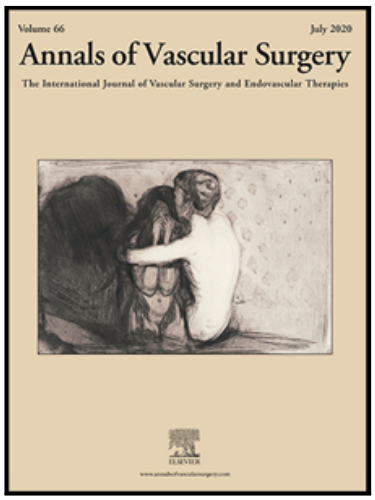

Associations of clinical frailty with severity of limb threat and outcomes in chronic limb-threatening ischaemia

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Highlights

- Frailty is highly prevalent in patients with chronic limb-threatening ischaemia
- Frailty is associated with greater severity of limb threat
- Frailty is associated with worse overall survival at one-year
- The Clinical Frailty Scale may be a useful adjunct to patient risk assessment

Associations of clinical frailty with severity of limb threat and outcomes in chronic limb-threatening ischaemia

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Category: Clinical research

Abstract

Objective

Investigate the relationship of frailty and severity of chronic limb-threatening ischaemia (CLTI), and their comparative associations with one-year outcomes, in patients presenting to a vascular limb salvage (VaLS) clinic.

Methods

This retrospective cohort study utilised data collected from a prospectively maintained VaLS clinic database. Patients aged ≥50 presenting to the VaLS clinic with CLTI between February 2018 and April 2019 were included. Frailty was measured using the Clinical Frailty Scale (CFS) and limb threat severity by the Wound, Ischaemia, and foot Infection (WIfI) score. Excessive polypharmacy was defined as ≥10 medications. Anticholinergic burden (ACB) score and Charlson comorbidity index (CCI) were calculated for all patients. The primary outcome measure was a composite endpoint of death or amputation at one-year. Associations with outcome were assessed using Cox regression and reported as hazards ratios (HR) with 95% confidence intervals (CI).

Results

A total of 198 patients were included, with CFS scores available for 190 patients. 98 patients (52%) were frail (CFS ≥5). 127 patients (67%) initially underwent endovascular revascularisation. Excessive polypharmacy was common (55 patients; 28%). Frailty was associated with increased WIfI stage (p=.025) as well as age, female sex, CCI score, number

of medications, excessive polypharmacy but not ACB score. Frail patients were more frequently managed non-operatively (p=.017).

Frailty (HR 1.91; 95% CI 1.09, 3.34; p=.024) and WIfI stage 4 (HR 3.29; 95%CI 1.23, 8.80; p=.018) were associated with death or amputation on univariable analysis. WIfI stage 4 (HR 2.80; 95%CI 1.04, 7.57; p=.042) and CCI score (HR 1.21; 95%CI 1.03, 1.41; p=.015), but not frailty (HR 1.25; 95%CI 0.67, 2.33; p=.474), were independently associated with death or amputation on multivariable analysis.

Conclusions

Frailty is highly prevalent among CLTI patients and related to severity of limb threat. The CFS may be a useful adjunct to patient risk assessment in CLTI.

Keywords:

Frailty, Frail elderly, Chronic limb-threatening ischaemia, Critical limb ischaemia, Peripheral arterial disease, Polypharmacy.

1. Introduction

Chronic limb-threatening ischaemia (CLTI) is the end-stage of peripheral arterial disease (PAD) where the affected limb is threatened by the degree of ischaemia and/or tissue loss.[1] Individuals with CLTI tend to be older, with multiple comorbidities, and high levels of frailty are observed in the CLTI population.[2-4] Decision making in CLTI is complex, considering severity of disease, revascularisation options, patient fitness, and patient choice to determine appropriate management strategies and often requires input from a multi-disciplinary team.[1, 5] The Global vascular guidelines (GVG) on the management of CLTI

advocate the Patient risk, Limb threat severity, and ANatomical complexity (PLAN) approach to evidence-based management.[1] The guidelines recommend the Wound, Ischaemia, foot Infection (WIfI) score to assess severity of limb threat:[1, 6] however, estimating patient risk is challenging and described models are predominantly based on patient demographics and comorbidity.[1, 7] Frailty assessment is a promising, simple adjunct to assessing patient risk and is increasingly being utilised in patients with CLTI.[5]

