Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Frailty With Treatment Selection and Long-Term Outcomes Among Patients With Chronic Limb-Threatening Ischemia

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BACKGROUND: The optimal treatment strategy for patients with chronic limb-threatening ischemia (CLTI) is often unclear. Frailty has emerged as an important factor that can identify patients at greater risk of poor outcomes and guide treatment selection, but few studies have explored its utility among the CLTI population. We examine the association of a health record-based frailty measure with treatment choice and long-term outcomes among patients hospitalized with CLTI.

METHODS AND RESULTS: We included patients aged >65 years hospitalized with CLTI in the Medicare Provider Analysis and Review data set between October 1, 2009 and September 30, 2015. The primary exposure was frailty, defined by the Claims-based Frailty Indicator. Baseline frailty status and revascularization choice were examined using logistic regression. Cox proportional hazards regression was used to determine the association between frailty and death or amputation, stratifying by treatment strategy. Of 85 060 patients, 35 484 (42%) were classified as frail. Frail patients had lower likelihood of revascularization (adjusted odds ratio [OR], 0.78; 95% CI, 0.75–0.82). Among those revascularized, frailty was associated with lower likelihood of surgical versus endovascular treatment (adjusted OR, 0.76; CI, 0.72–0.81). Frail patients experienced increased risk of amputation or death, regardless of revascularization status (revascularized: adjusted hazard ratio [HR], 1.34; CI, 1.30–1.38; non-revascularized: adjusted HR, 1.22; CI, 1.17–1.27). Among those revascularized, frailty was independently associated with amputation or death irrespective of revascularization strategy (surgical: adjusted HR, 1.36; CI, 1.31–1.42; endovascular: aHR, 1.29; CI, 1.243–1.35).

CONCLUSIONS: Among patients hospitalized with CLTI, frailty is an important independent predictor of revascularization strategy and longitudinal adverse outcomes.

Key Words: chronic limb-threatening ischemia ■ frailty ■ outcomes

Chronic limb-threatening ischemia (CLTI) represents the most severe stage of peripheral artery disease and has devastating consequences if left untreated, with a 22% cardiovascular mortality rate and a 22% major amputation rate at 1 year.[1] Determining the optimal treatment strategy for each individual patient in the setting of these aggregate poor outcomes remains unclear. Although prompt revascularization is recommended in multiple major societal guidelines,[2,3] it is often uncertain whether an endovascular or surgical approach is superior for a particular patient, as each strategy carries its unique advantages and drawbacks.[4] Furthermore, there may be competing risks of morbidity and mortality that negate the benefit of

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Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023138

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Among patients hospitalized with chronic limb-threatening ischemia, frailty is an important independent predictor of revascularization strategy and longitudinal adverse outcomes.
- Frail patients with chronic limb-threatening ischemia were less likely to receive aggressive treatments and more likely to experience death or amputation, regardless of treatment strategy.

What Are the Clinical Implications?

- Clinicians should assess frailty in patients with chronic limb-threatening ischemia and use such information to guide shared decision-making with patients about their prognosis and the various treatment options available, ranging from invasive surgical revascularization to palliation.

Nonstandard Abbreviations and Acronyms

AFS	amputation-free survival
CFI	Claims-based Frailty Indicator
CLTI	chronic limb-threatening ischemia

revascularization altogether and may favor palliation. As such, it is critical that factors associated with prognosis are identified and used to guide clinical decision-making to improve CLTI outcomes.

Prior attempts at creating clinical risk stratification tools have focused on traditional comorbidities and their cumulative burden.[5–10] However, these characteristics may not fully represent a patient's risk or candidacy for a specific invasive strategy. Recently, frailty has emerged as an important prognostic factor that can guide treatment selection and help identify patients with cardiovascular disease at greater risk of poor outcomes.[11–13] Multiple methods have been adopted to measure frailty, including in-person and health record-based assessments. Despite the demonstrated utility of identifying patients with cardiovascular disease who are frail, the extension of these methods to larger CLTI populations is limited.[14,15]

Therefore, this study involving patients hospitalized with CLTI aimed to examine the association of a health record-based frailty measure with: (1) treatment choice and (2) outcomes. Such results can not only help inform shared decision-making with patients on CLTI treatment options but can also help guide future studies examining the optimal treatment strategy for patients with CLTI.

METHODS

Study Population

We included all unique adults aged ≥66 years with an inpatient hospitalization for CLTI in the Centers for Medicare and Medicaid Services Medicare Provider Analysis and Review (MedPAR) database between October 1, 2009 and September 30, 2015. The cut-off of the study corresponded with the transition to the *International Classification of Diseases, Tenth Revision* (*ICD-10*) coding, as the frailty measure used in this study relies on the *International Classification of Diseases, Ninth Revision* (*ICD-9*) claims codes and has yet to be validated in *ICD-10*. CLTI hospitalizations were identified based on whether patients had a primary discharge diagnosis code for atherosclerosis of arteries of the extremities with rest pain (440.22), ulceration (440.23), or gangrene (440.24), as has been done previously (Table S1).[16] CLTI hospitalizations were excluded if patients did not have at least 1 continuous year of data within the MedPAR data set before the CLTI episode, since these data were used to ascertain comorbidities, or if patients had a previous diagnosis of CLTI in this 1-year lookback period. We also excluded CLTI hospitalizations if patients died or received a major amputation during the index hospitalization, as we aimed to examine a population that was theoretically considered for a revascularization strategy as a definitive CLTI treatment. After exclusion criteria were applied, the first CLTI hospitalization for each patient was included in our study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Exposure

The primary exposure in the study was frailty, as measured by the Claims-based Frailty Indicator (CFI) developed by Segal et al,[17] based on administrative claims in the 12 months before CLTI admission. The CFI is a 21-variable indicator derived from a lookback of primarily *ICD-9* administrative claims that was validated against the Fried Frailty Phenotype, a clinical tool for measuring frailty, in the Cardiovascular Health Study (Tables S2 and S3). We examined an *ICD-9* code in any position in any of the admissions in the 12-month lookback period to identify frailty. The CFI has subsequently been externally validated,[18] and has been used extensively in studies of populations with cardiovascular disease.[12,13] Notably, this frailty measure does not directly include many of the traditional cardiovascular risk factors (eg, hypertension, hyperlipidemia, diabetes, obesity, smoking status), though it does consider congestive heart failure and stroke. For this study, we ascertained frailty status based on *ICD-9* codes from inpatient admissions in the year before the CLTI

hospitalization. We used the established CFI threshold of 0.25 to define frailty.[17] We also performed multiple sensitivity analyses using different CFI score thresholds to supplement these results, as outlined below.

Characteristics

Patient characteristics included demographics (age, sex, race), Elixhauser comorbidities,[19] and current or prior tobacco use given known prior associations between these variables and outcomes. All comorbidities were ascertained during the 1-year lookback period. Revascularization was defined as either endovascular or surgical using claims-based *ICD-9* procedure codes from the index hospitalization (Table S1).[16,20] If a revascularization code was not found during the index admission, a patient was considered not to have had revascularization. Patients who underwent revascularizations with both surgical and endovascular types of procedures during the same index hospitalization contributed data to the surgical revascularization group.

Outcomes

The primary outcome was amputation-free survival (AFS) measured from the discharge date. Amputation was defined as any major amputation and was identified through validated *ICD-9* and *ICD-10* coding algorithms (Table S1).[16,20] Mortality was determined using the vital status information from the Medicare Beneficiary Summary File. Secondary outcomes included the individual components of the composite outcome. Follow-up data were available through December 2017.

Statistical Analysis

All metrics and normally distributed variables were reported as mean±SD. Non-normally distributed variables were presented as median (interquartile range). Categorical variables were presented as frequency and percentage. Baseline characteristics were compared between those who were frail and not frail using standardized differences. A standardized difference ≥10% was considered significant.[21]

The association between frailty status and revascularization among patients with CLTI was then examined. Crude rates of revascularization versus no revascularization were compared by frailty status using chi-squared tests. Multivariable logistic regression was used to determine the adjusted association between revascularization and frailty status. The first model evaluated the association between revascularization (compared with no revascularization) and frailty status among all patients with CLTI, adjusting for demographics, Elixhauser comorbidities, and tobacco use. The second model evaluated the association between surgical revascularization (compared with endovascular revascularization) and frailty status among all patients who underwent a revascularization procedure, again adjusting for demographics, Elixhauser comorbidities, and tobacco use.

Finally, the association between frailty status and outcomes was analyzed, stratified by treatment strategy. Kaplan–Meier methods were used to estimate AFS by frailty status among patients who did not receive revascularization and, separately, among patients who received revascularization. In addition, among patients who received revascularization, patients were stratified by frailty status among those receiving endovascular treatment and, separately, surgical treatment. Cox proportional hazards regression was then used to evaluate the association between frailty status and outcomes, adjusted for patient characteristics. The proportional hazards assumption was evaluated by plotting the hazard ratios (HRs) between frail and non-frail individuals with survival over time (Figure S1). Because of the possibility of unmeasured confounding and treatment selection bias, we elected to create separate models for patients who did not receive revascularization and for patients who received revascularization. Patients receiving revascularization were further stratified into those receiving endovascular or surgical treatment. To account for the competing risk of death, Fine-Gray methods were used to analyze the outcome of major amputation.[22]

As sensitivity analyses, the relationship between the degree of frailty and the risk of death or major amputation at 1 year was evaluated, considering frailty as a continuous variable using a cubic spline model with 4 knots. We additionally examined baseline characteristics and receipt of revascularization across quartiles of the frailty indicator, and repeated Kaplan–Meier analyses of AFS by quartiles among patients who did not receive revascularization and, separately, among patients who received revascularization. Similarly, we repeated Kaplan–Meier analyses of AFS by quartiles among patients who received surgical revascularization and, separately, among patients who received endovascular revascularization.

A 2-sided $P<0.05$ was considered statistically significant without adjustment for multiple comparisons. All analyses were performed using SAS 9.4 (Cary, NC, USA). The study was approved by the institutional review board of Beth Israel Deaconess Medical Center, with a waiver of informed consent for retrospective data analysis.

RESULTS

During the study period, 85 060 patients met criteria and were included in the analysis, of which 35 484 (42%) were classified as frail (Figures S2 and S3). Median follow-up in the whole cohort was 2.34 years

(interquartile range, 3.32 years). Patients who were frail were more likely to be older, women, of Black or other race, and non-smokers (Table 1). Frail patients also had a greater burden of both cardiovascular and non-cardiovascular conditions, including congestive heart failure, valvular heart disease, pulmonary circulation

Table 1. Baseline Characteristics of Patients With CLTI by Frailty Status

Subject characteristic	Not frail (n=49 576)	Frail (n=35 484)	Standardized difference*
Demographics			
Age (y), mean (SD)	75.77 (5.36)	86.01 (6.01)	−1.798
Men	28 833 (58.16)	13 655 (38.48)	0.402
Race			
White	41 773 (84.26)	26 081 (73.50)	0.266
Black	6043 (12.19)	6777 (19.10)	−0.191
Other†	1760 (3.55)	2626 (7.40)	−0.170
Elixhauser comorbidity variables			
Summary comorbidity index, mean (SD)	3.79 (2.05)	4.58 (2.40)	0.35
Acquired immune deficiency syndrome	45 (0.09)	13 (0.04)	0.020
Alcohol abuse	147 (0.30)	40 (0.11)	0.042
Chronic blood loss anemia	893 (1.80)	847 (2.39)	−0.041
Chronic pulmonary disease	15 984 (32.24)	9881 (27.85)	0.096
Coagulopathy	2436 (4.91)	2422 (6.83)	−0.082
Congestive heart failure	6798 (13.71)	12 670 (35.71)	−0.527
Deficiency anemias	10 665 (21.51)	11 509 (32.43)	−0.248
Depression	2797 (5.64)	4374 (12.33)	−0.236
Diabetes w/ chronic complications	10 659 (21.50)	7570 (21.33)	0.004
Diabetes w/o chronic complications	19 750 (39.84)	12 933 (36.45)	0.070
Drug abuse	34 (0.07)	13 (0.04)	0.013
Fluid and electrolyte disorders	12 826 (25.87)	14 613 (41.18)	−0.329
Hypertension	39 953 (80.59)	28 786 (81.12)	−0.013
Hypothyroidism	5640 (11.38)	6529 (18.40)	−0.198
Liver disease	605 (1.22)	352 (0.99)	0.022
Lymphoma	452 (0.91)	358 (1.01)	−0.010
Metastatic cancer	603 (1.22)	336 (0.95)	0.026
Obesity	3788 (7.64)	1837 (5.18)	0.101
Other neurological disorders	3189 (6.43)	5895 (16.61)	−0.323
Paralysis	2031 (4.10)	2677 (7.54)	−0.147
Peptic ulcer disease without bleeding	21 (0.04)	24 (0.07)	−0.013
Psychoses	973 (1.96)	1531 (4.31)	−0.135
Pulmonary circulation disease	1032 (2.08)	1931 (5.44)	−0.177
Renal failure	12 660 (25.54)	12 404 (34.96)	−0.206
Rheum. arthritis/collagen vascular diseases	1930 (3.89)	2131 (6.01)	−0.098
Solid tumor w/out metastasis	1452 (2.93)	1129 (3.18)	−0.015
Valvular disease	1607 (3.24)	2968 (8.36)	−0.220
Weight loss	3482 (7.02)	5160 (14.54)	−0.244
Additional variables			
Smoking	25 386 (51.21)	11 626 (32.76)	0.381
No. admissions preceding index (mean, SD)‡	1.20 (1.79)	2.14 (2.48)	0.435

*Standardized difference calculated as: $(\bar{x}_{frail} - \bar{x}_{not\ frail})/((s^2_{frail}+s^2_{not\ frail})/2)^{(1/2)}$ for continuous variables and $(\hat{p}_{frail} - \hat{p}_{not\ frail})\ /[(\hat{p}_{frail}\times(1-\hat{p}_{frail})+\hat{p}_{not\ frail}\times(1-\hat{p}_{not\ frail}))/2]^{(1/2)}$ for categorical variables. Comorbidities were ascertained during both the index admission and the 1-year lookback period.

†Other race or ethnicity includes those who identify as Asian, Hispanic, North American Native, or Other and those with race unknown.

‡Number of admissions preceding index admission was not included in adjusted models given collinearity with frailty measure.

CLTI indicates chronic limb-threatening ischemia.

disease, renal failure, and anemia. Mean number admissions before the index admission among non-frail patients was 1.2 versus 2.1 for frail patients.

Frailty and Treatment Choice

In unadjusted analyses, frail patients were less likely to receive revascularization than non-frail patients (60.2% versus 76.4%, respectively; *P*<0.001) (Table 2). This relationship persisted after adjustment (adjusted OR, 0.78; 95% CI, 0.75–0.82; *P*<0.001). Of patients who received revascularization, those who were frail were more likely to receive endovascular treatment when compared with non-frail patients (59.5% versus 40.0%, respectively; *P*<0.001). Conversely, non-frail patients who underwent revascularization were more likely to receive surgical treatment (60.0% versus 40.5% of frail patients; *P*<0.001). After adjustment, being classified as frail remained associated with a lower likelihood of receiving surgical treatment (adjusted OR, 0.76; 95% CI, 0.72–0.81; *P*<0.001).

