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Unmasking frailty in coronary artery disease: impact on outcomes after lower limb amputation

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ABSTRACT

Background Frailty is a major determinant of outcomes in patients with coronary artery disease (CAD) undergoing lower limb amputation. This study evaluates the impact of frailty on in-hospital outcomes in these patients.

Methods We performed a retrospective analysis of the National Inpatient Sample (2016–2021) to identify adult patients with CAD who underwent lower limb amputation. Frailty was defined using the Johns Hopkins Adjusted Clinical Groups (ACG) frailty indicator. Multivariable logistic regression was used to assess the independent association of frailty with in-hospital outcomes, and propensity score matching (PSM) was performed to further account for confounding factors.

Results After PSM, 9,990 patients were included in each cohort. Frail patients experienced higher rates of in-hospital mortality (3.9% *vs.* 1.5%, P < 0.001), acute limb ischemia (3.8% *vs.* 3.1%, P = 0.015), fasciotomy (2.1% *vs.* 1.4%, P < 0.001), stump infection (7.9% *vs.* 6.6%, P < 0.001), cardiogenic shock (0.9% *vs.* 0.7%, P = 0.032), sudden cardiac arrest (2.7% *vs.* 2.1%, P = 0.004), mechanical circulatory support (0.3% *vs.* 0.2%, P = 0.028), major adverse cardiac and cerebrovascular events (7.7% *vs.* 5.4%, P < 0.001), and sepsis (18.3% *vs.* 13.8%, P < 0.001). In multivariable logistic regression analysis, frailty remained an independent predictor of in-hospital mortality and major complications.

Conclusion Frailty is independently associated with increased in-hospital mortality and adverse events among CAD patients undergoing lower limb amputation. Incorporating frailty assessment into preoperative evaluation may improve risk stratification and guide clinical decision-making in this high-risk population.

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide, with substantial implications for quality of life and healthcare systems. CAD is a subset of cardiovascular disease (CVD) which results from atherosclerotic plaque buildup within coronary arteries, leading to impaired myocardial perfusion and ischemia.[1,2] CAD often coexists with peripheral arterial disease (PAD), particularly in patients with risk factors such as diabetes mellitus, smoking, and advanced age. These patients frequently share common risk factors, including smoking, hypertension, and hyperlipidemia, which amplify their cardiovascular risk. PAD is characterized by the progressive narrowing of peripheral arteries, frequently resulting in critical limb ischemia (CLI). Left untreated, CLI often necessitates lower limb amputation (LLA) to manage gangrene and prevent systemic complications like sepsis. The presence of CAD is more frequent in CLI patients who require LLA than in those who do not.[3,4] The interplay of CAD and PAD in patients undergoing LLA creates a complex clinical scenario due to shared pathophysiological mechanisms and overlapping risk factors. This patient population is at an elevated risk of adverse outcomes, including perioperative myocardial infarction

(MI), arrhythmias, wound infections, and prolonged hospital stays, underscoring the need for meticulous perioperative management.[4,5]

Frailty, a clinical syndrome marked by reduced physiological reserves and increased vulnerability to external stressors, is increasingly recognized as a critical factor influencing outcomes in older adults and patients with chronic diseases. It encompasses physical, psychological, and social dimensions, manifesting as unintentional weight loss, muscle weakness, fatigue, and slowed mobility. Frailty disrupts homeostasis, impairing the ability to recover from acute stressors such as surgery.[6-8] Frailty is strongly associated with an increased risk of all-cause mortality and is also a significant predictor of cause-specific mortality from cardiovascular disease.[9,10] Frail individuals often experience poor outcomes after surgery due to impaired adaptive capacity. Similarly, frailty is a critical determinant of outcomes in patients undergoing lower limb amputation, where it has been linked to higher rates of perioperative complications, prolonged hospital stays, and mortality.[11,12] Despite its established association with poor surgical outcomes in other patient populations, the specific impact of frailty in CAD patients undergoing LLA has not been thoroughly investigated.

This study aims to assess the impact of frailty on the in-hospital outcomes of patients with CAD undergoing lower limb amputation. Understanding this relationship could enhance perioperative risk stratification and inform interventions to improve outcomes for this high-risk group.