Frailty is a distinct health state of increased vulnerability to poor recovery from a stressor (such as acute illness or surgery) and is associated with mortality and institutionalisation.[8, 9] Among vascular surgery patients, frailty is related to higher rates of post-operative complications and long-term mortality.[10] Polypharmacy, the use of multiple concomitant medications, and the use of multiple medications with anticholinergic effects are also associated with frailty, as well as worse long-term mortality, and poorer cognitive and functional outcomes in older adults.[11-13] In vascular surgery patients, polypharmacy has been shown to be independently associated with one- and five-year mortality.[14-16]

Crucially, despite the high prevalence of frailty and functional impairment among individuals with CLTI, the relationship between limb threat and frailty has not been described and may be bi-directional. Lower limb disability in CLTI impacts on global functional status which may, in turn, influence degree of frailty.[17-19] The primary aim of this study was to investigate the association of frailty with limb threat severity, and compare their prognostic association with one-year outcomes of individuals presenting with CLTI. Secondary aims included investigating the associations of frailty with initial management strategy and baseline variables such as polypharmacy and multi-morbidity.

2. Materials and methods

The Leicester Vascular Limb Salvage (VaLS) clinic is a rapid-access clinic for individuals with suspected CLTI.[20] All patients undergo an assessment of frailty using the Clinical Frailty Scale (CFS) and limb threat assessed using the WIfI score at their first VaLS clinic attendance.[6, 21] The CFS is clinician assessed, based on patient-reported functional performance over the preceding two-weeks, and rated on a 9-point scale representing increasing frailty.[22] WIfI scores are converted to clinical stages (1 least severe; 4 most severe) to estimate the risk of amputation.[6] Additionally, data regarding comorbidities and regular medications are collected for all patients as part of a standardised proforma.

A retrospective analysis of a prospectively maintained VaLS clinic database was performed. All individuals aged ≥50 years attending the VaLS clinic between inception (February 2018) and April 2019 who were subsequently diagnosed with CLTI were included. CLTI was defined as ≥2 weeks of symptoms of rest pain, ulceration or gangrene and WIfI ischaemia grade ≥1. Individuals where ankle- or toe-pressures were not documented, or deemed unreliable, were included if they had a documented clinical diagnosis of CLTI. All included patients also had an arterial duplex confirming significant PAD. All assessments were performed as part of standard care in the VaLS clinic and data routinely collected into the VaLS clinic database. Data were analysed as part of a local service improvement project (aiming to improve the management of vascular surgery patients with frailty) which was prospectively approved and registered with the University Hospitals of Leicester NHS Trust audit department: no additional ethical approval or individual patient consent was required. All data were fully anonymised prior to analysis.

Patients with CFS score ≥5 were classified as frail. Charlson Comorbidity Index scores (updated weighting) were calculated retrospectively for individual patients as a measure of

multi-morbidity.[23] Polypharmacy was defined as ≥5 regular prescription medications and excessive polypharmacy defined as ≥10 regular prescription medications.[24] Anticholinergic burden (ACB) scores were calculated for individual patients using an online calculator (http://www.acbcalc.com) to estimate the cumulative anticholinergic effects of an individual's regular medications.[25] Initial management strategy was classified into four groups: endovascular revascularisation, open surgical/hybrid revascularisation (including covered endovascular reconstruction of the aortic bifurcation), primary major amputation, and non-operative management (medical management with either a watchful-waiting or palliative approach). Major amputation was defined as any amputation of the lower limb proximal to the ankle.

The primary outcome measure was amputation-free survival (AFS) (composite endpoint of major amputation or death) at one-year. Secondary outcome measures included freedom from major amputation and overall survival at one-year.

Baseline variables were presented in tables with data for frail (CFS ≥5) and non-frail (CFS <5) patients separately. Categorical and ordinal variables were presented as frequencies (%). Histograms of continuous data were constructed to assess for normality of distribution. Normally distributed data were presented as means (standard deviation) and skewed data as medians (interquartile ranges). Associations of baseline variables with frailty were investigated using X^2 test for categorical data, t-test for normally distributed continuous data, and Kruskal-Wallis test for both skewed continuous data and ordinal data. Associations of frailty with outcomes were presented as Kaplan-Meier survival curves and the log-rank test was used to test differences between groups. A p-value <.050 was considered statistically significant.

The associations of frailty, WIfI stage, and other baseline variables with one-year outcomes were investigated using Cox regression analysis and reported as hazards ratios (HR) with 95% confidence intervals (CI). A multivariable model was constructed using pre-selected variables (frailty, WIfI stage, age and CCI score) to investigate the independent association of frailty and WIfI stage with outcome. Missing CFS and WIfI stage data were imputed with multiple imputation to enable entry of all patients into the Cox regression analyses. The multiple imputation model included age, sex, CCI score and number of medications. Rubin's formula was used to combine the parameter estimates and standard errors from 100 imputations into a single set of results.[26, 27] As the CFS is only validated in those aged ≥65, sensitivity analyses were performed excluding those aged 50-64 from the analyses to ensure validity of the conclusions. To account for patients managed palliatively, sensitivity analyses including only those patients undergoing revascularisation were also performed. All statistical analyses were performed using Stata (V. 16, StataCorp. College Station, TX, USA).