Frailty and Outcomes

Overall, the median AFS was 2.5 years (interquartile range, 0.7 years–4.1 years) for non-frail patients and 0.8 years (interquartile range, 0.2 years–2.6 years) for frail patients. The Kaplan–Meier cumulative estimate of AFS at 8.25 years of follow-up was greater among non-frail patients compared with frail patients for both those who were revascularized (17.9% non-frail versus 4.0% frail, *P*<0.001) and those who were not revascularized (10.8% non-frail versus 1.8% frail, *P*<0.001) (Figure 1). The association between frailty and worse AFS also persisted when all patients were considered in aggregate (Figure S4). Of those who received revascularization, non-frail patients also had a greater cumulative AFS than frail patients, irrespective of revascularization strategy (surgical: 19.9% non-frail versus 5.0% frail, *P*<0.001; endovascular: 15.1% non-frail versus 3.4% frail, *P*<0.001) (Figure 2).

In adjusted analysis, frailty remained associated with an increased risk of death or major amputation, regardless of whether revascularization was performed (revascularized cohort: hazard ratio [HR], 1.34; 95% CI, 1.30–1.38; *P*<0.001; non-revascularized cohort: HR, 1.22; 95% CI, 1.17–1.27; *P*<0.001) (Figure 1). The difference in death or major amputation was primarily driven by an increased risk of death among those that were frail (Figures S5 and S6). Notably, frailty was a stronger independent predictor of death or major amputation compared with many traditional risk factors (including tobacco use, diabetes, and obesity), among both the revascularized and non-revascularized cohorts (Figure 3, Table S4).

Of patients who were revascularized, frailty was also a strong independent predictor of AFS, irrespective of revascularization strategy (surgical cohort: adjusted HR, 1.36; 95% CI, 1.31–1.42; *P*<0.001; endovascular cohort: adjusted HR, 1.29; 95% CI, 1.24–1.35; *P*<0.001) (Figure 2). The difference in death or major amputation was again primarily driven by an increased risk of death among those that were frail (Figures S7 and S8). Frailty was a stronger predictor of death or major amputation compared with many traditional risk factors, including age, race, sex, tobacco use, diabetes, and obesity (Figure 3, Table S5).

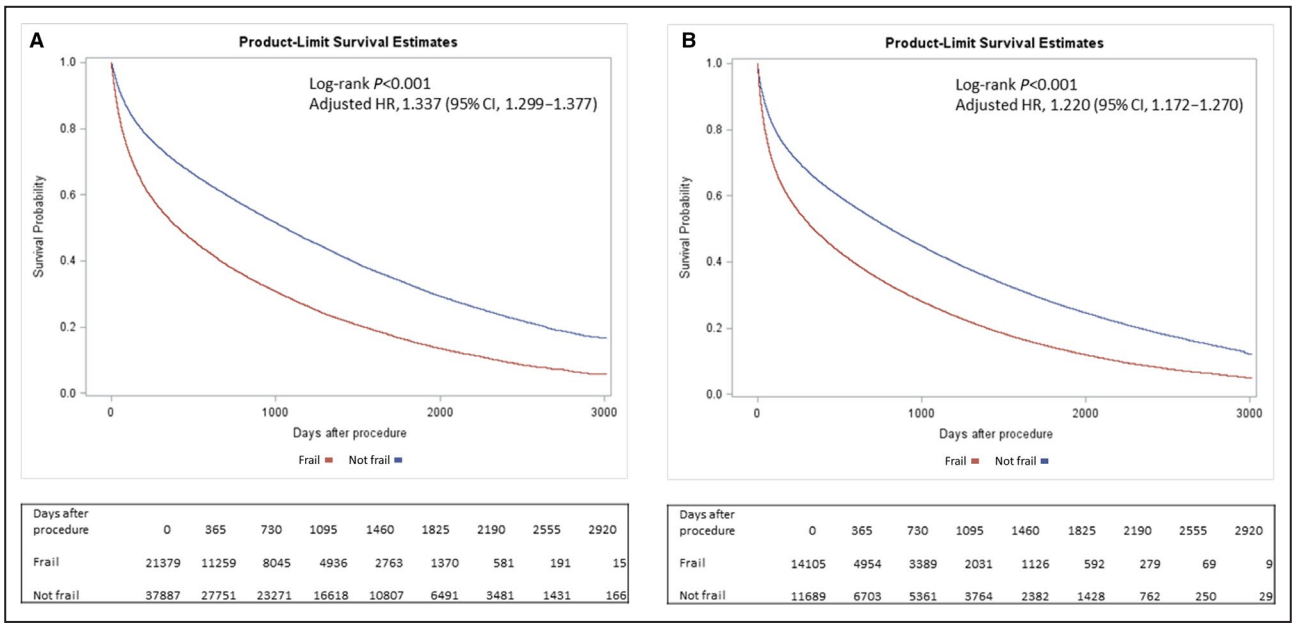
Frailty as a Continuous Measure

When frailty was examined as a continuous variable, higher values of frailty were associated with a higher risk of death or major amputation at 1 year among the total cohort, as well as when stratified by revascularization status (Figure S9). When frailty was examined by quartiles, patients with greater degree of frailty showed greater burden of both cardiovascular and non-cardiovascular conditions as well as a sequentially lower likelihood of receiving any revascularization, as well as surgical revascularization, if revascularized (Tables S6 and S7). Patients with a greater degree of

Table 2. Association of Treatment Choice for CLTI by Frailty Status

Cohort	Not frail n (%)	Frail n (%)	Chi-squared *P* value	Adjusted OR for treatment modality for frailty vs non-frail individuals* (95% CI)	*P* value
All patients	49 576	35 484	<0.0001	0.784 (0.746–0.824)†	<0.0001
Revascularization	37 887 (76.4)	21 379 (60.2)			
No revascularization	11 689 (23.6)	14 105 (39.8)			
Patients treated with revascularization	37 887	21 379	<0.0001	0.764 (0.724–0.808)‡	<0.0001
Surgical	22 734 (60.0)	8654 (40.5)			
Endovascular	15 153 (40.0)	12 725 (59.5)			

CLTI indicates chronic limb-threatening ischemia; and OR, odds ratio.
*Multivariable logistic regression models controlling for all covariates listed in Table 1 unless otherwise specified.
†OR of revascularization (relative to no revascularization).
‡OR of surgical treatment (relative to endovascular treatment).



Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	21379	11259	8045	4936	2763	1370	581	191	15
Not frail	37887	27751	23271	16618	10807	6491	3481	1431	166

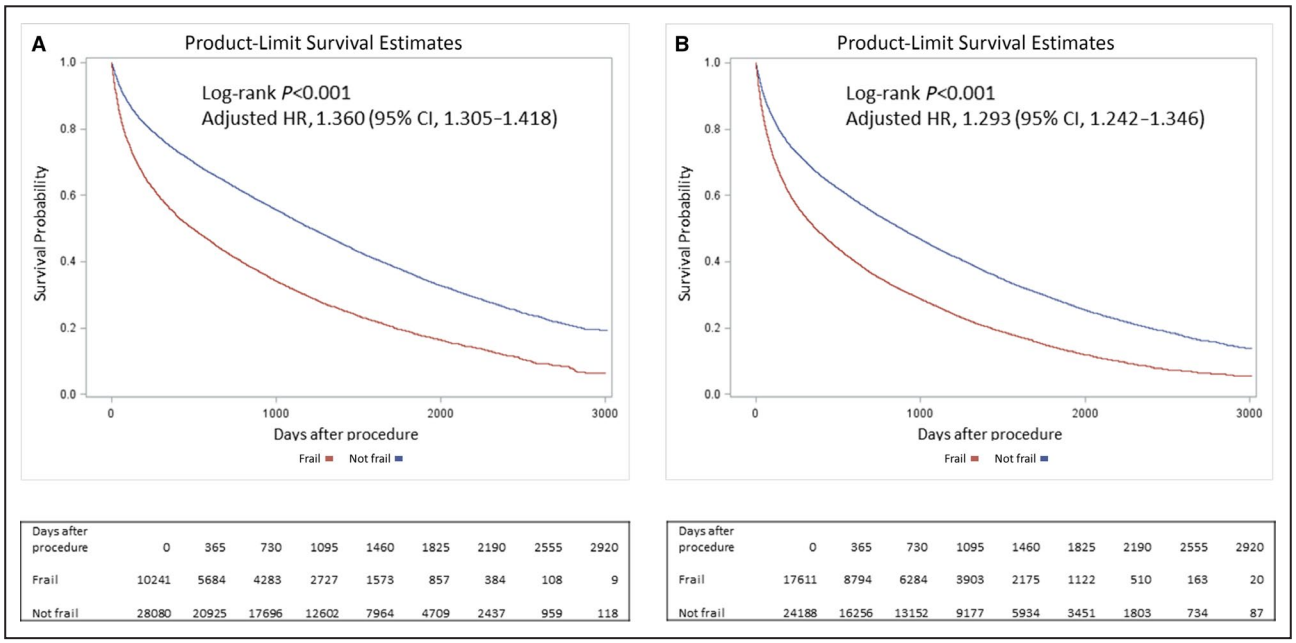
Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	14105	4954	3389	2031	1126	592	279	69	9
Not frail	11689	6703	5361	3764	2382	1428	762	250	29

Figure 1. Amputation-free survival among patients with chronic limb-threatening ischemia by frailty status, stratified by treatment choice.
A, Among patients undergoing revascularization. **B**, Among patients not undergoing revascularization. HR indicates hazard ratio.

frailty had sequentially worse outcomes, regardless of whether revascularization was pursued or the type of revascularization (Figures S10 and S11).

DISCUSSION

In this retrospective cohort study of Medicare beneficiaries with long-term follow-up, we evaluated the impact of a claims-based measurement of frailty on treatment selection and outcomes among patients hospitalized with CLTI. We found the following notable results. Patients hospitalized for CLTI were, on average, more frail than the community-dwelling Medicare beneficiary population.[18] Frailty was a useful tool to discriminate whether a patient underwent a revascularization strategy versus a non-invasive treatment approach,



Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	10241	5684	4283	2727	1573	857	384	108	9
Not frail	28080	20925	17696	12602	7964	4709	2437	959	118

Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	17611	8794	6284	3903	2175	1122	510	163	20
Not frail	24188	16256	13152	9177	5934	3451	1803	734	87

Figure 2. Amputation-free survival among patients with chronic limb-threatening ischemia undergoing revascularization by frailty status, stratified by revascularization strategy.
A, Surgical revascularization. **B**, Endovascular revascularization. HR indicates hazard ratio.

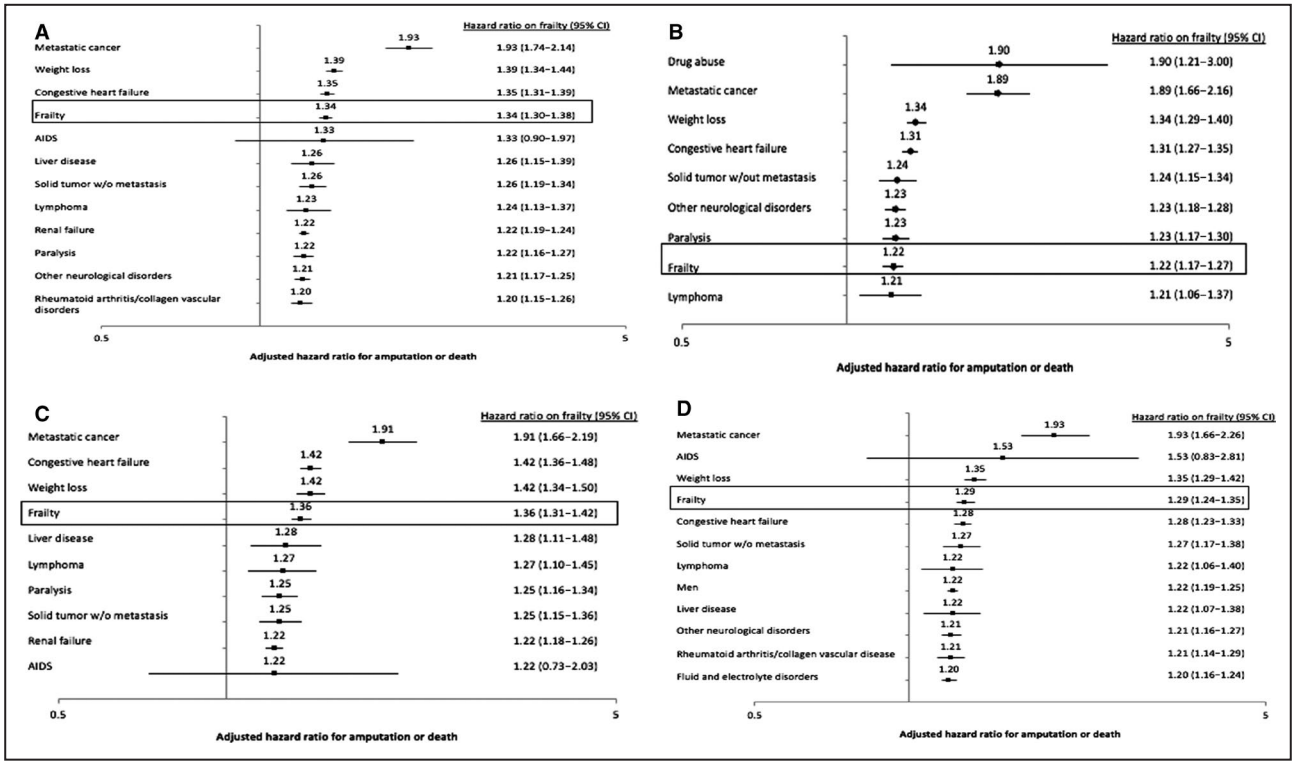


Figure 3. Top predictors of amputation or death for patients with chronic limb-threatening ischemia using Cox proportional hazards.

A, Among patients undergoing revascularization. **B**, Among patients not undergoing revascularization. **C**, Among patients undergoing surgical revascularization. **D**, Among patients undergoing endovascular revascularization. Figures include predictors with hazard ratio >1.2. See Tables S4 and S5 for full model results.

irrespective of most traditional comorbidities. The presence of frailty also impacted who underwent an endovascular revascularization strategy versus surgical. Furthermore, regardless of treatment strategy, frailty was independently associated with worse outcomes, even after adjusting for an array of demographics and comorbidities. This association was primarily driven by an increased risk of death and not necessarily by differences in amputation. These results suggest that frailty can be used to prognosticate future outcomes and guide shared decision-making with patients about the various treatment options available.

We found evidence that treatment selection for patients hospitalized with CLTI is influenced by frailty, a multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors.[23] Previous studies have shown that patients with CLTI who receive conservative or endovascular therapy are likely to have more comorbidities than those who receive surgical therapy.[5,6] Guidelines currently recommend endovascular over surgical treatment for CLTI in patients with substantial comorbidities, which may place them at higher risk of postoperative complications from surgical revascularization.[3] Our finding that frail patients are more likely to receive endovascular intervention, despite controlling for comorbidities, reflects how clinicians may already consider frailty in the selection of appropriate treatment options for patients with CLTI. However, a frailty assessment may be one method to improve communication about what characteristics of the patient may make them a better or worse candidate for a particular revascularization strategy, thereby improving patient counseling and comprehension.