METHODS

Database Description

Our study sought to comprehensively investigate the relationship between frailty and cardiovascular outcomes among patients with CAD undergoing lower limb amputation. Our dataset consisted of records from the National Inpatient Sample (NIS) database from 2016 to 2021. The NIS is part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ), and the largest publicly available all-payer inpatient healthcare database in the United States, providing nationally representative estimates of inpatient utilization, access, outcomes, cost, and quality.[13] A 20% random sample of patients within each stratum is selected, and their demographic information, diagnoses, and resource utilization are entered into the database. Each discharge is then weighted (weight = total number of discharges from all U.S. acute care hospitals/number of discharges in the 20% sample) to ensure the NIS is nationally representative. The database provides information regarding patient demographic information, resource utilization such as length of stay (LOS) and total hospitalization charges, hospital characteristics, insurance status, in-hospital outcomes, and primary and secondary procedures, all identified using codes from the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM).[13,14] Our study follows the methodological design checklist proposed by Khera, *et al.*[15] to address common study design errors in NIS-based research. Since the NIS is a publicly available, anonymized national database with prior ethical approval from the AHRQ, our study was exempt from Institutional Review Board (IRB) approval.

Study Population

We included adult patients (≥ 18 years of age) who were admitted to the hospital with a principal procedural diagnosis of lower limb (LL) amputation and who had a history of CAD between January 1st, 2016, and December 31st, 2021. Patients were divided into two groups based on the presence of frailty. Frailty was defined using the Johns Hopkins Adjusted Clinical Groups (ACG) frailty-defining diagnoses indicator, which is an instrument based on 10 clusters of frailty-defining diagnoses, including malnutrition, impaired vision, dementia, urinary incontinence, weight loss, decubitus ulcer, barriers to healthcare access, poverty, walking difficulty, and falls. This binary indicator identifies frailty by the presence of ≥ 1 diagnostic cluster that has been designed and validated for research on frailty-related outcomes and resource use using administrative data.[16] Johns Hopkins ACG's definition of frailty has been employed in previous NIS studies.[17-19] The list of ICD-10 codes used for extracting the population of interest and frailty-defining diagnoses are demonstrated in Table S1.

Definitions and Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes were: (1) morbidity as measured by the development of major adverse cardiac and cerebrovascular events (MACCE), acute heart failure, acute stroke, cardiogenic shock, sudden cardiac arrest (SCA), pulmonary embolism (PE), need for percutaneous coronary intervention (PCI), and sepsis, (2) lower limb specific outcomes such as acute limb ischemia (ALI), fasciotomy, percutaneous thrombectomy, stump infection, and phantom limb syndrome, (3) resource utilization as measured by LOS and total hospitalization charges and costs. All the abovementioned outcomes were identified using ICD-10-CM diagnoses and procedure codes (Tables S2 and S3). Patients' demographics, LOS, and total hospitalization charges were directly obtained from the NIS database. Total hospital charges reflect the amount a patient was billed for the entire hospital stay, but they do not reflect the actual cost of care. The HCUP provides data with hospital-specific cost-to-charge ratios based on inpatient costs across all payers.[20] Using this information, total hospital costs were calculated by multiplying the hospital charges by the corresponding cost-to-charge ratio. All hospitalization costs and charges were adjusted for inflation over time using the hospital services part of the consumer price index and are represented in 2021 US dollars.[21]

Statistical Analysis

Descriptive statistics of demographic characteristics and comorbidities were compared among those with and without frailty. Continuous variables were compared using the Student's *t-test* in the unadjusted analyses and are presented as mean ± SD. Continuous variables were tested for normality of distribution using the Shapiro-Wilk test and reported as means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on their distribution. Categorical variables were compared with the chi-square test for unadjusted analyses and are presented as frequencies and percentages.

All analyses utilized weighted NIS data in compliance with the HCUP guidelines.[22] We did not exclude missing data; instead, we addressed and treated the missing data using multiple imputations by predictive mean matching, preserving the distribution and variability of the observed data while incorporating the relationships among variables.[23,24] Trends in hospitalizations, mortality, and study outcomes over time were analyzed using Jonckheere-Terpstra and Cuzick's trend tests. A two-stage multivariable mixed-effects logistic regression model was used to identify independent predictors of in-hospital outcomes and complications among CAD patients undergoing lower limb amputation, stratified by frailty status. The model incorporated patient-level variables (demographics, comorbidities, and socioeconomic indicators) as fixed effects and accounted for hospital-level clustering by including hospital identifiers as random effects. This hierarchical approach allowed for adjustment of both measured and unmeasured variability across institutions, consistent with the structure of the NIS dataset.