3. Results

A total of 198 patients were included in the study. Of these, 190 had a CFS score documented and 98 patients (52%) were classified as frail. WIfI scores were missing/incomplete for six patients. Only 50 patients (25%) were prescribed <5 regular medications, therefore only associations with excessive polypharmacy (55 patients; 28%) were investigated further.

3.1. Associations of frailty with baseline variables and initial management

Comparison of baseline data by frailty status is summarised in Table 1. Frailty was associated with a greater degree of limb threat (p=.025). Over two-thirds of patients with WIfI stage 4 disease were classified as frail. Frailty was also associated with increased age,

female sex, diabetes and multi-morbidity (increased CCI score). Mean number of regular prescribed medications was higher for frail patients, and frailty was associated with excessive polypharmacy but not anticholinergic burden (ACB score).

There was also an association of frailty with initial management plan (p=.017). Proportionally fewer frail patients initially underwent surgical revascularisation and frail patients were more frequently managed non-operatively (27% frail vs 11% non-frail). However, similar proportions of frail and non-frail patients underwent endovascular intervention.

3.2. Associations with one-year outcomes

Twelve-month follow-up data was available for all patients. At one-year 19 patients (10%) had undergone a major amputation and 41 patients (21%) had died. The overall AFS rate at one-year was 72%. Frail patients had a worse AFS (p=.022; Figure 1) and overall survival (p=.003; Figure 2) but had a similar freedom from major amputation (p=.856; Figure 3).

3.2.1. Composite endpoint of death or amputation

Frailty was associated with death or amputation at one-year (HR 1.91; 95% CI 1.09, 3.34; p=.024) on univariable analysis, however there was no statistically significant association on multivariable analysis (HR 1.25; 95%CI 0.67, 2.33; p=.474). WIfI stage 4 (HR 2.80; 95%CI 1.04, 7.57; p=.042) and CCI score (HR 1.21; 95%CI 1.03, 1.41; p=.015) were the only factors independently associated with the composite endpoint of death or amputation at one-year.

3.2.2. Major amputation

Frailty was not associated with major amputation at one-year on either univariable or multivariable analyses. WIfI Stage 4 was the only factor associated with major amputation (HR 8.32; 95%CI 1.04, 66.31; p=.045).

3.2.3. Mortality

Frailty was strongly associated with mortality at one-year on univariable analysis (HR 2.76; 95% CI 1.38, 5.53; p=.004), but again there was no statistically significant association on multivariable analysis (HR 1.61; 95%CI 0.75, 3.46; p=.227). In the multivariable analysis, age (HR 1.06; 95%CI 1.02, 1.10; p=.002) and CCI score (HR 1.26; 95%CI 1.06, 1.49; p=.009) were the only factors associated with mortality.

3.3. Sensitivity analyses of one-year outcomes

There were no changes to direction of association with outcomes at one-year on sensitivity analyses (Tables S1 & S2; Figures 4 & S1-S5). When those aged <65 (43 patients) were excluded, the strength of the independent association of WIfI stage 4 with death or amputation was reduced (HR 1.98; 95%CI 0.71, 5.51; p=.190) whilst CCI score remained independently associated (HR 1.24; 95%CI 1.06, 1.47; p=.009). Similarly, only CCI score remained independently associated with death or amputation (HR 1.24; 95%CI 1.04, 1.48; p=.017) when those managed non-operatively (39 patients) and undergoing primary amputation (1 patient) were excluded. Frailty remained associated with one-year mortality on univariable analysis (HR 2.18; 95%CI 1.04, 4.57; p=.039) in this sensitivity analysis, including only those that underwent revascularisation, however mortality rates only diverged at 6-months (Figure 4).