This study extends existing investigation about factors affecting CLTI outcomes. Several risk scores have been developed to predict 30-day or 1-year amputation-free survival among patients with CLTI undergoing surgical revascularization,[8,9] or mortality after endovascular or surgical revascularization at 2 or 5 years.[7,10] However these scores only capture select comorbidities and are not frequently used in clinical practice.[24] We include many of these risk score components in our multivariate analysis and show that frailty remains a strong, independent factor that improves patient risk stratification for future clinically important events, regardless of treatment strategy. As such, frailty may be a final common pathway that

integrates information from other established factors and risk scores. Several studies using varied frailty metrics have shown an association between frailty and adverse functional outcomes after peripheral artery disease procedures more broadly.[25] Additionally, small, single-center studies have found that frailty was associated with a lower AFS or overall survival at 2 years among patients with CLTI who received revascularization.[14,15] We found similar results in a large national sample of >85 000 Medicare beneficiaries with CLTI with follow-up available up to 8 years. Additionally, we found that frailty was associated with worse outcomes among hospitalized patients who do not receive revascularization, which comprises a large proportion of Medicare patients with CLTI. Thus, our study further establishes the role of phenotypic frailty as a strong, independent secular predictor of CLTI outcomes, independent of physician management.

These results have important implications for the treatment of patients hospitalized with CLTI and for future studies evaluating CLTI treatment options. These findings suggest that physicians should routinely assess frailty in clinical management of patients hospitalized with CLTI. While multiple different conceptualizations of frailty exist,[26] the one used for the current study, which is anchored to a physical phenotype, can be easily quantified using a comprehensive geriatric assessment, and is thus readily translatable into practice. Therefore, clinicians can use such information to guide shared decision-making with patients about their prognosis and the various treatment options available, ranging from invasive surgical revascularization to palliation. For instance, if a frail patient hospitalized with CLTI is informed of an expected overall median AFS of 0.8 years (versus 2.5 years in a non-frail patient) in considering treatment options and recovery times, less invasive treatment may be chosen in shared decision-making. These results highlight the need for team-based care of patients with CLTI as well as the need for additional patient-centered outcomes to enhance the shared-decision making process. Additionally, the additive prognostic value of frailty suggests that observational studies comparing treatment options among patients hospitalized with CLTI may be confounded if frailty is not considered. Finally, our evidence that frailty affects CLTI outcomes suggests that future randomized trials of CLTI treatment should consider examining outcomes among frail patients separately, to individualize treatment for this high-risk subgroup.

Our analysis must be interpreted in light of its limitations. First, for the primary analysis, we considered frailty as a dichotomous exposure for pragmatism. However, in supplemental analysis, similar relationships between quartiles of frailty and AFS were observed, and a continuous measure of frailty was associated with increased 1-year mortality in a dose-dependent manner, further emphasizing the importance of frailty as a predictor of outcomes. Second, given evidence that frailty likely impacts treatment selection, we chose not to compare outcomes among frail patients across different treatment strategies to avoid confounding by indication. Third, the frailty scale used is based on longitudinal *ICD-9* claims data. As such, the application of this specific scale for future investigation or clinical utility is limited, both by the availability of these data and by the transition to the *ICD-10* coding system, though work to crosswalk these claims to *ICD-10* codes is ongoing. Furthermore, we studied a more historic cohort of patients; although this enabled us to capture long-term follow-up of these patients, treatment options may have since evolved. Nonetheless, the utility of this analysis is supported by the correlation between the claims-based frailty scale used in this study and the widely adopted in-person Fried frailty assessment.[27] Fourth, we do not account for patients who may become frail in the follow-up time; however, such analysis pertains primarily to the treatment decision faced at time of CLI and time-updating is of modest benefit with a non-frail median survival of 2.4 years. Fifth, we only included patients hospitalized for CLTI, which may represent a more severe form of the disease and did not include the minority of patients who were discharged with plans for outpatient intervention or treated primarily in the outpatient setting. Lastly, the MedPAR data set lacks granular anatomical and procedural characteristics or medications that may also be prognostic of future adverse events.

CONCLUSIONS

In this large nationwide analysis of hospitalized Medicare beneficiaries with CLTI, we find that frailty is an important independent predictor of revascularization strategy and longitudinal adverse outcomes in patients who did and did not undergo revascularization. Future work investigating the optimal treatment strategy for this high-risk subgroup is warranted.

ARTICLE INFORMATION

Received July 5, 2021; accepted November 8, 2021.

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Sources of Funding

None.

Disclosures

Dr Butala is funded by the John S. LaDue Memorial Fellowship at Harvard Medical School, Boston, MA and reports consulting fees and ownership interest in HiLabs, outside the submitted work. Dr Secemsky receives grants from AstraZeneca, BD Bard, Boston Scientific, Cook Medical, CSI, Medtronic, Philips, and UCSF. He consults for CSI, Medtronic, and Philips and is on the speaking bureau of BD Bard, Cook Medical and Medtronic, outside the submitted work. Dr Schermerhorn has received support from Abbott, Cook Medical, Endologix, Medtronic, and Philips, outside the submitted work. Dr Beckman has served as a consultant for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Novo Nordisk, and Sanofi; and has served on the Data Safety and Monitoring Board of Bayer and Novartis, outside the submitted work. Dr Shishehbor has served on the Scientific Advisory Boards of Medtronic, Abbott Vascular, Phillips, Terumo, and Boston Scientific, outside the submitted work. Dr Yeh reports additional grant support from Abiomed, Astra Zeneca, and Boston Scientific and consulting fees from Abbott, Boston Scientific, Medtronic, and Teleflex, outside the submitted work. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S7
Figures S1–S11

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SUPPLEMENTAL MATERIAL

Table S1. Diagnostic and procedure billing codes

Diagnostic Codes for Critical Limb Ischemia		
	ICD-9	ICD-10
Rest pain	440.22	
Ulcer	440.23	
Gangrene	440.24	
Procedure Codes for Peripheral Arterial Revascularization		
Surgical Revascularization		
Aorto-iliac femoral bypass	39.25	
Peripheral bypass	39.29	
Incision of lower limb arteries	38.08	
Endarterectomy of abdominal arteries	38.16	
Endarterectomy of lower limb arteries	38.18	
Resection of vessel with anastomosis	38.38	
Resection of vessel with replacement	38.48	
Other excision of vessel	38.68	
Other surgical occlusion of vessels	38.88	
Endovascular Revascularization		
Angioplasty or atherectomy of non-coronary vessel	39.50	
Insertion of non-drug eluting, non-coronary artery stent	39.90	
Insertion of drug eluting peripheral vessel stent	00.55	
Insertion of stent into femoral artery	00.60	
Procedure Codes for Amputation of Lower Extremity		
Amputation of upper leg, lower leg, or foot	84.10, 84.13, 84.14, 84.15, 84.16, 84.17, 84.3	0Y6C0Zx, 0Y6D0Zx, 0Y6F0ZZ, 0Y6G0ZZ, 0Y6H0Zx, 0Y6J0Zx, 0Y6M0Z0, 0Y6N0Z0
Other		
Tobacco use	305.1, 649.00–649.04, and V15.82	

Table S2. Variables Operationalized for Inclusion in Frailty Model with SAS code (Alphabetically).

Musculoskeletal problems	length musculo_probs 3; musculo_probs=0; if dx (‘7130’ ‘7131’ ‘7132’ ‘7133’ ‘7134’ ‘7135’ ‘7136’ ‘7137’ ‘7138’ ‘71600’ ‘71601’ ‘71602’ ‘71603’ ‘71604’ ‘71605’ ‘71606’ ‘71607’ ‘71608’ ‘71609’ ‘71620’ ‘71621’ ‘71622’ ‘71623’ ‘71624’ ‘71625’ ‘71626’ ‘71627’ ‘71629’ ‘71629’ ‘71630’ ‘71631’ ‘71632’ ‘71633’ ‘71634’ ‘71635’ ‘71636’ ‘71637’ ‘71638’ ‘71639’ ‘71640’ ‘71641’ ‘71642’ ‘71643’ ‘71644’ ‘71645’ ‘71646’ ‘71647’ ‘71648’ ‘71649’ ‘71650’ ‘71651’ ‘71652’ ‘71653’ ‘71654’ ‘71655’ ‘71656’ ‘71657’ ‘71658’ ‘71659’ ‘71660’ ‘71661’ ‘71662’ ‘71663’ ‘71664’ ‘71665’ ‘71666’ ‘71667’ ‘71668’ ‘71680’ ‘71681’ ‘71862’ ‘71683’ ‘71684’ ‘71685’ ‘71686’ ‘71687’ ‘71688’ ‘71689’ ‘71690’ ‘71691’ ‘71692’ ‘71693’ ‘71694’ ‘71695’ ‘71696’ ‘71697’ ‘71698’ ‘71699’ ‘71810’ ‘71811’ ‘71812’ ‘71813’ ‘71814’ ‘71815’ ‘71817’ ‘71818’ ‘71819’ ‘71820’ ‘71821’ ‘71822’ 71823’ ‘71824’ ‘71825’ ‘71826’ ‘71827’ ‘71828’ ‘71829’ ‘71850’ ‘71851’ ‘71852’ ‘71853’ ‘71854’ ‘71855’ ‘71856’ ‘71857’ ‘71858’ ‘71859’ ‘71860’ ‘71865’ ‘71870’ ‘71871’ ‘71872’ ‘71873’ ‘71874’ ‘71875’ ‘71876’ ‘71877’ ‘71878’ ‘71879’ ‘71880’ ‘71881’ ‘71882’ ‘71883’ ‘71884’ ‘71885’ ‘71886’ ‘71887’ ‘71888’ ‘71889’ ‘71890’ ‘71891’ ‘71892’ ‘71893’ ‘71894’ ‘71895’ ‘71897’ ‘71898’ ‘71899’ ‘71900’ ‘71901’ ‘71902’ ‘71903’ ‘71904’ ‘71905’ ‘71906’ ‘71907’ ‘71908’ ‘71909’ 71910’ ‘71911’ ‘71912’ ‘71913’ ‘71914’ ‘71915’ ‘71916’ ‘71917’ ‘71918’ ‘71919’ ‘71920’ ‘71921’ ‘71922’ ‘71923’ ‘71924’ ‘71925’ ‘71926’ ‘71927’ ‘71928’ ‘71929’ ‘71930’ ‘71931’ ‘71932’ ‘71933’ ‘71934’ ‘71935’ ‘71936’ ‘71937’ ‘71938’ ‘71939’ ‘71940’ ‘71941’ ‘71942’ ‘71943’ ‘71944’ ‘71945’ ‘71946’ ‘71947’ ‘71948’ ‘71949’ ‘71950’ ‘71951’ ‘71952’ ‘71953’ ‘71954’ ‘71955’ ‘71956’ ‘71957’ ‘71958’ ‘71959’ ‘71960’ ‘71961’ ‘71962’ ‘71963’ ‘71964’ ‘71965’ ‘71966’ ‘71967’ ‘71968’ ‘71969’ ‘7197’ ‘71970’ ‘71975’ ‘71976’ ‘71977’ ‘71978’ ‘71979’ ‘71980’ ‘71981’ ‘71982’ ‘71983’ ‘71984’ ‘71985’ ‘71986’ ‘71987’ ‘71988’ ‘71989’ ‘71990’ ‘71991’ ‘71992’ ‘71993’ ‘71994’ ‘71995’ ‘71996’ ‘71997’ ‘71998’ ‘71999’ ‘7201’ ‘7202’ ‘72081’ ‘72089’ ‘7209’ ‘7210’ ‘7211’ ‘7212’ ‘7213’ ‘72141’ ‘72142’ ‘7215’ ‘7216’ ‘7217’ ‘7218’ ‘72190’ ‘72191’ ‘7220’ ‘72210’ ‘72211’ ‘7222’ ‘72230’ ‘72231’ ‘72232’ ‘72239’ ‘7224’ ‘72251’ ‘72252’ ‘7226’ ‘72270’ ‘72271’ ‘72272’ ‘72273’ ‘72280’ ‘72281’ ‘72282’ ‘72283’ ‘72290’ ‘72291’ ‘72292’ ‘72293’ ‘7230’ ‘7231’ ‘7232’ ‘7233’ ‘7234’ ‘7235’ ‘7236’ ‘7237’ ‘7238’ ‘7239’ ‘72400’ ‘72401’ ‘72402’ ‘72403’ ‘72409’ ‘7241’ ‘7242’ ‘7243’ ‘7244’ ‘7245’ ‘7246’ ‘72470’ ‘72471’ ‘72479’ ‘7248’ ‘7249’ ‘73300’ ‘73301’ ‘73302’ ‘73393’ ‘73309’ ‘7331’ ‘73310’ ‘73311’ ‘73312’ ‘73313’ ‘73314’ ‘73315’ ‘73316’ ‘73319’ ‘73393’ ‘73394’ ‘73395’ ‘73396’ ‘73397’ ‘73398’ ‘V1351’ ‘4350’ ‘4351’ ‘4352’ ‘4353’ ‘4358’ ‘4359’) then musculo_prob=1
Falls	length falls 3; falls=0; if dx (‘E8800’ ‘E8801’ ‘E8809’ ‘E8810’ ‘E8811’ ‘E882’ ‘E8830’ ‘E8831’ ‘E8832’ ‘E8839’ ‘E8840’ ‘E8841’ ‘E8842’ ‘E8843’ ‘E8844’ ‘E8845’ ‘E8846’ ‘E8849’ ‘E885’ ‘E8850’ ‘E8851’ ‘E8852’ ‘E8853’ ‘E8854’ ‘E8859’ ‘E8860’ ‘E8869’ ‘E888’ ‘E8880’ ‘E8881’ ‘E8888’ ‘E8889’ ‘E9681’ ‘E9870’ ‘E9871’ ‘E9872’ ‘E9879’) then falls=1
Impaired mobility	length impair_mob 3; impair_mob=0; if dx (‘V46.3’) then impair_mob=1 – Also NEEDS HCPCS codes - E1050-E1093, E1100-E1110, E1130-E1161, E1170-E1200, E1220-E1239; E1240-E1270; E1280-E1298; E1280-E1298;
Depression	length depression 3; depression=0; if dx (‘3090’ ‘3091’ ‘30922’ ‘30923’ ‘30924’ ‘30928’ ‘30929’ ‘3093’ ‘3094’ ‘30982’ ‘30983’ ‘30989’ ‘3099’ ‘29383’ ‘29600’ ‘29601’ ‘29602’ ‘29603’ ‘29604’ ‘29605’ ‘29606’ ‘29610’ ‘29611’ ‘29612’ ‘29613’ ‘29614’ ‘29615’ ‘29616’ ‘29620’

