as a useful adjunct for assessment of overall cardiac risk, particularly as treatment options are being contemplated.

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Figure 1.

Adjusted Kaplan-Meier estimates of time to major adverse cardiac events (MACE) by frailty categories of low ($n=38$), medium ($n=72$), and high ($n=19$) based on the modified frailty index (mFI). Trend test $P=0.0004$. The vertical dashed line indicates the cutoff for a standard error $>10\%$ for the high frailty score group only. All values of the low and medium frailty score groups had a standard error $<10\%$.

Figure 2.
The proportion of major adverse cardiac events (MACE) by frailty categories and Lee Criteria scores.

Table I

Canadian Study of Health and Aging frailty index parameters with associated modified frailty index variables¹⁵.

CSHA-FI	mFI
Problems with getting dressed, bathing, personal grooming, cooking, going out alone	Partially or totally dependent function status
History of diabetes mellitus	Insulin or non-insulin dependent diabetes
Lung or respiratory problems	History of severe COPD or current pneumonia
Congestive heart failure	Congestive heart failure within 30 days
Myocardial infarction	History of myocardial infarction within 6 months
Cardiac problems	Prior percutaneous coronary intervention, prior cardiac surgery, history of angina within 1 month
Arterial hypertension	Hypertension requiring medications
Delirium or history of cognitive impairment	Impaired sensorium
Cerebrovascular problems	History of transient ischemic attack
Stroke	Cerebrovascular accident with residual deficit
Decreased peripheral pulses	History of peripheral revascularization or amputation; rest pain or gangrene

Table IIBaseline characteristics of patients, stratified by modified frailty index [^].

	Low (n=38)	Medium (n=72)	High (n=19)	P-Value
General Characteristics	n (%)	n (%)	n (%)	
Age (years), median (IQR)	66.5 (62, 74)	67 (64, 73)	67 (64, 73)	0.66
Male gender	36 (95)	71 (99)	19 (100)	0.34
BMI, kg/m ² , mean $\pm$ SD	28.6 $\pm$ 4.5	28.3 $\pm$ 5.4	28.1 (6.4)	0.92
Rutherford Index, median (IQR)	2 (1, 3)	2 (1, 3)	3 (2, 3)	0.16
Index ABI, mean $\pm$ SD	0.76 $\pm$ 0.12	0.75 $\pm$ 0.16	0.65 $\pm$ 0.17	0.04*
Medications				
Aspirin	22 (57.9)	58 (80.6)	15 (78.9)	0.04*
Statin	25 (65.8)	65 (90.3)	15 (78.9)	0.006*
β -Blocker	14 (36.8)	47 (65.3)	15 (78.9)	0.003*
ACE inhibitor	13 (34.2)	38 (52.8)	9 (47.4)	0.18
PAD Risk Factors				
Coronary artery disease	6 (16)	33 (46)	16 (84)	<0.001*
History of smoking	36 (94.7)	65 (90.3)	19 (100)	0.19
Diabetes mellitus	1 (2.6)	36 (50.0)	10 (52.6)	<0.0001*
Total cholesterol, mg/dL, median (IQR)	170 (144, 222)	148 (127, 170)	172 (122, 188)	0.005*
Triglycerides, mg/dL, median (IQR)	123 (86, 190)	120 (85, 178)	171 (107, 198)	0.12
HDL, mg/dL, median (IQR)	43 (36, 57)	42 (36, 51)	42 (34, 58)	0.79
LDL, mg/dL, median (IQR)	94 (68, 146)	74 (58, 91)	87 (49, 107)	0.004*
Creatinine, mg/dL, median (IQR)	0.95 (.84, 1.1)	1.05 (.88, 1.27)	1.10 (.99, 1.38)	0.06
Albumin, g/dL, mean $\pm$ SD	4.04 $\pm$ 0.28	4.06 $\pm$ 0.36	3.96 $\pm$ 0.34	0.39
Baseline inflammation				
hsCRP, mg/L, median (IQR)	2.3 (1.2, 5.5)	2.5 (1.7, 6.2)	2.0 (1.0, 5.4)	0.44

[^] mFI categorized as low (0-0.09), medium (0.18-0.27), and high (>0.36).

ABI, ankle-brachial index; ACE, angiotensin-converting enzyme; BMI, body mass index; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PAD, peripheral artery disease.

Table IIICox Proportional Hazards Model for Modified Frailty Index Category $\hat{mFI}$ and MACE (n=129).

Predictor	Multivariable Analysis		
	HR	95% CI	P-value
mFI Category: ref Low	-	-	-
Medium	4.3	1.37 - 13.7	0.01*
High	9.2	2.6 – 32.4	0.001*
Smoking Status: ref Never Smoker	-	-	-
Current Smoker	0.54	0.16 - 1.8	0.32
Former Smoker	0.18	0.05 - 0.64	0.008*
Diabetes Mellitus	0.38	0.16 - 0.88	0.02*
Age	1.0	0.99 - 1.1	0.08

$\hat{mFI}$ categorized as low (0-0.09), medium (0.18-0.27), and high (>0.36).