We applied propensity score matching to corroborate the associations from the primary multivariable analysis and enhance the robustness of our results. Propensity scores were estimated using a multivariable logistic regression model incorporating demographic characteristics (age, race, sex, primary payer), hospital factors (bed size, region, teaching status), type of admission (elective *vs.* non-elective), and relevant comorbidities (Tables S4 and S5). One-to-one nearest-neighbor matching without replacement was performed using a caliper width of 0.2 standard deviations of the logit of the propensity score. The model demonstrated acceptable discrimination (C-statistic = 0.73) (Supplementary Figure 3). Covariate balance was assessed using standardized mean differences (SMDs), with all matched variables achieving SMDs < 5%, indicating excellent post-match balance (Supplementary Table 9).[25] All statistical analyses were performed using STATA statistical software version 18 (Stata Corp LLC, College Station, TX), with a two-sided $P < 0.05$ considered statistically significant.

RESULTS

Patient and Hospital Characteristics

A total of 345,325 patients with CAD undergoing amputation were identified. Of these, 52,735 (15.3%) had frailty, while 292,589 (84.7%) did not have frailty (Figure 1). Of CAD patients undergoing amputation with frailty, 67% were males, while 33% were women. Even in the CAD patients undergoing amputation without frailty, males (74.3%) were greater than females (25.7%). There was a preponderance of the White population in both groups. The mean age of CAD patients undergoing amputation with frailty was 72.5 years, and for those without frailty, it was 65.9 years (Figure S1). When looking at the comorbidities, CAD patients undergoing amputation with frailty had a higher prevalence of protein-energy malnutrition (PEM) (44.6% *vs.* 3.4%, $P < 0.001$),

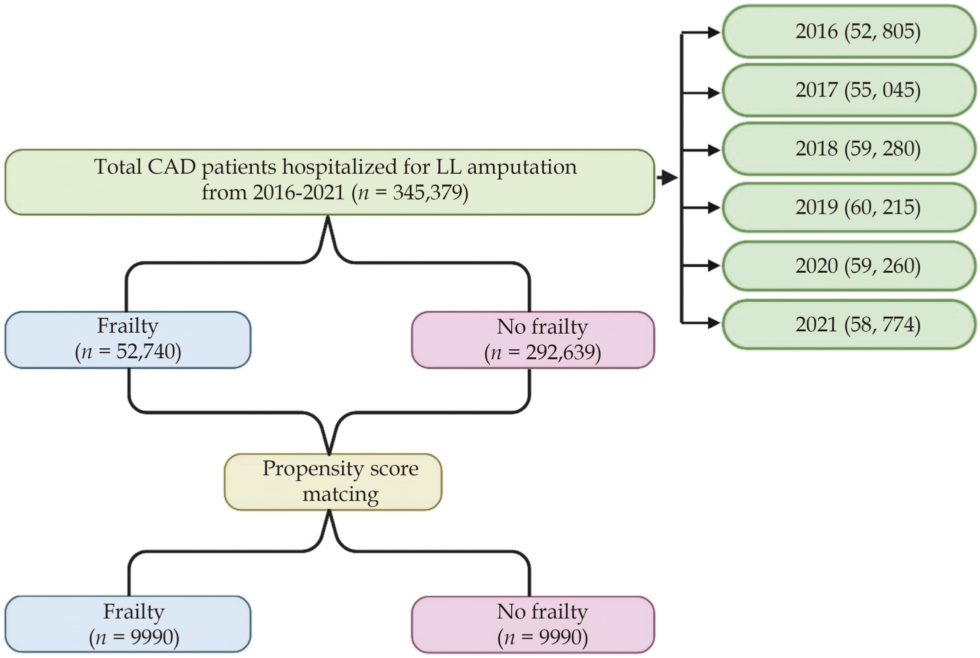

Figure 1 Flow diagram of included study population. CAD: Coronary artery disease, LL: Lower limb.

pulmonary disease (22.3% *vs.* 19.3%, $P < 0.001$), hypothyroidism (13.7% *vs.* 11.7%, $P < 0.001$), and anemia (8.9% *vs.* 6.7%, $P < 0.001$). While CAD without frailty had a higher prevalence of obesity (23.1% *vs* 12.9%, $P <$ 0.001), hypertension (91.1% *vs.* 90.2%, $P < 0.001$), dyslipidemia (62.7% *vs* 58.7% $P < 0.001$), smoking (29.3% *vs.* 27.2%, $P < 0.001$), prior MI (25.7% *vs.* 22%, $P < 0.001$), prior PCI (22.4% *vs.* 15.8%, $P < 0.001$), obstructive sleep apnea (12.1% *vs.* 7.1%, $P < 0.001$), and diabetes mellitus (61.1% *vs.* 53%, $P < 0.001$) (Table 1).