	'29621' '29622' '29623' '29624' '29625' '29626' '29630' '29631' '29632' '29633' '29634' '29635' '29636' '29640' '29641' '29642' '29643' '29644' '29645' '29646' '29650' '29651' '29652' '29653' '29654' '29655' '29656' '29660' '29661' '29662' '29663' '29664' '29665' '29666' '2967' '29680' '29681' '29682' '29689' '29690' '29699' '3004' '311') then depression=1
Congestive Heart Failure	length con_heart_failure 3; con_heart_failure=0; if dx in ('39891' '4280' '4281' '42820' '42821' '42822' '42823' '42830' '42831' '42832' '42833' '42840' '42841' '42843' '4289) then con_heart_failure=1
Arthritis	length arthritis 3; arthritis=0; if dx ('7140' '7141' '7142' '71430' '71431' '71432' '71433' '7144' '71481' '71489' ' 7149' '7200' '71500' '71504' '71509' '71510' '71511' '71512' '71513' '71514' '71515' '71516' '71517' '71518' '71520' '71521' '71522' '71523' '71524' '71525' '71526' '71527' '71528' '71530' '71531' '71532' '71533' '71534' '71535' '71536' '71537' '71538' '71580' '71589' '71590' '71591' '71592' '71593' '71594' '71595' '71596' '71597' '71598' 'V134') then arthritis=1
Cognitive impairment	length cogn_impair 3; cong_impair=0; if dx in ('2900' '29010' '29011' '29012' '29013' '29020' '29021' '2903' '29040' '29041' '29042' '29043' '2908' '2909' '2930' '2931' '2940' '2941' '29410' '29411' '29420' '29421' '2948' '2949' '3100' '3102' '3108' '31081' '31089' '3109' '3310' '3311' '33111' '33119' '3312' '33182' '797') then cong_impair=1
Stroke	length stroke 3; stroke=0; if dx ('34660' '34661' '34662' '34663' '430' '431' 4320' '4321' '4329' '43301' '43311' '43321' '43331' '43381' '43391' '4340' '43400' '43401' '4341' '43410' '43411' '4349' '43490' '43491' '436' '438' '4380' '43810' '43811' '43812' '43813' '43814' '43819' '43820' '43821' '43822' '43840' '43841' '43842' '43850' '43851' '43852' '43853' '4386' '4387' '43881' '43882' '43883' '43884' '43885' '43889' '4389') then stoke=1
Paranoia	length para_feat 3; para_feat=0; if dx ('29381' '29382' '29500' '29501' '29502' '29503' '29504' '29505' '29510' '29511' '29512' '29513' '29514' '29515' '29520' '29521' '29522' '29523' '29524' '29525' '29530' '29531' '29532' '29533' '29534' '29535' '29540' '29541' '29542' '29543' '29544' '29545' '29550' '29551' '29552' '29553' '29554' '29555' '29560' '29561' '29562' '29563' '29564' '29565' '29570' '29571' '29572' '29573' '29574' '29575' '29580' '29581' '29582' '29583' '29584' '29585' '29590' '29591' '29592' '29593' '29594' '29595' '2970' '2971' '2972' '2973' '2978' '2979' '2980' '2981' '2982' '2983' '2984' '2988' '2989') then para_feat=1
Mycoses	1100 1101 1102 1103 1104 1105 1106 1108 1109 1110 1111 1112 1113 1118 1119 1120 1121 1122 1123 1125 11282 11284 11285 11289 1129 1141 1143 1149 11500 11509 11510 11519 11590 11599 1160 1161 1162 1170 1171 1172 1173 1174 1175 1176 1177 1178 1179 118
Parkinson`s disease	3320
Pneumonia (except that caused by tuberculosis or sexually transmitted disease)	00322 0203 0204 0205 0212 0221 0310 0391 0521 0551 0730 0830 1124 1140 1144 1145 11505 11515 11595 1304 1363 4800 4801 4802 4803 4808 4809 481 4820 4821 4822 4823 48230 48231 48232 48239 4824 48240 48241 48242 48249 4828 48281 48282 48283 48284 48289 4829 483 4830 4831 4838 4841 4843 4845 4846 4847 4848 485 486 5130 5171

Gout and other crystal arthropathies	2740 27400 27401 27402 27403 27410 27411 27419 27481 27482 27489 2749 71210 71211 71212 71213 71214 71215 71216 71217 71218 71219 71220 71221 71222 71223 71224 71225 71226 71227 71228 71229 71230 71231 71232 71233 71234 71235 71236 71237 71238 71239 71280 71281 71282 71283 71284 71285 71286 71287 71288 71289 71290 71291 71292 71293 71294 71295 71296 71297 71298 71299
Chronic ulcer of skin	7070 70700 70701 70702 70703 70704 70705 70706 70707 70709 7071 70710 70711 70712 70713 70714 70715 70719 70720 70721 70722 70723 70724 70725 7078 7079
Skin and subcutaneous tissue infections	0201 0210 0220 0311 03285 035 0390 6800 6801 6802 6803 6804 6805 6806 6807 6808 6809 68100 68101 68102 68110 68111 6819 6820 6821 6822 6823 6824 6825 6826 6827 6828 6829 684 6850 6851 6860 68600 68601 68609 6861 6868 6869
Urinary tract infections	03284 59000 59001 59010 59011 5902 5903 59080 59081 5909 5950 5951 5952 5953 5954 59581 59582 59589 5959 5970 59780 59781 59789 59800 59801 5990
Charlson comorbidity index (binary indicator)	All patients had PVD so value equated to 1 for all

Table S3. Variables in Claims-Based Frailty Indicator

B- coefficient	Variable
1.24	Impaired mobility
0.54	Depression
0.50	Congestive Heart Failure
0.50	Parkinson's disease
−0.49	White race
0.43	Arthritis (any type)
0.33	Cognitive impairment
0.31	Charlson comorbidity index (>0, 0)
0.28	Stroke
0.24	Paranoia
0.23	Chronic skin ulcer
0.21	Pneumonia
−0.19	Male sex
0.18	Skin and soft tissue infection
0.14	Mycoses
0.09	Age (in 5 year categories)
0.09	Admission in past 6 months
0.08	Gout or other crystal-induced arthropathy
0.08	Falls
0.05	Musculoskeletal problems
0.05	Urinary tract infection

Table S4. Adjusted hazard ratio of frailty on amputation or death among all patients with CLTI using Cox proportional hazards stratified by revascularization status (full model)

A. Among patients who underwent revascularization

Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Metastatic cancer	1.927	1.737	2.137	<.0001
Weight loss	1.387	1.337	1.439	<.0001
Congestive heart failure	1.351	1.313	1.389	<.0001
Frailty	1.337	1.299	1.377	<.0001
Acquired immune deficiency syndrome	1.329	0.899	1.965	0.1541
Liver disease	1.263	1.147	1.391	<.0001
Solid tumor w/out metastasis	1.261	1.189	1.338	<.0001
Lymphoma	1.241	1.126	1.368	<.0001
Renal failure	1.216	1.189	1.243	<.0001
Paralysis	1.215	1.161	1.272	<.0001
Other neurological disorders	1.205	1.166	1.247	<.0001
Rheumatoid arthritis/collagen vascular disorders	1.203	1.147	1.262	<.0001
Male sex	1.187	1.163	1.211	<.0001
Diabetes w/ chronic complications	1.185	1.155	1.215	<.0001
Chronic lung disease	1.180	1.154	1.206	<.0001
Fluid and electrolyte disorders	1.173	1.147	1.199	<.0001
Pulmonary circulation disease	1.119	1.053	1.190	0.0003
Coagulopathy	1.110	1.062	1.159	<.0001
Chronic blood loss anemia	1.093	1.024	1.166	0.0075
Valvular disease	1.090	1.039	1.144	0.0004
Diabetes w/o chronic complications	1.087	1.064	1.110	<.0001
Psychoses	1.065	1.000	1.135	0.0518
Deficiency anemias	1.063	1.039	1.089	<.0001
Age as of date of admission	1.029	1.027	1.031	<.0001
Depression	0.965	0.930	1.001	0.0562
Peptic ulcer disease with bleeding	0.957	0.588	1.557	0.8593
Hypothyroidism	0.946	0.920	0.974	0.0001
Tobacco use	0.945	0.926	0.965	<.0001
Obesity	0.865	0.829	0.902	<.0001
Black race 1	0.864	0.837	0.892	<.0001
Alcohol abuse	0.849	0.654	1.101	0.2162
Hypertension	0.818	0.798	0.839	<.0001
Black race 2	0.815	0.777	0.855	<.0001
Drug abuse	0.676	0.358	1.277	0.2275

B. Among patients who did not undergo revascularization

Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Drug abuse	1.902	1.205	3.002	0.0058
Metastatic cancer	1.894	1.659	2.162	<.0001
Weight loss	1.342	1.287	1.399	<.0001
Congestive heart failure	1.311	1.272	1.352	<.0001
Solid tumor w/out metastasis	1.239	1.145	1.340	<.0001
Other neurological disorders	1.231	1.183	1.280	<.0001
Paralysis	1.228	1.165	1.296	<.0001
Frailty	1.220	1.172	1.270	<.0001
Lymphoma	1.206	1.062	1.370	0.0040
Fluid and electrolyte disorders	1.181	1.146	1.216	<.0001
Male sex	1.165	1.132	1.199	<.0001
Liver disease	1.165	1.031	1.316	0.0144
Renal failure	1.145	1.111	1.180	<.0001
Chronic pulmonary disease	1.114	1.080	1.150	<.0001
Valvular disease	1.112	1.061	1.164	<.0001
Diabetes w/ chronic complications	1.099	1.063	1.136	<.0001
Pulmonary circulation disease	1.091	1.029	1.156	0.0033
Rheumatoid arthritis/collagen vascular disorders	1.090	1.025	1.158	0.0060
Peptic ulcer disease with bleeding	1.053	0.628	1.766	0.8440
Coagulopathy	1.044	0.988	1.103	0.1219
Diabetes w/o chronic complications	1.043	1.013	1.074	0.0050
Age as of date of admission	1.031	1.028	1.033	<.0001
Chronic blood loss anemia	1.020	0.929	1.119	0.6820
Depression	1.015	0.967	1.065	0.5588
Psychoses	1.009	0.935	1.089	0.8226
Deficiency anemias	1.000	0.969	1.031	0.9860
Tobacco use	0.995	0.965	1.026	0.7544
Hypothyroidism	0.977	0.941	1.014	0.2142
Black race 1	0.946	0.911	0.983	0.0041
Acquired immune deficiency syndrome	0.935	0.597	1.464	0.7694
Hypertension	0.891	0.861	0.923	<.0001
Black race 2	0.878	0.827	0.933	<.0001
Alcohol abuse	0.857	0.626	1.173	0.3356
Obesity	0.811	0.767	0.858	<.0001

Table S5. Adjusted hazard ratio of frailty on amputation or death among patients with CLTI receiving revascularization using Cox proportional hazards stratified by revascularization strategy (full model)

A. Among patients who underwent surgical revascularization

Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Metastatic cancer	1.935	1.659	2.256	<.0001
Acquired immune deficiency syndrome	1.530	0.834	2.807	0.1695
Weight loss	1.351	1.286	1.419	<.0001
Frailty	1.293	1.242	1.346	<.0001
Congestive heart failure	1.281	1.234	1.330	<.0001
Solid tumor w/out metastasis	1.273	1.171	1.383	<.0001
Lymphoma	1.222	1.064	1.403	0.0046
Male sex	1.219	1.185	1.254	<.0001
Liver disease	1.216	1.069	1.383	0.0028
Other neurological disorders	1.213	1.161	1.267	<.0001
Rheumatoid arthritis/collagen vascular disorders	1.212	1.136	1.294	<.0001
Fluid and electrolyte disorders	1.200	1.163	1.238	<.0001
Renal failure	1.186	1.151	1.223	<.0001
Chronic lung disease	1.181	1.144	1.219	<.0001
Paralysis	1.176	1.108	1.248	<.0001
Coagulopathy	1.153	1.083	1.227	<.0001
Diabetes w/ chronic complications	1.146	1.108	1.185	<.0001
Pulmonary circulation disease	1.130	1.041	1.226	0.0035
Chronic blood loss anemia	1.104	1.003	1.214	0.0430
Diabetes w/o chronic complications	1.077	1.046	1.109	<.0001
Valvular disease	1.076	1.009	1.148	0.0254
Deficiency anemias	1.044	1.011	1.079	0.0088
Psychoses	1.041	0.955	1.134	0.3628
Age as of date of admission	1.026	1.024	1.029	<.0001
Depression	0.973	0.926	1.023	0.2804
Tobacco use	0.972	0.943	1.001	0.0591
Hypothyroidism	0.968	0.932	1.005	0.0926
Obesity	0.841	0.794	0.890	<.0001
Black race 1	0.832	0.798	0.868	<.0001
Hypertension	0.824	0.795	0.854	<.0001
Peptic ulcer disease with bleeding	0.816	0.384	1.733	0.5966
Alcohol abuse	0.815	0.521	1.275	0.3709
Black race 2	0.806	0.759	0.857	<.0001
Drug abuse	0.309	0.100	0.958	0.0419

B. Among patients who underwent endovascular revascularization

Variable	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Metastatic cancer	1.908	1.664	2.188	<.0001
Congestive heart failure	1.421	1.362	1.482	<.0001
Weight loss	1.417	1.342	1.496	<.0001
Frailty	1.360	1.305	1.418	<.0001
Liver disease	1.281	1.109	1.481	0.0008
Lymphoma	1.266	1.104	1.451	0.0007
Paralysis	1.248	1.164	1.339	<.0001
Solid tumor w/out metastasis	1.246	1.145	1.355	<.0001
Renal failure	1.222	1.181	1.263	<.0001
Acquired immune deficiency syndrome	1.221	0.734	2.031	0.4429
Chronic lung disease	1.197	1.162	1.234	<.0001
Diabetes w/ chronic complications	1.195	1.150	1.242	<.0001
Rheumatoid arthritis/collagen vascular disorders	1.180	1.101	1.265	<.0001
Other neurological disorders	1.176	1.117	1.238	<.0001
Male sex	1.167	1.134	1.202	<.0001
Fluid and electrolyte disorders	1.152	1.116	1.190	<.0001
Peptic ulcer disease with bleeding	1.127	0.609	2.085	0.7038
Psychoses	1.099	1.001	1.206	0.0473
Valvular disease	1.098	1.023	1.179	0.0097
Pulmonary circulation disease	1.097	1.001	1.202	0.0474
Chronic blood loss anemia	1.097	1.004	1.199	0.0401
Diabetes w/o chronic complications	1.085	1.053	1.117	<.0001
Deficiency anemias	1.084	1.048	1.121	<.0001
Coagulopathy	1.081	1.018	1.149	0.0117
Age as of date of admission	1.030	1.028	1.033	<.0001
Drug abuse	1.014	0.446	2.304	0.9734
Depression	0.951	0.902	1.004	0.0676
Tobacco use	0.946	0.919	0.974	0.0002
Hypothyroidism	0.917	0.879	0.957	<.0001
Black race 1	0.892	0.851	0.935	<.0001
Obesity	0.886	0.833	0.943	0.0001
Alcohol abuse	0.884	0.640	1.221	0.4550
Hypertension	0.821	0.792	0.851	<.0001
Black race 2	0.805	0.745	0.870	<.0001