4. Discussion

The results of this study show that frailty is highly prevalent among CLTI patients. Importantly, the results demonstrate that frailty is associated with severity of limb threat in CLTI. A higher proportion of frail patients had WIfI stage 4 disease and proportionally fewer frail patients underwent surgical revascularisation. Despite this, frailty was not associated with major amputation at one-year and the univariable association of frailty with the composite endpoint of death or amputation was entirely due to its strong univariable association with mortality at one-year. It is therefore likely that the frailest patients with end-stage CLTI were more frequently managed palliatively, either declining or not being offered a major amputation during follow-up. The early mortality divergence between frail and non-frail patients in the main analysis (Figure 2) was not present in the sensitivity analysis including only patients undergoing revascularisation (Figure 4) suggesting appropriate non-operative management in those with very limited life-expectancy. Notably, the majority of frail patients (72%) underwent revascularisation and, while frailty status may highlight a need for tailored peri-operative management to minimise complications, it should not be used in isolation to decline offering intervention.[10, 28]

The results of this study support the assessment of patient risk separately from limb threat severity as part of the PLAN approach described in the GVG.[1] Limb threat severity was independently associated with major amputation but not overall survival and *vice versa* for age and multi-morbidity. Given that age and CCI score were better predictors of survival, tools such as the Vascular Quality Initiative CLTI Mortality Prediction Model that take in to account age and comorbidities (among other factors) are likely to be better predictors of survival than frailty status alone.[7] However, frailty assessments may better characterise the potential risks and benefits of intervention on quality of life, and provide a frame to shared decision making, as they consider global functional status beyond just ambulation and frailty

itself is associated with loss of independence as well as mortality.[7-9, 29] Whilst the multivariable analysis did not demonstrate a statistically significant association of frailty with overall survival, the effect estimate was imprecise due to the moderate sample size and does not provide strong evidence of no independent association. No single factor was associated with both major amputation and mortality during follow-up, which highlights a deficiency of AFS as an outcome measure. The results of this study suggest the primary outcome measure of future research investigating frailty and CLTI should be mortality and not AFS or major amputation.

Clinical frailty assessments are likely to be superior to frailty indices predominantly based on comorbidities.[4, 10, 30] The simplicity and ease of use of the CFS, coupled with its strong univariable association with overall survival support its potential as a rapid, global adjunct to assessing patient risk in CLTI. It is also being widely adopted in numerous healthcare settings internationally, including vascular surgery.[22, 29, 31] The CFS is a rapid, reliable measure of frailty in emergency hospital admissions and vascular surgery clinic, and is easier to administer in these contexts than other clinical frailty tools.[32, 33] Given the impact CLTI has on lower limb function and disability, most CLTI patients will score ≥4 on the CFS which is a limitation to its use among CLTI patients. Although, most other clinical frailty assessment tools also either directly or indirectly account for lower limb function in their design.[8, 10] Ongoing research may provide further useful information regarding assessment of frailty, physical function and cognitive impairment, as well as other outcomes such as quality of life and durability of revascularisation, in patients with CLTI.[34]

Previous research has also demonstrated associations with frailty and outcomes over ≥1 year[3, 4, 35-37] Takeji *et al.* (643 patients) showed higher CFS scores were independently

associated with worse overall survival and AFS at two-years, adjusting for tissue loss in their multivariable model.[3] Using the critical limb ischaemia (CLI) frailty index, a novel three-item frailty score, Morisaki *et al.* (266 patients) showed an independent association of frailty with worse overall survival and AFS.[35] However, their follow-up study (127 patients) showed only an independent association with overall survival, and the CLI frailty index is only validated to predict risk, not its ability to identify frailty.[10, 35, 36] Soon *et al* (233 patients) used the modified frailty index (mFI) and also found an association of frailty with worse one-year mortality but not major amputation in CLTI.[37] However, the utility of the mFI as a frailty tool has been questioned.[10, 30] Drudi *et al.* utilised multiple frailty tools in patients undergoing revascularisation for claudication or CLTI (148 patients; 89 with CLTI).[4] The prevalence of frailty differed significantly depending on which frailty tool was used, as did their prognostic value.[4] Among the CLTI population, frailty identified using the Groningen Frailty Indicator or modified Essential Frailty Toolset was independently associated with mortality or worsening disability at one-year.[4] None of these studies included patients managed non-operatively.[3, 4, 35-37] No previously published research has reported the relationship of frailty with limb threat or polypharmacy in CLTI.

Polypharmacy was highly prevalent among patients included in this study and associated with frailty. Polypharmacy is commonest in older, multi-morbid patients, and, among vascular surgery patients, those with PAD have the highest combined comorbidity-polypharmacy scores.[16, 38] However, polypharmacy may be most inappropriate in older, multi-morbid patients as they are rarely included in trials from which clinical guidelines are developed and also are at greatest risk of adverse drug reactions.[39, 40] Other negative consequences of polypharmacy include non-adherence with medications, falls and delirium, which may be mitigated by stopping unnecessary medications.[41] Not all polypharmacy may

be inappropriate however. To attempt to investigate this, ACB score was calculated for each patient. Secondary preventative medications for PAD (e.g. antiplatelets and statins) do not have anticholinergic effects.[25] Whilst many analgesics prescribed in CLTI (e.g. opiates) do, the majority of regular medications contributing to ACB score in patients in this study were likely prescribed for comorbidities rather than CLTI.[25] A third of patients had an ACB score ≥3, which in a general older adult population carries higher risk of confusion, falls and death.[25] However, ACB score was not related to outcome in this study.