In-hospital Outcomes

Multivariable-adjusted outcomes

On multivariable logistic regression, frailty in patients with CAD undergoing lower limb amputation was independently associated with higher odds of in-hospital mortality (aOR = 1.48, 95% CI: 1.25–1.76, $P < 0.001$), sepsis (aOR = 1.19, 95% CI: 1.12–1.29, $P < 0.001$), acute heart failure (aOR = 1.83, 95% CI: 1.26–2.91, $P < 0.001$), cardiogenic shock (aOR = 1.24, 95% CI: 1.09–1.46, $P =$ 0.045), MACCE (aOR = 1.16, 95% CI: 1.06–2.45, $P =$ 0.030), and MI (aOR = 1.89, 95% CI: 1.17–2.04, $P = 0.014$). No significant differences were observed in the incidence of acute limb ischemia, fasciotomy, thrombolysis, stump infection, phantom limb syndrome, percutaneous coronary intervention, acute stroke, sudden cardiac arrest, pulmonary embolism, or the use of mechanical circulatory support (all $P > 0.05$) (Table 2).

Propensity score-matched outcomes

PSM yielded two well-balanced cohorts of 9,990 patients each (all SMDs < 5%). The model demonstrated good discrimination with a C-statistic of 0.73. In the matched analysis, frail patients had significantly higher rates of in-hospital mortality (3.9% *vs.* 1.5%, $P < 0.001$), acute limb ischemia (3.8% *vs.* 3.1%, $P = 0.015$), fasciotomy (2.1% *vs.* 1.4%, $P < 0.001$), stump infection (7.9% *vs.* 6.6%, $P < 0.001$), cardiogenic shock (0.9% *vs.* 0.7%, $P =$ 0.032), sudden cardiac arrest (2.7% *vs.* 2.1%, $P = 0.004$), mechanical circulatory support (0.3% *vs.* 0.2%, $P = 0.028$), major adverse cardiac and cerebrovascular events (7.7% *vs.* 5.4%, $P < 0.001$), and sepsis (18.3% *vs.* 13.8%, $P <$ 0.001) compared with non-frail patients. No significant differences were observed in percutaneous thrombectomy, phantom limb syndrome, PCI, acute heart failure, acute stroke, or pulmonary embolism (Table 3, Figure S2). Detailed SMDs and the Love plot are presented in Figure 2.

Resource Utilization

Frail patients experienced a longer mean length of stay (12.8 *vs.* 9.8 days) and incurred significantly higher total hospitalization charges ($149,686 *vs.* $116,355) compared

Table 1 Baseline characteristics of patients with coronary artery disease undergoing lower limb amputation, stratified by frailty status.

Variable	CAD patients without frailty (*n* = 292,639)	CAD patients with frailty (*n* = 52,740)	*P*-value
Mean age	65.9 ± 11.1	72.5 ± 10.8	< 0.001
Male	217,529 (74.3%)	35,350 (67%)	< 0.001
Female	75,060 (25.7%)	17,385 (33%)	< 0.001
Race			< 0.001
White	193,974 (69.2%)	31,385 (62.4%)	
African American	46,305 (16.5%)	11,430 (22.7%)	
Hispanic	32,490 (11.6%)	6,340 (12.6%)	
Asian/PI	4,405 (1.6%)	795 (1.6%)	
Native American	3,040 (1.1%)	370 (0.7%)	
Payer type			< 0.001
Medicare	202,149 (70.7%)	43,105 (83.1%)	
Medicaid	32,515 (11.4%)	3,800 (7.3%)	
Private	44,850 (15.7%)	4,400 (8.5%)	
Self-pay	6,030 (2.1%)	515 (1%)	
Others	375 (0.1%)	30 (0.1%)	
Admission status			< 0.001
Non-elective	232,869 (79.8%)	43,155 (82%)	
Elective	59,120 (20.2%)	9,460 (18%)	
Hospital bed size			0.025
Small	54,119 (18.5%)	9,255 (17.5%)	
Medium	86,519 (29.6%)	16,200 (30.7%)	
Large	152,000 (51.9%)	27,285 (51.7%)	
Hospital location and teaching status			0.261
Rural	21,945 (7.5%)	3,705 (7%)	
Urban non-teaching	53,915 (18.4%)	9,765 (18.5%)	
Urban teaching	216,779 (74.1%)	39,270 (74.5%)	
Hospital region			0.002
Northeast	52,405 (17.9%)	8,590 (16.3%)	
Midwest	68,880 (23.5%)	12,835 (24.3%)	
South	126,335 (43.2%)	23,145 (43.9%)	
West	45,019 (15.4%)	8,170 (15.5%)	
Transfer In Status			< 0.001
Not transferred	260,979 (89.6%)	43,615 (83.1%)	
Transferred from another acute hospital	19,895 (6.8%)	4,665 (8.9%)	
Transferred from another type of health facility	10,340 (3.6%)	4,225 (8%)	
Transfer out indicator			< 0.001
Not a transfer	150,610 (51.5%)	15,710 (29.8%)	
Transferred out to a different acute care hospital	3,885 (1.3%)	670 (1.3%)	
Transferred out to another type of health facility	138,025 (47.2%)	36,335 (68.9%)	
Weekend admission			0.280
Monday-Friday	251,179 (85.8%)	45,060 (85.4%)	
Sat/Sun	41,455 (14.2%)	7,680 (14.6%)	