Table S6. Baseline characteristics of patients with CLTI by frailty quartile

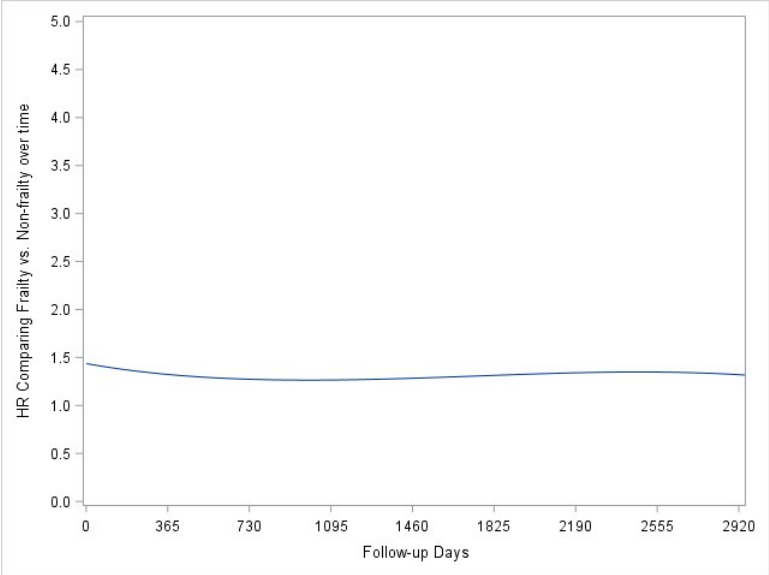
Subject Characteristic	Less frail Q1 (N=21258)	Q2 (N=21272)	Q3 (N=21261)	More frail Q4 (N=21269)
Demographics				
Age (yrs)	72.31 (3.41)	77.57 (4.79)	82.42 (5.39)	87.86 (5.71)
Male	13800 (64.92)	11587 (54.47)	9892 (46.53)	7209 (33.89)
Race				
White	19009 (89.42)	17180 (80.76)	16663 (78.37)	15002 (70.53)
Black	1179 (8.37)	3172 (14.91)	3325 (15.64)	4544 (21.36)
Other	470 (2.21)	920 (4.32)	1273 (5.99)	1723 (8.10)
Elixhauser summary index				
Acquired immune deficiency syndrome	24 (0.11)	17 (0.08)	10 (0.05)	7 (0.03)
Alcohol abuse	68 (0.32)	59 (0.28)	41 (0.19)	19 (0.09)
Chronic blood loss anemia	324 (1.52)	426 (2.00)	468 (2.20)	522 (2.45)
Chronic pulmonary disease	7134 (33.56)	6760 (31.78)	6144 (28.90)	5827 (27.40)
Coagulopathy	878 (4.13)	1141 (5.36)	1329 (6.25)	1510 (7.10)
Congestive heart failure	1574 (7.40)	3643 (17.13)	5388 (25.34)	8863 (41.67)
Deficiency anemias	3758 (17.68)	5016 (23.58)	6037 (28.39)	7363 (34.62)
Depression	797 (3.75)	1441 (6.77)	1836 (8.64)	3097 (14.56)
Diabetes w/ chronic complications	4010 (18.86)	5004 (23.52)	4897 (23.03)	4318 (20.30)
Diabetes w/o chronic complications	8284 (38.97)	8652 (40.67)	8261 (38.86)	7486 (35.20)
Drug abuse	18 (0.08)	12 (0.06)	10 (0.05)	7 (0.03)
Fluid and electrolyte disorders	4421 (20.80)	6126 (28.80)	7369 (34.66)	9523 (44.77)
Hypertension	17093 (80.41)	17211 (80.91)	17054 (80.21)	17381 (81.72)
Hypothyroidism	2008 (9.45)	2604 (12.24)	3366 (15.83)	4191 (19.70)
Liver disease	276 (1.30)	270 (1.27)	220 (1.03)	191 (0.90)
Lymphoma	172 (0.81)	220 (1.03)	209 (0.98)	209 (0.98)
Metastatic cancer	262 (1.23)	260 (1.22)	236 (1.11)	181 (0.85)
Obesity	1807 (8.50)	1563 (7.35)	1234 (5.80)	1021 (4.80)
Other neurological disorders	956 (4.50)	1555 (7.31)	2436 (11.46)	4137 (19.45)
Paralysis	577 (2.71)	1044 (4.91)	1289 (6.06)	1798 (8.45)
Peptic ulcer disease x bleeding	5 (0.02)	10 (0.05)	11 (0.05)	19 (0.09)
Psychoses	269 (1.27)	483 (2.27)	693 (3.26)	1059 (4.98)
Pulmonary circulation disease	271 (1.27)	541 (2.54)	820 (3.86)	1331 (6.26)
Renal failure	4540 (21.36)	5959 (28.01)	6798 (31.97)	7767 (36.52)
Rheumatoid arthritis/collagen vascular disorders	578 (2.72)	1006 (4.73)	1169 (5.50)	1308 (6.15)
Solid tumor w/out metastasis	589 (2.77)	641 (3.01)	678 (3.19)	673 (3.16)
Valvular disease	456 (2.15)	796 (3.74)	1313 (6.18)	2010 (9.45)
Weight loss	1074 (5.05)	1726 (8.11)	2351 (11.06)	3491 (16.41)
Additional Comorbidities				
Smoking	12233 (57.55)	10201 (47.96)	8242 (38.77)	6336 (29.79)

Table S7. Association of treatment choice for CLTI by frailty quartile

	Less frail Q1 (N=21258)	**Q2 (N=21272)**	**Q3 (N=21261)**	**More frail Q4 (N=21269)**	**P-value***
	n (% of column)	n (% of column)	n (% of column)	n (% of column)	
All patients					<.0001
No revascularization	4124 (19.40)	5487 (25.79)	6881 (32.36)	9302 (43.74)	
Revascularization	17134 (80.60)	15785 (74.21)	14380 (67.64)	11967 (56.26)	
Among those with revascularization					<.0001
Endovascular	5783 (33.75)	6929 (43.90)	7402 (51.47)	7764 (64.88)	
Surgical	11351 (66.25)	8856 (56.10)	6978 (48.53)	4203 (35.12)	
*p-value calculated from test of trend.					

Figure S1. Plot of hazard ratio for death or amputation between frail and non-frail individuals with survival over time.

a. Among patients undergoing revascularization



b. Among patients not undergoing revascularization

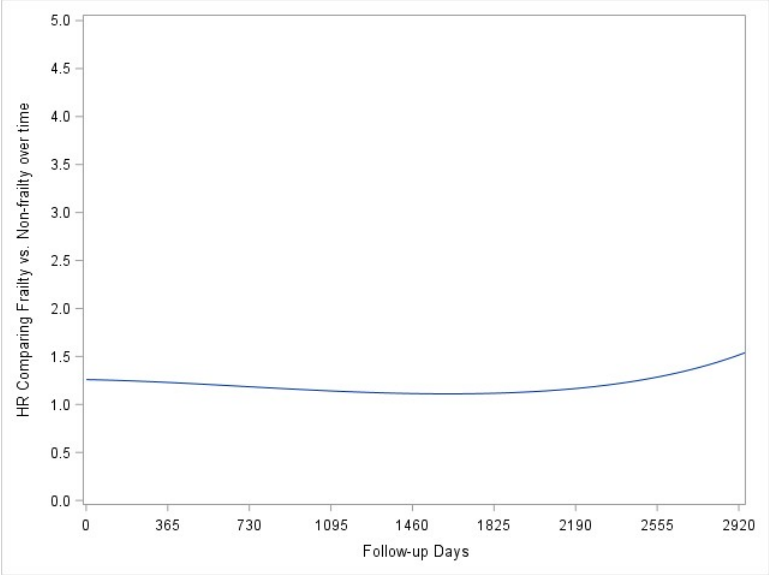


Figure S2. Sample flow chart

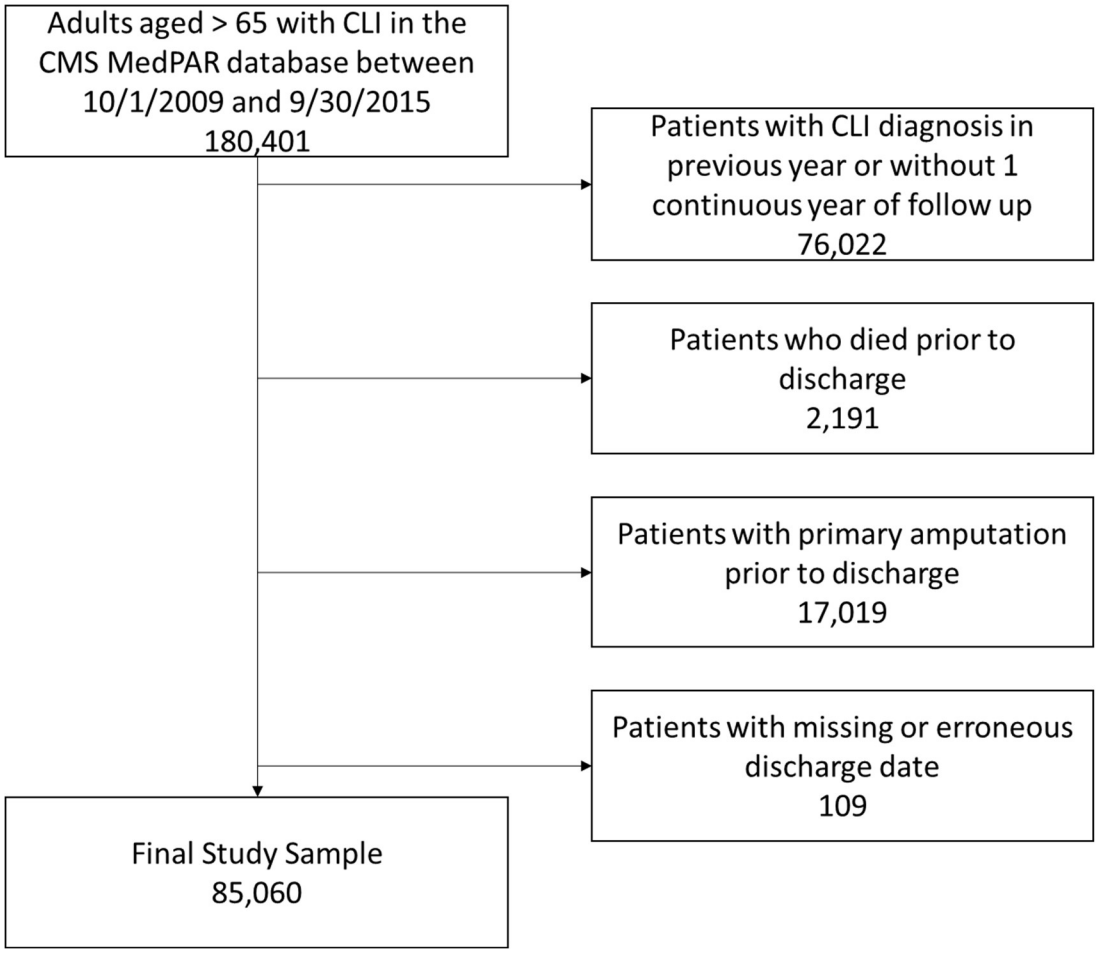
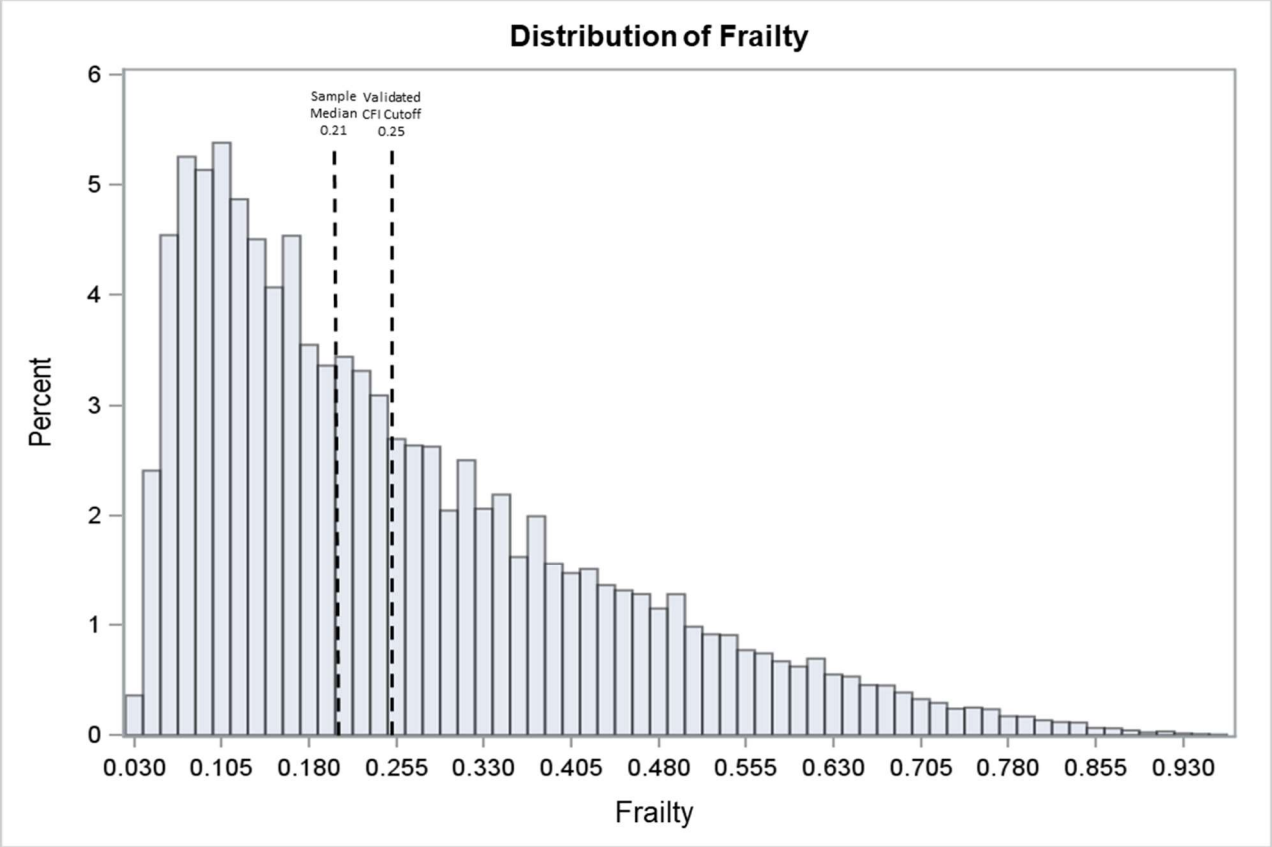
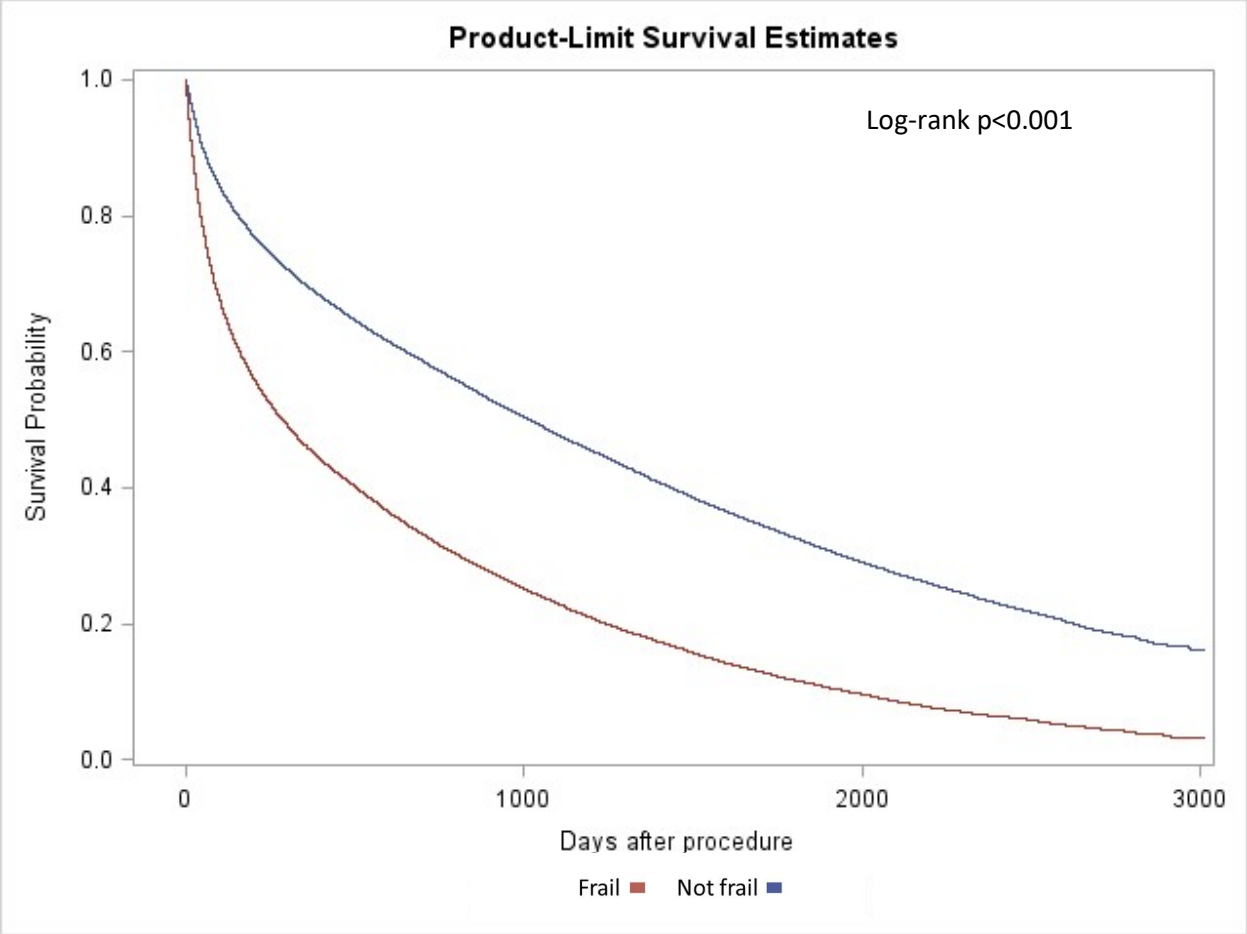


