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The Relationship between Clinical Frailty Score, CT-Derived Body Composition, Systemic Inflammation, and Survival in Patients with Chronic Limb-Threatening Ischemia

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Background: Frailty is a chronic condition with complex etiology and impaired functional performance that has been associated with altered body composition and chronic inflammation. Chronic limb-threatening ischemia (CLTI) carries significant morbidity and mortality and is associated with poor quality of life. The present study aims to examine these relationships and their prognostic value in patients with CLTI.

Methods: Consecutive patients presenting as unscheduled admissions to a single tertiary center with CLTI were included over a 12-month period. Frailty was diagnosed using the Clinical Frailty Scale (CFS). Body composition was assessed using computerised tomography (CT) at the L3 vertebral level (CT-BC) to generate visceral and subcutaneous fat indices, skeletal muscle index, and skeletal muscle density. Skeletal muscle index and skeletal muscle density were combined to form the CT-sarcopenia score (CT-SS). Systemic inflammation was assessed by the modified Glasgow prognostic score (mGPS). The primary outcome was overall mortality.

Results: There were 190 patients included with a median (interquartile range) follow-up of 22 (6) months (range 15−32 months) and 79 deaths during the follow-up period. One hundred patients (53%) had a CFS >4. CFS >4 (hazard ratio [HR] 2.14, 95% confidence interval [CI] 1.25−3.66, $P < 0.01$), CT-SS (HR 1.47, 95% CI 1.03−2.09, $P < 0.05$), and mGPS (HR 1.54, 95% CI 1.11−2.13, $P < 0.01$) were independently associated with increased mortality. CT-SS (odds ratio 1.88, 95% CI 1.09−3.24, $P < 0.01$) was independently associated with CFS >4. Patients with CT-SS 0 and CFS ≤4 had 90% (standard error [SE] 5%) 1-year survival, compared with 35% (SE 9%) in patients with CT-SS 2 and CFS >4 ($P < 0.001$). Patients with mGPS 0 and CFS ≤4 had 94% (SE 4%) 1-year survival compared with 44% (SE 6%) in the mGPS 2 and CFS >4 subgroup ($P < 0.001$).

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Conclusions: Frailty assessed by CFS was associated with CT-BC. CFS, CT-SS, and mGPS were associated with poorer survival in patients presenting as unscheduled admissions with CLTI. CT-SS and mGPS may contribute to part of frailty and prognostic assessment in this patient cohort.

INTRODUCTION

Frailty is a complex multisystem disorder characterized by inferior functional status, loss of independence, and impaired physiological reserve,[1] which can be assessed using validated scoring systems such as the Clinical Frailty Scale (CFS). An association between frailty and outcomes in surgical patients has been described, though the literature specific to vascular surgery is limited by heterogeneity in assessment methodology.[2]

Chronic limb-threatening ischemia (CLTI) is considered the most severe form of peripheral arterial disease (PAD). CLTI is defined by the 2019 Global Vascular Guidelines as ''the presence of PAD in combination with rest pain, gangrene, or lower limb ulceration of >2 weeks duration''.[3] CLTI carries significant morbidity and mortality and is associated with poor quality of life.[3]

Sarcopenia is characterized by progressive loss of skeletal muscle volume and progressive reduction in skeletal muscle function (EWGSOP2 definition) and is associated with frailty, increasing age, poor physiological reserve, and chronic illness.[4] The use of computerised tomography-derived body composition analysis (CT-BC) to measure sarcopenia has been widely performed in a range of patient cohorts, with majority of the literature based on patients with cancer,[5] though there are studies describing a prognostic role of CT-BC in vascular cohorts[6,7][A]. The effect that body composition has on functional performance, including frailty, has been reported previously,[8] though the evidence base in noncancer patients is limited. The literature describing CT-BC in patients CLTI is limited to small series with heterogenous methodology,[9–12] chief of which is a lack of standardized thresholds to determine abnormal CT-BC parameters. Validated CT-BC thresholds have been widely reported in patients with cancer,[13] though these have not been widely described in noncancer populations.

Activation of the systemic inflammatory response (SIR) is an etiological factor in the development of sarcopenia,[4] and has been associated with inferior prognosis in patients with and without cancer.[14,15] The modified Glasgow prognostic score (mGPS) is a prognostic inflammation-based scoring system originally described in patients with cancer and subsequently evaluated in a range of patient cohorts.[16] Activation of the SIR appears to be associated with inferior prognosis in patients with CLTI, though the evidence is limited to small series, and mGPS has not been evaluated in this patient group.[17,18] Furthermore, there appears to be an association between altered CT-BC parameters and activation of the SIR,[19,20] though this association is poorly described in noncancer populations. Finally, an association between clinical frailty and activation of the SIR has been reported.[21]

The present study examines the association between clinical frailty, CT-BC, systemic inflammation, and survival in patients with unscheduled CLTI presentations to a single tertiary vascular surgical unit.