Continued

Variable	CAD patients without frailty (*n* = 292,639)	CAD patients with frailty (*n* = 52,740)	*P*-value
Comorbidities			
PEM	9,865 (3.4%)	23,505 (44.6%)	< 0.001
Obesity	67,550 (23.1%)	6,825 (12.9%)	< 0.001
HTN	266,489 (91.1%)	47,500 (90.1%)	< 0.001
Dyslipidemia	183,560 (62.7%)	30,945 (58.7%)	< 0.001
Smoking	85,635 (29.3%)	14,325 (27.2%)	< 0.001
Pulmonary disease	56,560 (19.3%)	11,735 (22.3%)	< 0.001
Prior MI	75,065 (25.7%)	11,595 (22%)	< 0.001
Prior PCI	65,680 (22.4%)	8,310 (15.8%)	< 0.001
Prior CABG	1,105 (0.4%)	270 (0.5%)	0.043
OSA	35,320 (12.1%)	3,730 (7.1%)	< 0.001
Immunocompromised	575 (0.2%)	90 (0.2%)	0.576
Hypothyroidism	34,325 (11.7%)	7,225 (13.7%)	< 0.001
Anemia	19,735 (6.7%)	4,690 (8.9%)	< 0.001
Diabetes Mellitus	178,660 (61.1%)	27,935 (53%)	< 0.001
Liver disease	2,945 (1%)	490 (0.9%)	0.464

CABG: coronary artery bypass grafting; CAD: coronary artery disease; HTN: hypertension; MI: myocardial infarction; PCI: percutaneous coronary intervention; PEM: protein-energy malnutrition; OSA: obstructive sleep apnea; PI: pacific islander.

Table 2 Univariable and multivariable logistic regression analysis of outcomes based on frailty status.

Outcomes	Unadjusted odd's ratio			Adjusted odd's ratio		
	uOR	95% CI	*P*-value	aOR	95% CI	*P*-value
Mortality	2.08	1.86–2.34	< 0.001	1.48	1.25–1.76	< 0.001
ALI	1.49	1.34–1.68	< 0.001	1.09	0.94–1.26	0.238
Fasciotomy	1.49	1.29–1.73	< 0.001	0.99	0.82–1.21	0.965
Percutaneous thrombectomy	1.09	0.99–1.19	0.071	0.89	0.79–0.99	0.048
Thrombolysis	1.07	0.90–1.28	0.419	0.85	0.68–1.05	0.140
Stump infection	1.28	1.18–1.38	< 0.001	1.08	0.98–1.19	0.134
Phantom syndrome	1.27	1.12–1.44	< 0.001	1.08	0.92–1.27	0.322
PCI	0.97	0.74–1.27	0.841	0.78	0.54–1.11	0.172
MI	1.20	1.07–1.34	0.001	1.89	1.17–2.04	0.014
Acute Heart Failure	1.25	1.16–1.34	< 0.001	1.83	1.26–2.91	0.033
Acute stroke	1.87	1.41–2.48	< 0.001	1.02	0.70–1.48	0.900
Cardiogenic shock	1.48	1.18–1.85	0.001	1.24	1.09–1.46	0.045
SCA	1.37	1.20–1.56	< 0.001	0.99	0.85–1.17	0.979
Pulmonary embolism	1.64	1.24–2.18	0.001	1.15	0.79–1.67	0.477
MCS	1.61	1.11–2.34	0.011	0.74	0.42–1.31	0.298
MACCE	1.56	1.44–1.69	< 0.001	1.16	1.06–2.45	0.030
Sepsis	1.52	1.44–1.60	< 0.001	1.19	1.12–1.29	< 0.001