Figure S3. Distribution of frailty in sample of patients with critical limb ischemia hospitalization



CFI=claims-based frailty indicator

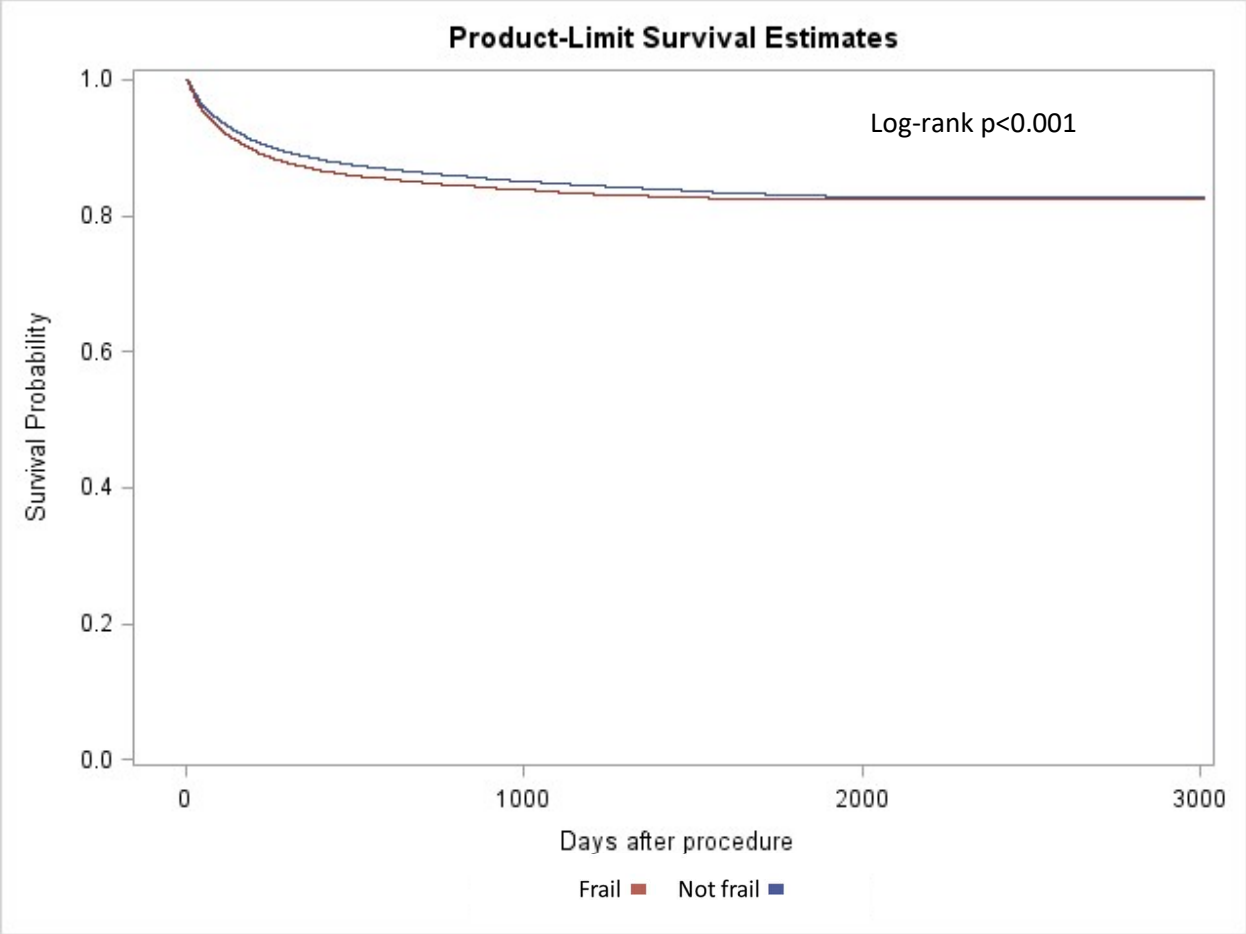
Figure S4. Amputation-free survival among CLTI patients by frailty status in aggregate



Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	35484	16213	11434	6967	3889	1962	860	260	24
Not frail	49576	34454	28632	20382	13189	7919	4243	1681	195

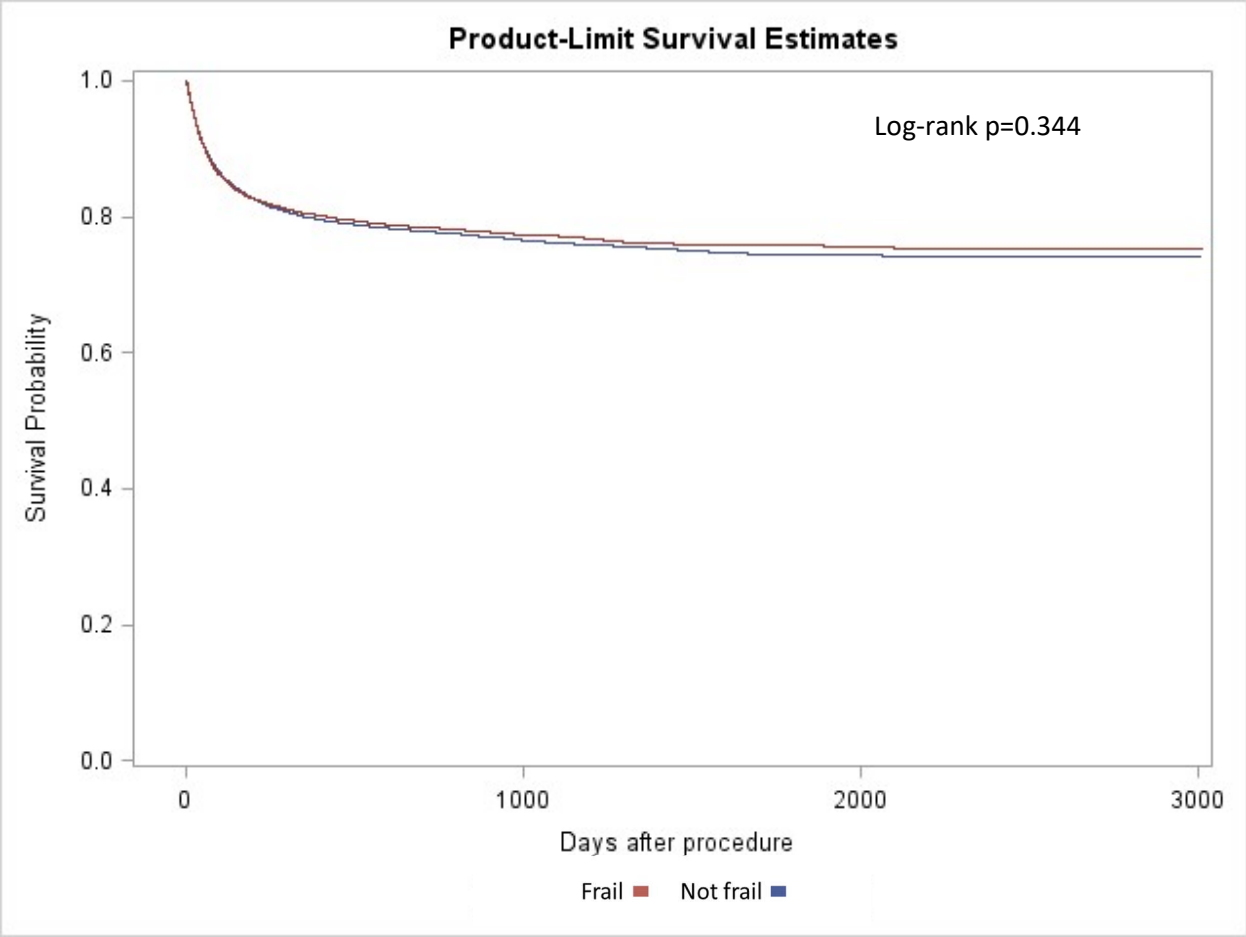
Figure S5. Amputation by frailty status among CLTI patients

a. Among patients undergoing revascularization



Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	21379	11259	8045	4936	2763	1370	581	191	15
Not Frail	37887	27751	23271	16618	10807	6491	3481	1431	166

b. Among patients not undergoing revascularization



Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	14105	4954	3389	2031	1126	592	279	69	9
Not Frail	11689	6703	5361	3764	2382	1428	762	250	29

Figure S6. Adjusted hazard ratio of frailty on outcomes of all patients with CLTI using Cox proportional hazards stratified by revascularization status

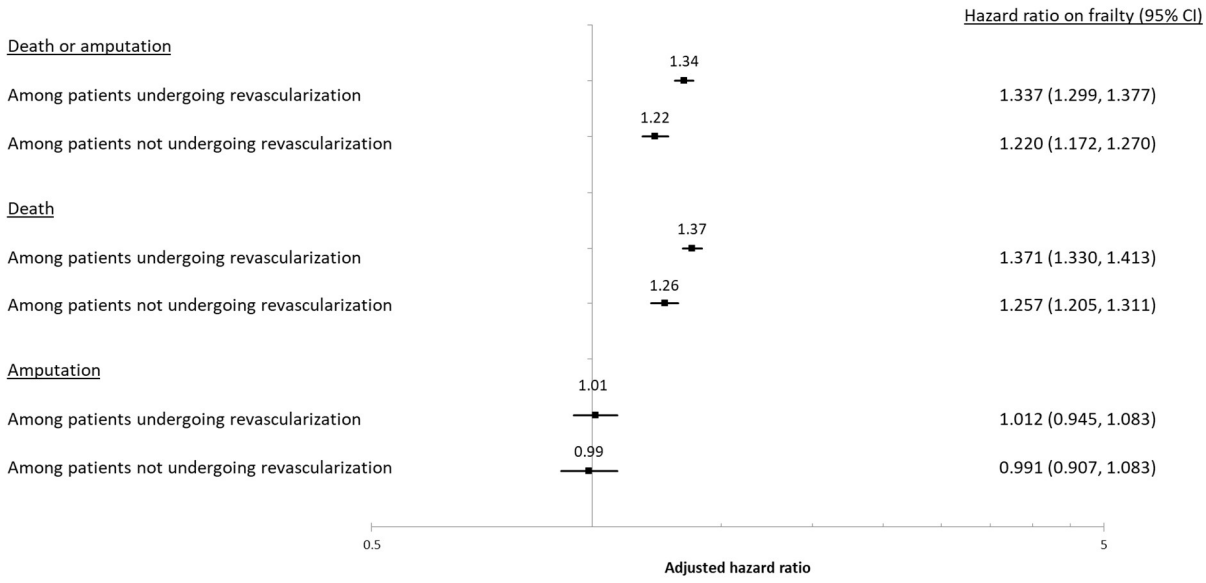
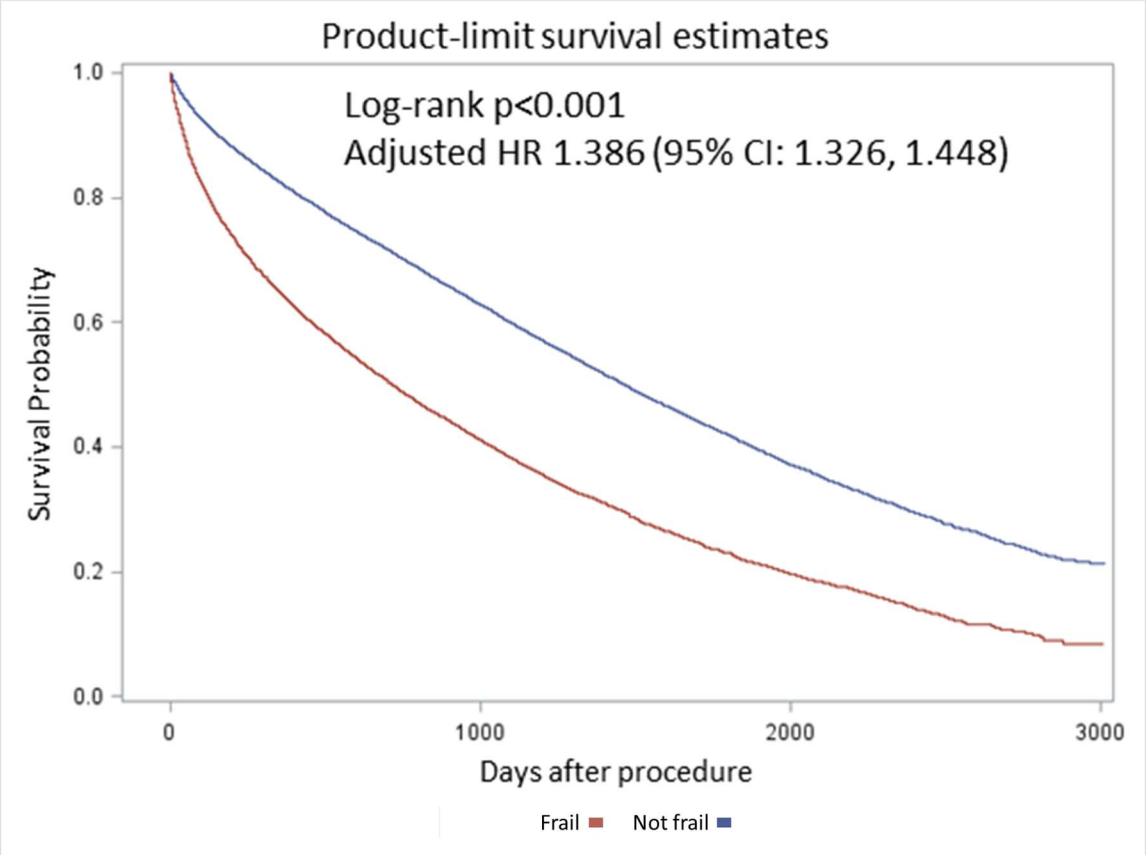