No studies to date have investigated strategies to mitigate long-term risks for frail CLTI patients. A randomised trial by Partridge *et al.* of pre-operative comprehensive geriatric assessment (CGA) and optimisation in patients undergoing major vascular surgery showed reduced length of stay, post-operative complications and post-operative delirium.[42] However, a particular challenge in CLTI is that treatment delays may be associated with worse limb salvage outcomes, limiting time for pre-operative optimisation.[43] Improvements in post-operative outcomes have been demonstrated by integration of specialist, multi-disciplinary older-person care for emergency general surgery patients and also shown benefits in vascular surgery patients.[44, 45] Deprescribing of unnecessary/inappropriate medications is another potential intervention given the high rates of polypharmacy identified in this study. In the trial by Partridge *et al*., far more patients in the CGA group had changes to their medications prior to surgery (86% vs 4%), suggesting there may be a significant role for medication review in CLTI.[42] Frailty assessment may identify and triage CLTI patients in whom pre-operative CGA and optimisation, and multi-disciplinary team supported shared decision making may be most appropriate.

4.1. Strengths and limitations of the study

The main strengths of this study are that both frailty status and severity of CLTI were investigated, patients managed non-operatively were included, and complete follow-up data were available for all patients. There are, however, several limitations. This was a single-centre study and only patients attending the VaLS clinic were included, limiting the generalisability of the results and conclusions. Performance bias may have a significant effect on the results, with CFS scores influencing decision-making both initially and during follow-up. Similarly, data on previous interventions, outcomes of multi-disciplinary reviews and discussions outside of the VaLS clinic, and reasons for specific treatment decisions were not collected. Whilst the database from which data was collected for this study is maintained prospectively, this was a retrospective study and inclusion was based on documentation consistent with a diagnosis of CLTI. Additionally, associations with short-term outcomes (such as length of stay, post-operative complications, delirium, falls and non-home discharge) could not be investigated as these are not routinely collected. Furthermore, there were some missing data which may have influenced the results and conclusions. Multiple imputation was used to enable inclusion of all patients in the analyses. The moderate sample size (198 patients) limited the number of covariables included in the multivariable analyses. Age, CCI score, WIfI stage and frailty were pre-selected based on their known or hypothesised influence on AFS, however there was insufficient power to also include number of medications into the model due to its correlation with multi-morbidity. Similarly, there was insufficient power to investigate the interaction between frailty and severity of CLTI (WIfI stage). WIfI stage was analysed as a categorical variable as the differences between groups were not designed to be linear. The small sample size and low event rate of major amputations (only one among patients with WIfI stage 1) mean that the effect estimates are imprecise (reflected in the wide confidence intervals). Inclusion of

patients aged 50-64 in this study is unlikely to have had a significant influence as sensitivity analyses (limited to patients aged ≥65) showed very similar results.

4.2. Conclusions

Frailty is highly prevalent among patients with CLTI and associated with greater severity of limb threat. Frailty assessment may be a useful adjunct to characterising patient risk and informing shared decision making in CLTI.

Author contributions:

Study design: JSMH, ATON, LJG, HS, VJH, RSMD, RDS.

Data collection: JSMH, ATON, JRH, JD, SD.

Data analysis: JSMH, LJG.

Interpretation of results: All authors.

Writing the manuscript: JSMH.

Revision of the manuscript: All authors.

Conflicts of interest:

None.

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Figure legends

Figure 1: Kaplan-Meier curves for amputation free survival over one-year follow up stratified by frailty status.