Unadjusted (crude) outcomes were derived from univariable logistic regression. Adjusted outcomes were derived from multivariable logistic regression, accounting for baseline characteristics including age, sex, race, primary payer, medical comorbidities such as hypertension, diabetes mellitus, chronic kidney disease, heart failure, prior myocardial infarction, and hospital characteristics such as teaching status, location, setting and bed size. ALI: acute Limb Ischemia; MACCE: major adverse cardiac and cerebrovascular events; MCS: mechanical circulatory support; MI: myocardial infarction; PCI: percutaneous coronary intervention; SCA: sudden cardiac arrest.

Table 3 Propensity-score matched outcomes of patients with coronary artery disease undergoing lower limb amputation based on frailty.

Outcomes	No frailty (n = 9,990)	Frailty (n = 9,990)	P-value
In-patient mortality	150 (1.5%)	388(3.9%)	< 0.001
ALI	307 (3.1%)	369 (3.8%)	0.015
Fasciotomy	137 (1.4%)	202 (2.1%)	< 0.001
Percutaneous thrombectomy	624 (6%)	600 (5.7%)	0.480
Stump infection	662 (6.6%)	793 (7.9%)	< 0.001
Phantom syndrome	304 (3.0%)	319 (3.2%)	0.541
PCI	70 (0.7%)	64 (0.6%)	0.603
Acute heart failure	915 (8.7%)	951 (9.1%)	0.383
Acute stroke	57 (0.5%)	65 (0.6%)	0.468
Cardiogenic shock	66 (0.7%)	93 (0.9%)	0.032
SCA	211 (2.1%)	273 (2.7%)	0.004
Pulmonary embolism	41 (0.4%)	60 (0.6%)	0.058
MCS	16 (0.2%)	31 (0.3%)	0.028
MACCE	543 (5.4%)	770 (7.7%)	< 0.001
Sepsis	1,379 (13.8%)	1,833 (18.3%)	<0.001
Mean LOS (days)	9.8	12.8	
TOTCHG (USD)	116,355	149,686	

Data are presented as n (%). ALI: acute limb ischemia; LOS: length of stay; MACCE: major adverse cardiac and cerebrovascular events; MCS: mechanical circulatory support; MI: myocardial infarction; PCI: percutaneous coronary intervention; SCA: sudden cardiac arrest; TOTCHG: total hospitalization charges.

with their non-frail counterparts. Among CAD patients undergoing lower limb amputation, most hospitalizations occurred at urban teaching hospitals (74.5% in the frailty group *vs.* 74.1% in the non-frailty group). Geographically, the southern region accounted for the largest proportion of admissions (43.9% *vs.* 43.2%). The majority of hospitalizations were non-elective (82.0% *vs.* 79.8%) and occurred on weekdays (85.4% *vs.* 85.8%). Most patients were admitted directly rather than being transferred from another facility (83.1% *vs.* 89.6%). Medicare was the predominant primary payer, covering 70.7% of patients with frailty compared to 83.1% of those without frailty (Table S8).

DISCUSSION

Our study provides valuable insights into the influence of frailty on outcomes in CAD patients undergoing LLA. While frailty has been extensively studied as a determinant of poor surgical outcomes, its specific impact in the high-risk subgroup of CAD patients undergoing LLA has been underexplored. Our findings address this gap, shedding light on the heightened risks faced by this often-underrepresented population in frailty research.

In terms of in-hospital mortality, our results are consistent with prior research highlighting frailty as a critical predictor of adverse outcomes. Asemota, *et al.*[18,26] reported significantly higher in-hospital mortality rates among frail patients (1.46% *vs.* 0.37%, P < 0.001), and our study aligns with this, showing an even greater disparity (3.88% *vs.* 1.50%, P < 0.001). Similarly, Makary, *et al.*[11,12] established frailty as a predictor of complications and mortality in older adults undergoing surgery, and Fang, *et al.*[11,12] specifically linked frailty to adverse outcomes in lower extremity amputations.