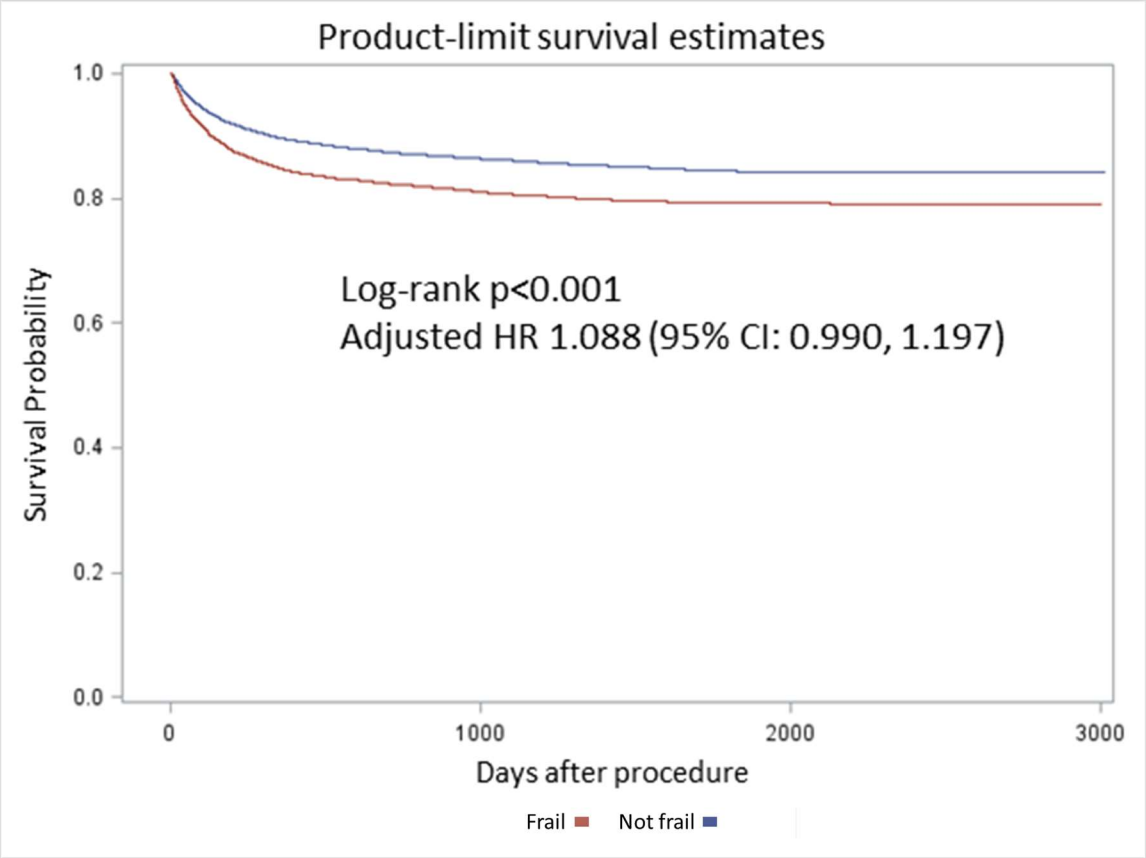
Figure S7. Outcomes by frailty status among CLTI patients undergoing surgical revascularization

A. Survival



Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	10241	6575	5069	3344	1975	1086	512	144	15
Not frail	28080	23043	19861	14422	9290	5556	2891	1157	146

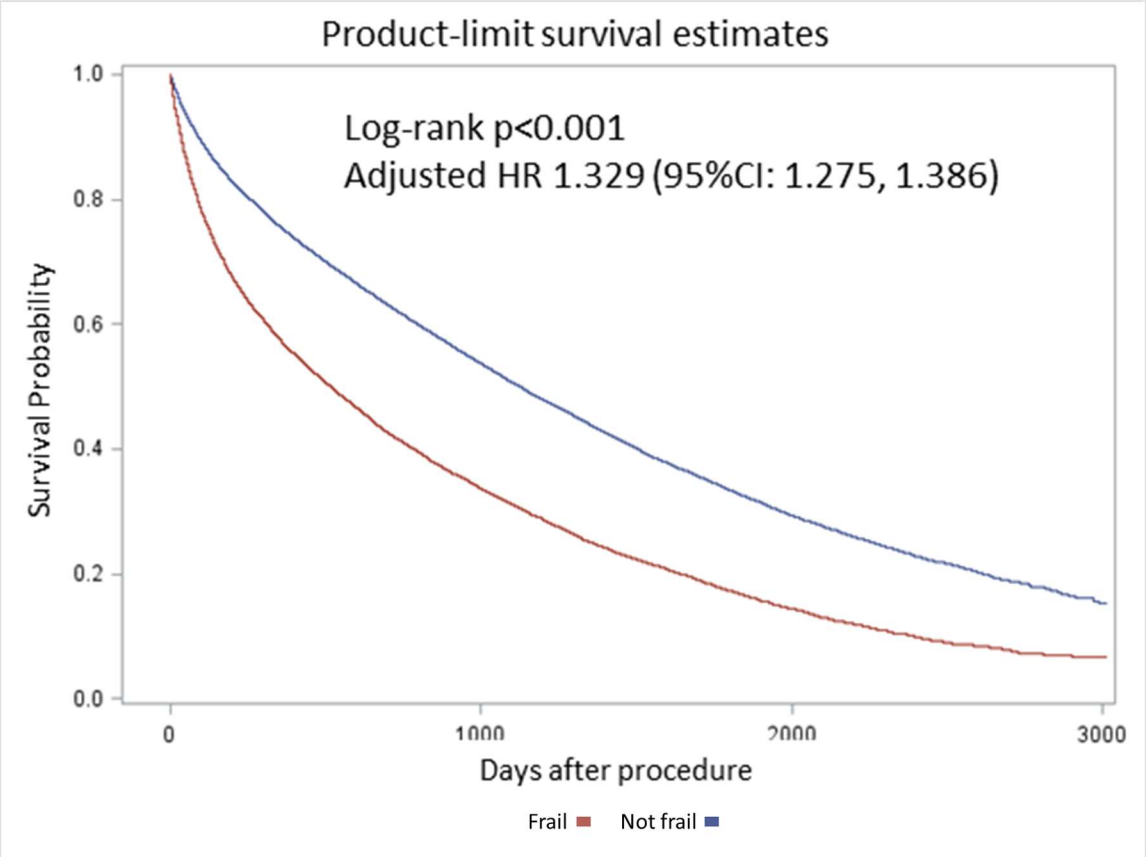
B. Freedom from Amputation



Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	10241	5684	4283	2727	1573	857	384	108	9
Not frail	28080	20925	17696	12602	7964	4709	2437	959	118

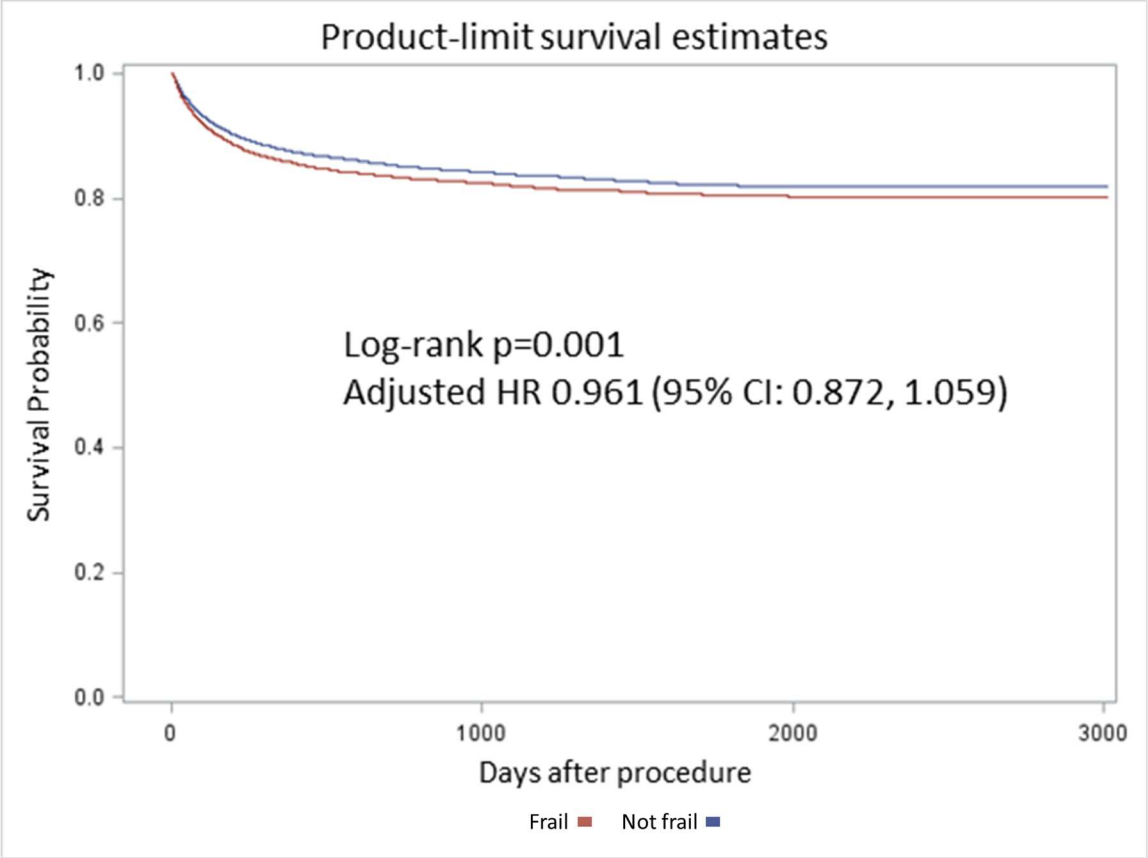
Figure S8. Outcomes by frailty status among CLTI patients undergoing endovascular revascularization

A. Survival



Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	17611	10000	7336	4658	2625	1380	629	204	29
Not frail	24188	18175	15021	10672	6952	4086	2148	892	109

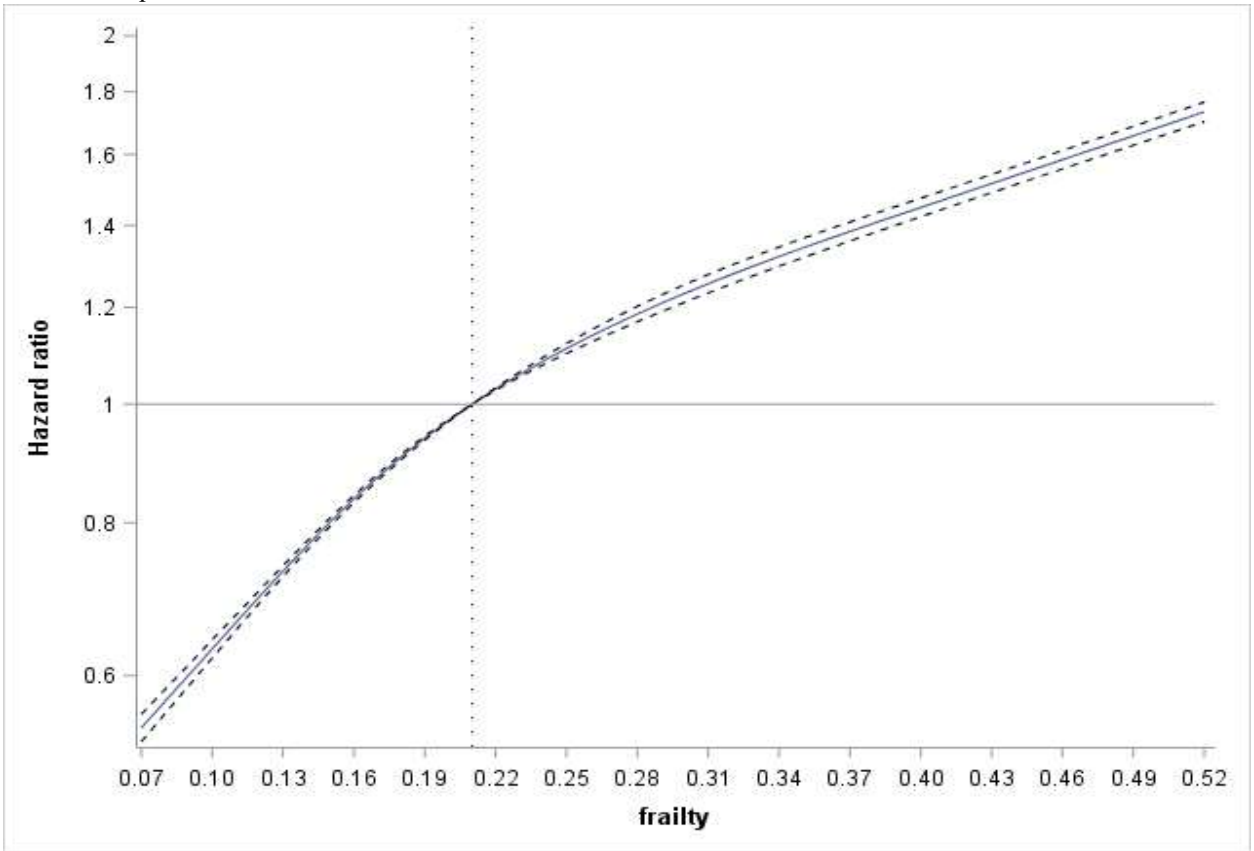
B. Freedom from amputation



Days after procedure	0	365	730	1095	1460	1825	2190	2555	2920
Frail	17611	8794	6284	3903	2175	1122	510	163	20
Not frail	24188	16256	13152	9177	5934	3451	1803	734	87