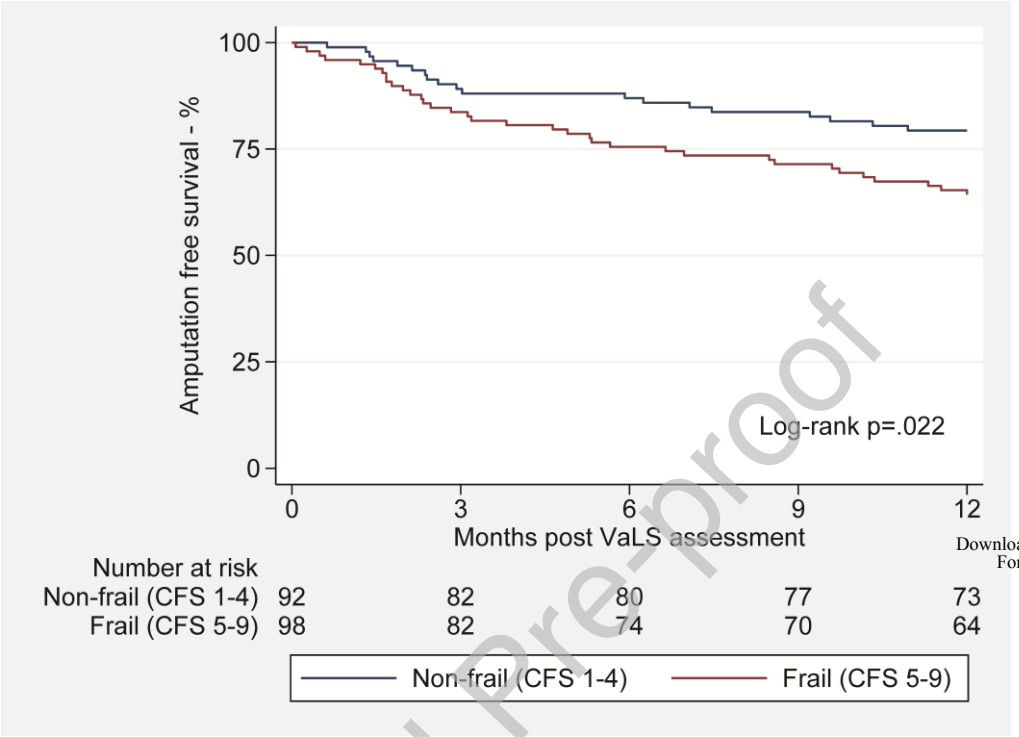

Figure 2: Kaplan-Meier curves for overall survival over one-year follow up stratified by frailty status.

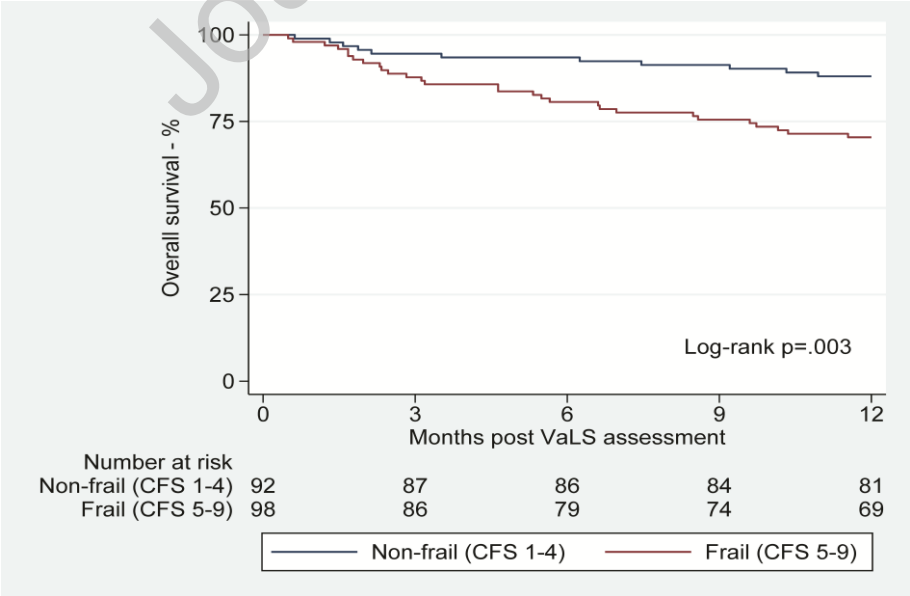

Figure 3: Kaplan-Meier curves for freedom from major amputation over one-year follow up stratified by frailty status.