Tsai, *et al.*[27,28] in a study of over 1,000 amputations conducted in Veterans Affairs (VA) hospitals, reported no significant association between frailty and mortality. However, Tse, *et al.*[27,28]In a separate VA-based study, identified a correlation between frailty and an increased likelihood of complications as well as 30-day mortality. Similarly, Fang, *et al.* found no link between worsening frailty and 30-day mortality but observed higher risks of readmissions and adverse events within 30 days. [12] In another study examining the impact of frailty on post-CABG patients, Kochar, *et al.*[29] demonstrated a signific-

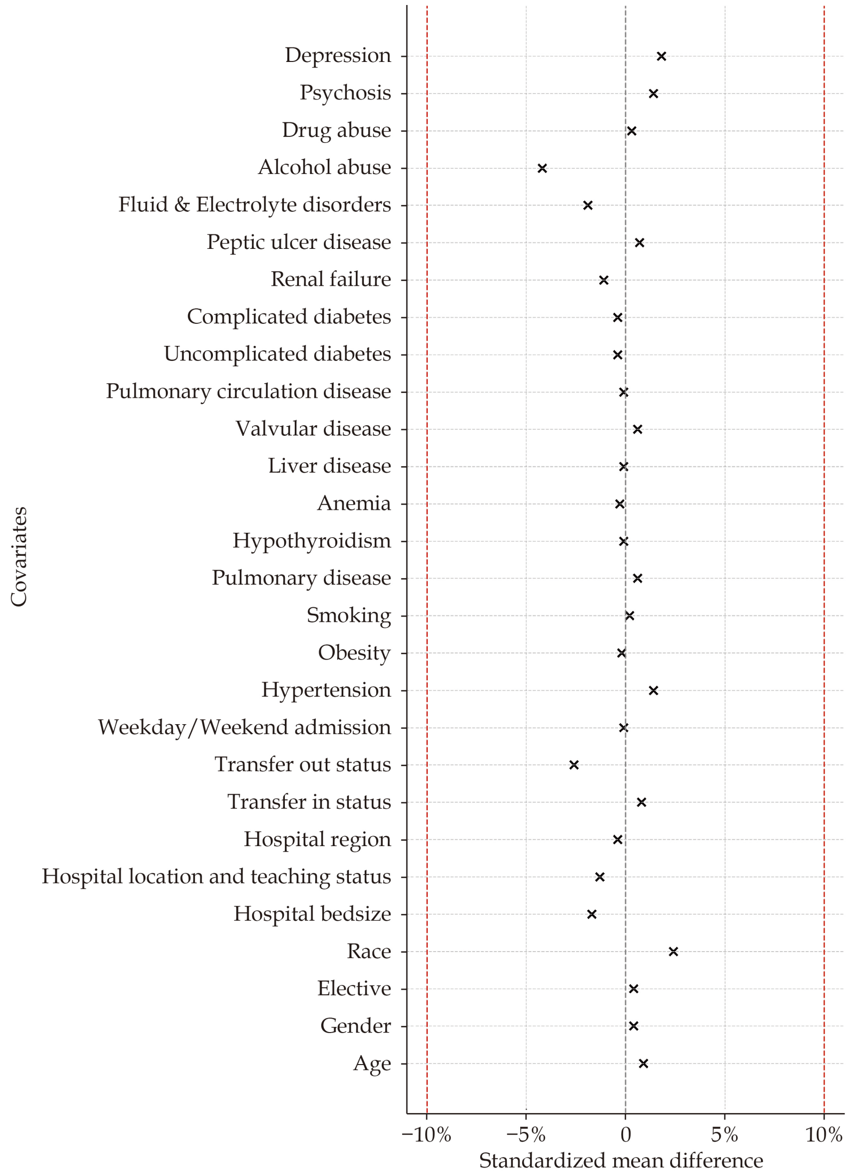

Figure 2 Covariate balance after propensity score matching. SMD for all covariates included in the propensity score models are shown after 1: 1 matching. All variables achieved an SMD below 5%, indicating excellent post-match balance. The red dashed lines mark the ± 10% threshold commonly used to denote acceptable balance. SMD: standardized mean differences

ant association between frail and pre-frail states and increased cumulative all-cause mortality.

Frail patients in our study experienced longer hospital stays (mean LOS 12.8 *vs.* 9.8 days) and incurred significantly higher hospitalization charges, findings that are in line with existing literature.[19,30] These outcomes highlight the additional healthcare resource utilization associated with frailty in this patient group.