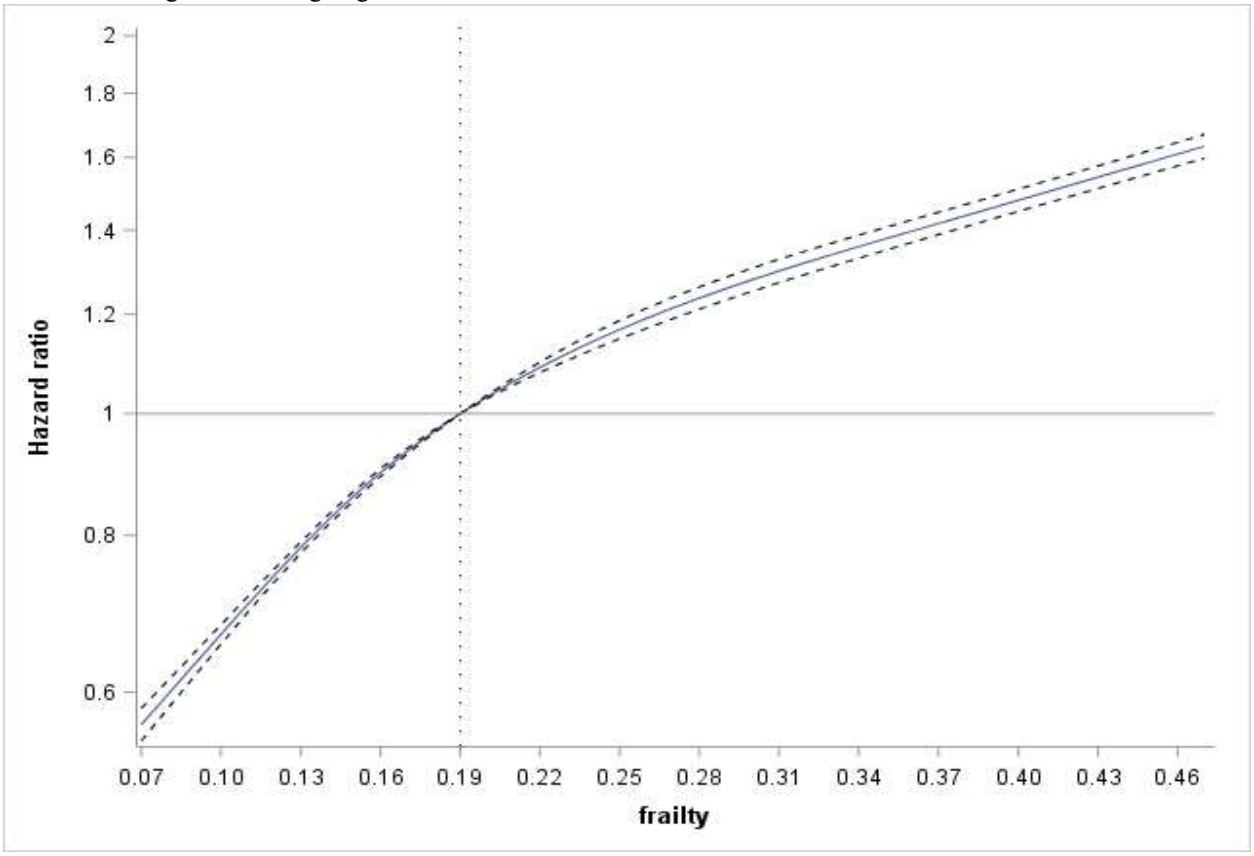
Figure S9. Relationship between degree of frailty and risk of death or amputation at 1 year

A. All patients



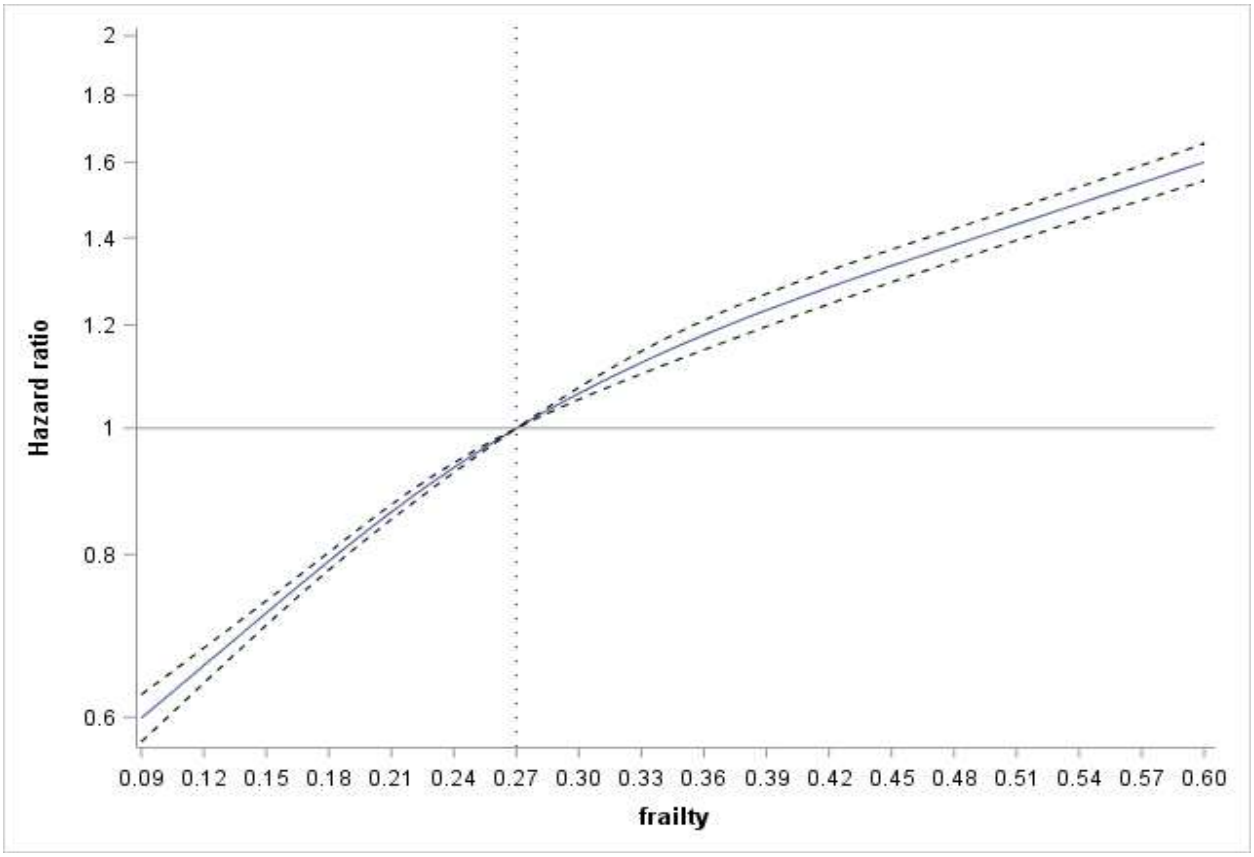
Knots in cubic spline model were defined as the 20th, 40th, 60th, and 80th percentile of frailty score.

B. Among those undergoing revascularization



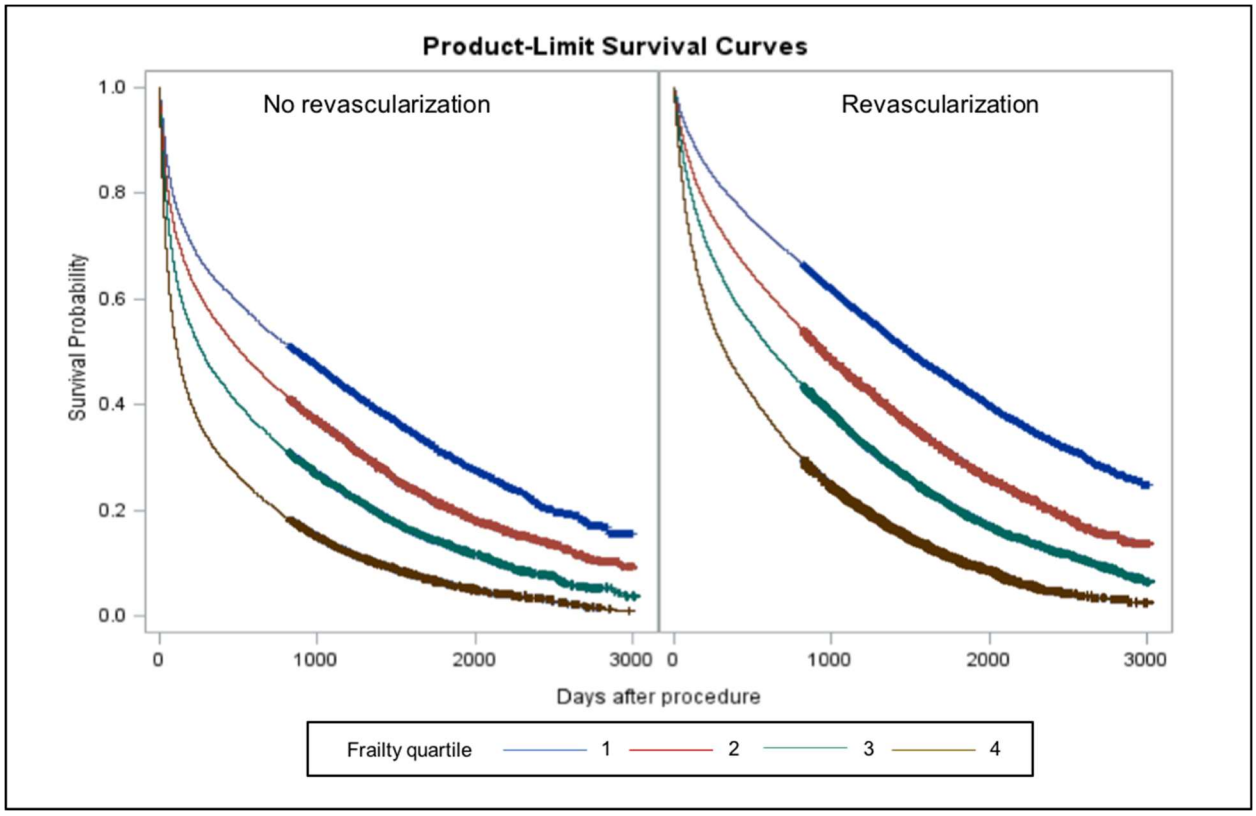
Knots in cubic spline model were defined as the 20th, 40th, 60th, and 80th percentile of frailty score.

C. Among those not undergoing revascularization



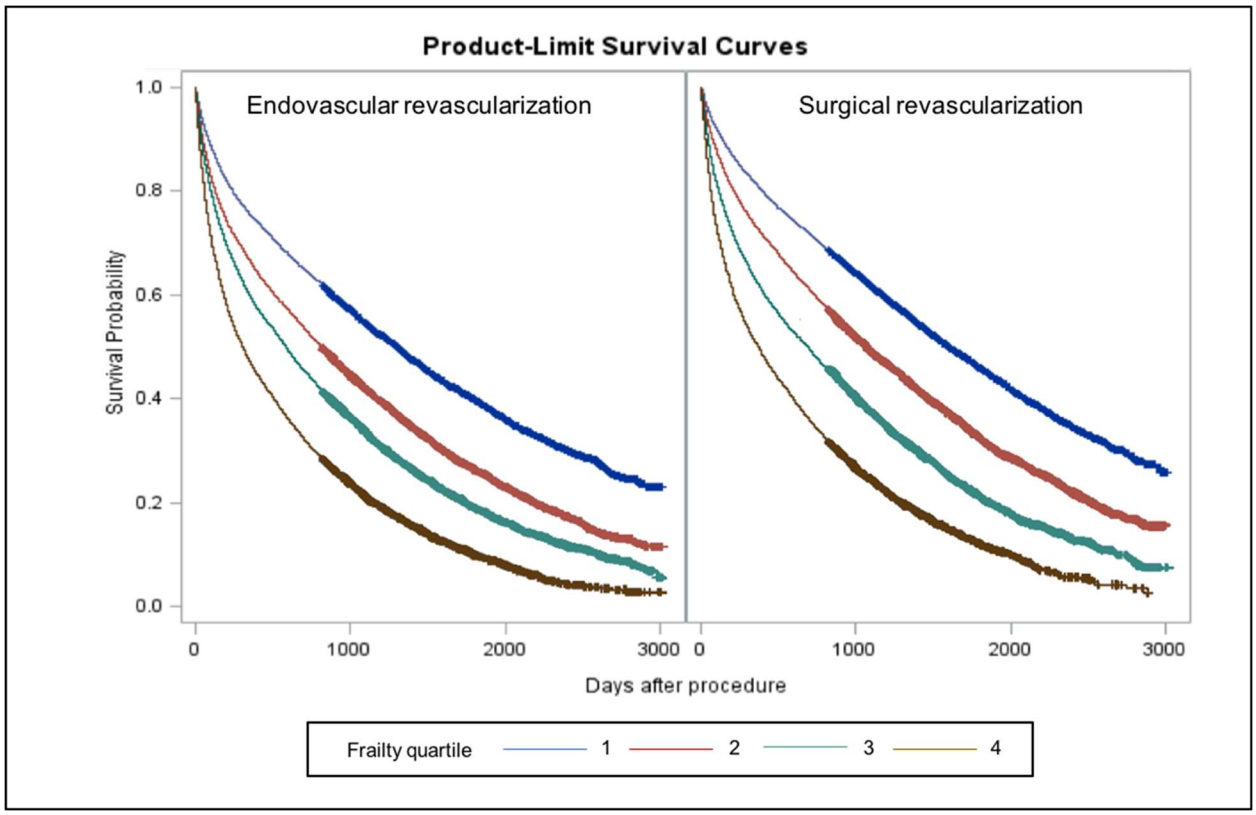
Knots in cubic spline model were defined as the 20th, 40th, 60th, and 80th percentile of frailty score.

Figure S10. Kaplan-Meier curves depicting amputation-free survival by frailty quartile, stratified by treatment choice



Lower quartile indicative of less frail patients.

Figure S11. Kaplan-Meier curves depicting amputation-free survival by frailty quartile, stratified by revascularization strategy



Lower quartile indicative of less frail patients.