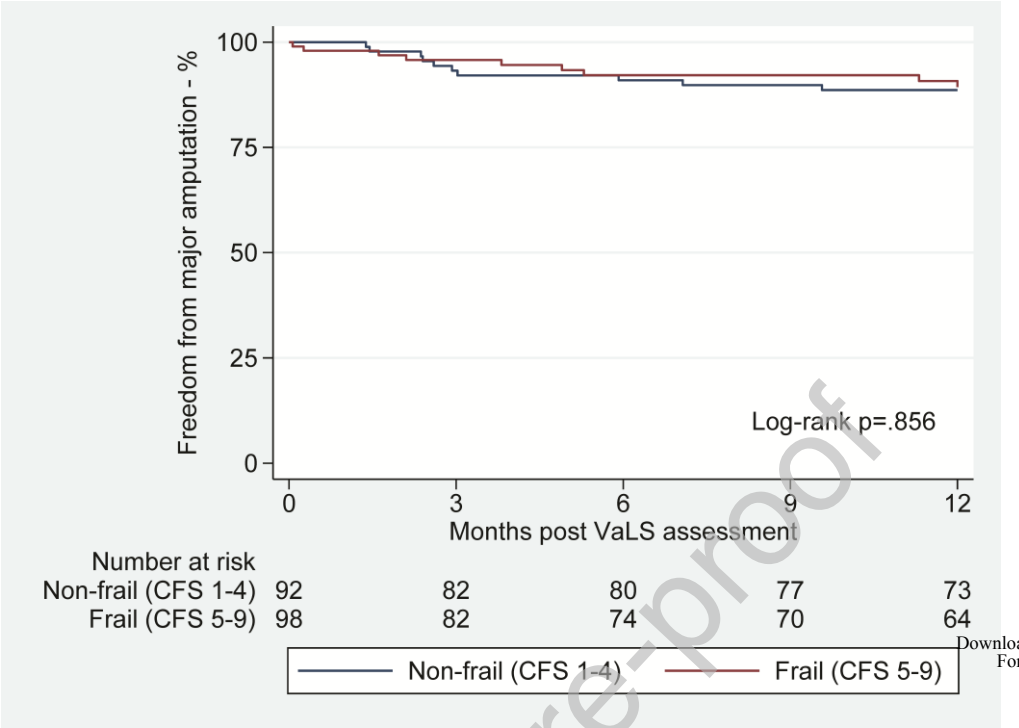

Figure 4: Kaplan-Meier curves for overall survival over one-year follow up stratified by frailty status from the sensitivity analysis including only patients undergoing initial revascularisation.

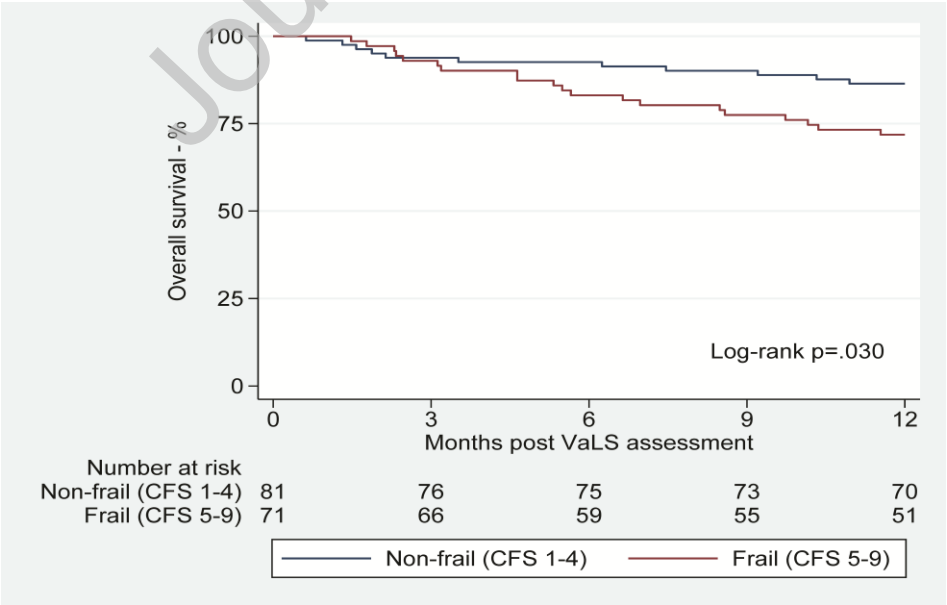

Table 1: Baseline Characteristics of included patients by frailty status

	Non-frail (CFS 1-4) (N=92)	Frail (CFS 5-9) (N=98)	P-value
Age	70.3 ±9.5	77.0 ±10.2	**<.001**
Female	22 (24)	42 (43)	**.006**
Diabetes	49 (53)	67 (68)	**.033**
CCI*	1 (1-2)	2 (1-3)	**<.001**
Smoking status:			
Never	20 (22)	30 (31)	**.019**
Ex	42 (46)	52 (54)	
Current	30 (33)	15 (15)	
No. Medications	7.1 ±3.4	9.4 ±3.9	**<.001**
Excessive Polypharmacy (≥10 medications)	19 (21)	34 (35)	**.031**
ACB score*	1 (0-3)	2 (1-3)	.084
WIfI stage:			
1	15 (17)	16 (17)	**.025**
2	39 (43)	24 (25)	
3	22 (24)	25 (26)	
4	14 (16)	30 (32)	
Initial Management			
Endovascular	64 (70)	63 (64)	**.017**
Hybrid/Open surgery	17 (18)	8 (8)	
Primary Amputation	0 (0)	1 (1)	
Non-operative	11 (12)	26 (27)	

*Data are presented as n (%) or mean ± standard deviation unless otherwise stated. *Data presented as median (interquartile range).*

ACB, Anticholinergic burden; CCI, Charlson comorbidity index; CFS, Clinical frailty scale; No., Number of; WIfI, Wound, ischaemia, and foot infection.