We observed a higher prevalence of men in both the frail (67%) and non-frail (74.3%) groups, which contrasts with the general trend of frailty being more common and severe in women for any age group.[31] This finding suggests a gender disparity specific to amputations in patients with CAD. Additionally, frail patients in our study were notably older (72.5 *vs.* 65.9 years), underscoring age as a significant contributor to frailty. These findings align with broader population data showing a about 10% prevalence of frailty among community-dwelling individuals aged 65 years and older.[32]

Our analysis revealed distinct comorbidity patterns between frail and non-frail patients. Frail patients had significantly higher rates of malnutrition and anemia, reflecting the classic frailty phenotype, whereas non-frail patients were more likely to exhibit traditional cardiovascular risk factors such as obesity, hypertension, and diabetes. This divergence suggests that frailty in CAD patients may follow unique pathophysiological pathways, differing from typical cardiovascular risk profiles. Therefore, tailored interventions focusing on malnutrition and anemia may be particularly beneficial for frail patients, complementing traditional cardiovascular risk management in non-frail individuals.

Increasing age and hypoalbuminemia, both indicators of frailty, have been identified as strong predictors of short- and long-term mortality in veteran patients undergoing major lower extremity amputations.[27] Similarly, our study found a significantly higher prevalence of malnutrition in the frail group compared to the non-frail group (44.6% *vs.* 3.4%, $P < 0.001$).

The propensity score matching analysis further highlights significant differences in perioperative outcomes, including higher rates of complications such as sepsis, MACCE, and stump infections in frail patients. These findings underscore the need for tailored preoperative optimization protocols and postoperative care pathways to address the unique vulnerabilities of frail CAD patients undergoing LLA. Similarly, a study by Shah, *et al.*[33] found that the frail group had a significantly higher likelihood of inpatient complications compared to the non-frail group.

Worse outcomes in frail patients may partly be due to their reduced ability to participate in postoperative rehabilitation, a key factor in recovery. Additionally, care preferences, such as do-not-resuscitate orders or avoiding invasive procedures, may also contribute to these disparities, reflecting a focus on comfort over aggressive treatment.

Our study provides compelling evidence for the independent impact of frailty on key post-amputation outcomes. The markedly higher mortality and sepsis rates in frail patients underscore the need for enhanced perioperative vigilance and preventive strategies.

The increased incidence of stump infections and ALI suggests that frail patients may benefit from specialized wound care protocols and more intensive post-operative monitoring. The higher rates of cardiovascular complications indicate that frail patients might require more rigorous cardiac optimization before surgery. However, the lack of difference in certain outcomes (like phantom syndrome and acute stroke) suggests that some complications are equally likely regardless of frailty status, helping clinicians focus resources on preventing the most impactful complications.

In our study, the resource utilization patterns highlight important systemic aspects of amputation care in CAD patients. The concentration of cases in urban teaching hospitals suggests a need for specialized expertise and resources, raising questions about access to care in rural settings. The high rate of non-elective admissions across both groups indicates potential opportunities for earlier intervention and better outpatient management. The significantly higher hospitalization charges for frail patients highlight a notable cost disparity that could guide resource allocation and the development of optimized care pathways. Additionally, the predominance of Medicare coverage underscores the substantial public health impact of these procedures.

Limitations

Our study results must be interpreted considering some limitations. First, the retrospective nature of the study precludes causal inferences. Second, frailty was defined using administrative data, which may not fully capture the complexity and dynamic nature of frailty.[34] Additionally, the analysis was restricted to in-hospital outcomes, leaving long-term recovery and functional outcomes unaddressed. Missing data, although addressed using multiple imputations, may still introduce residual bias. Finally, unmeasured confounders, such as lifestyle factors or psychosocial determinants, could have influenced the results.

Conclusion

Frailty significantly exacerbates the risk of adverse outcomes in CAD patients undergoing lower limb amputation. Our findings emphasize the need to incorporate frailty assessment into preoperative evaluation, counseling, and risk stratification. The observed increase in mortality, complications, and resource utilization among frail patients highlights the necessity for tailored perioperative strategies and multidisciplinary care pathways. Identifying frail individuals early may enable more informed clinical decision-making and targeted interventions to mitigate the disproportionate burden of frailty-related morbidity and mortality in this vulnerable population. These results support the development of standardized care protocols aimed at improving outcomes for high-risk surgical patients with coexisting CAD and frailty.

Conflict of Interests

None.

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