Table 2: Associations of baseline variables with one-year outcomes

	Major amputation or mortality (composite endpoint)			
	Univariable analyses		*Multivariable analysis*	
	95% CI	P-value	95% CI	P-value
Frailty (CFS 5-9)	**1.91 (1.09, 3.34)**	**.024**	1.25 (0.67, 2.33)	.474
WIfI stage 1*	-	-	-	-
WIfI stage 2	1.26 (0.45, 3.54)	.662	1.46 (0.51, 4.13)	.476
WIfI stage 3	2.38 (0.88, 6.48)	.089	2.33 (0.85, 6.39)	.099
WIfI stage 4	**3.29 (1.23, 8.80)**	**.018**	**2.80 (1.04, 7.57)**	**.042**
Age†	**1.04 (1.01, 1.06)**	.016	1.02 (0.99, 1.05)	.205
CCI score†	**1.28 (1.11, 1.48)**	**.001**	**1.21 (1.03, 1.41)**	**.015**

Sex (female)	1.17 (0.67, 2.02)	.550	-	-
No. Medications†	**1.10 (1.03, 1.18)**	**.005**	-	-
ACB score†	1.11 (0.99, 1.23)	.073	-	-
Diabetes	1.71 (0.95, 3.06)	.072	-	-
	Major amputation			
	Univariable analyses		*Multivariable analysis*	
	95% CI	P-value	95% CI	P-value
Frailty (CFS 5-9)	0.90 (0.37, 2.23)	.824	0.89 (0.33, 2.42)	.827
WIfI stage 1*	-	-	-	-
WIfI stage 2	0.98 (0.09, 10.80)	.986	0.87 (0.08, 9.63)	.909
WIfI stage 3	4.87 (0.60, 39.64)	.139	5.41 (0.66, 44.22)	.115
WIfI stage 4	7.40 (0.93, 58.52)	.058	**8.32 (1.04, 66.31)**	**.045**
Age†	0.97 (0.93, 1.01)	.176	0.96 (0.92, 1.01)	.102
CCI score†	0.96 (0.71, 1.30)	.782	0.91 (0.64, 1.29)	.586
Sex (female)	0.38 (0.11, 1.31)	.127	-	-
No. Medications†	1.07 (0.95, 1.20)	.255	-	-
ACB score†	1.12 (0.93, 1.35)	.223	-	-
Diabetes	2.62 (0.87, 7.88)	.088	-	-
	Mortality			
	Univariable analyses		*Multivariable analysis*	
	95% CI	P-value	95% CI	P-value
Frailty (CFS 5-9)	**2.76 (1.38, 5.53)**	**.004**	1.61 (0.75, 3.46)	.227
WIfI stage 1*	-	-	-	-
WIfI stage 2	1.46 (0.47, 4.52)	.516	1.90 (0.60, 5.98)	.272
WIfI stage 3	1.82 (0.58, 5.72)	.308	1.69 (0.53, 5.40)	.374
WIfI stage 4	2.56 (0.84, 7.81)	.098	1.94 (0.63, 6.01)	.251
Age†	**1.08 (1.04, 1.12)**	**<.001**	**1.06 (1.02, 1.10)**	**.002**
CCI score†	**1.37 (1.17, 1.60)**	**<.001**	**1.26 (1.06, 1.49)**	**.009**
Sex (female)	1.84 (0.99, 3.39)	.052	-	-
No. Medications†	**1.09 (1.01, 1.18)**	**.029**	-	-
ACB score†	1.07 (0.95, 1.22)	.268	-	-
Diabetes	1.29 (0.68, 2.47)	.434	-	-

*Data are presented as hazards ratios (95% confidence intervals). Values in bold are statistically significant. *Reference variable. †Data analysed as a continuous variable.*

ACB, Anticholinergic burden; CCI, Charlson comorbidity index; CFS, Clinical frailty scale; CI, Confidence interval; No., Number of; WIfI, Wound, ischaemia, and foot infection.