MATERIALS AND METHODS

Patient Selection

This study was a retrospective analysis of a preexisting prospectively maintained audit database. Consecutive patients presenting as unscheduled admissions with CLTI to a single tertiary vascular center between January 2020 and June 2021 were prospectively recorded as part of an ongoing institutional audit. West of Scotland Research Ethics Committee approval was obtained for the retrospective analysis of this database, which formed the cohort analyzed in the present study (Reference 21/WS/0146; approval granted November 23, 2021). Due to the retrospective study design, individual patient consent was not required for ethical approval. CLTI was diagnosed by the on-call vascular surgical team, and our institutional practice is to consider CLTI as per the 2019 Global Vascular Guidelines definition.[3] The study recruitment period occurred during the height of the COVID-19 pandemic; due to uncertainty regarding the potential confounding effect of COVID-19, any patient with a positive COVID-19 test within 1 month of admission was excluded. Patients who did not undergo CT imaging for CT-BC and patients with active malignancy (due to the potentially confounding effect on both CT-BC and systemic inflammation) were also excluded.

Primary Outcome

The primary outcome was overall mortality during the follow-up period. The secondary outcomes were 1-year mortality, chosen as this reflected a clinically relevant outcome in this patient group

and the minimum follow-up interval, and major amputation-free survival at 1 year. Outcome data were obtained from the Community Health Index registry, a routinely available registry maintained at a national health board level and populated from both primary and secondary care data. Specific cause of death was not available from this registry.

Baseline Data Collection

Clinical, demographic, and pathological data were recorded from electronic case records. Comorbidity was assessed using American Society of Anesthesiologists (ASA), which was recorded from operative records and subgrouped ($\leq 2/> 2$) in keeping with previous literature.[22] CFS was calculated on admission by the admitting medical team using an established institutional proforma, with visual prompts to aid clinicians' assessment as per Rockwood et al.[23] CFS ≤ 4 (considered nonfrail) and >4 (considered frail) was used to subgroup patients for comparison, in keeping with widely reported values from other studies that are used in existing clinical practice.[24] The presence of tissue loss was defined by the assessment made by the on-call vascular surgeon, who documented presence of absence of tissue loss as part of their initial clinical review. Systemic inflammation was assessed by mGPS, calculated as previously described (Supplemental Table 1),[16] based on the first blood sample taken on unscheduled admission. In order to control for the potentially confounding effect of tissue loss on mGPS, subgroup analyses on patients presenting with no tissue loss were performed. Nutritional state was assessed by the malnutrition universal screening tool (MUST) score, which is routinely collected by nursing staff in National Health Service Health Boards as part of an admission proforma, with MUST ≥ 2 considered high risk for malnutrition.

CT-Derived Body Composition Analysis

Body composition analysis was performed on CTs performed as part of existing patient care at the L3 vertebral level. Visceral fat area, subcutaneous fat area, skeletal muscle area, and skeletal muscle density (SMD) were manually measured using the freeware program ImageJ v1.53[25] using muscle tissue thresholds of −29 to + 150 Hounsfield Units, and adipose tissue thresholds of −190 to −30 Hounsfield Units. The areas obtained were normalized to height^2 to generate visceral fat index (VFI), subcutaneous fat index (SFI), and skeletal muscle index (SMI). In keeping with established methodology, SMD was not normalized. To determine optimal thresholds for dichotomization of body composition parameters into ''high'' and ''low'' based on prognostic value, the ''surv_cutpoint'' function of the ''survminer'' R package was used, using the maximally selected rank statistic technique. Sex-specific thresholds were derived to account for the established variation in body composition between males and females. Image compromise precluding CT-BC was assessed on a case-by-case and a parameter-by-parameter basis, and images were selectively excluded if compromise was deemed substantial. CT-sarcopenia score (CT-SS) was calculated as per McGovern et al.,[26] with each of SMI and SMD assigned an integer value of 0 (high SMI/SMD) or 1 (low SMI/SMD) and the combined score (range 0−2) calculated.

Statistical Analysis

Differences between continuous variables were assessed using the Mann-Whitney test, and differences between categorical variables were assessed using the chi-squared test. Time-to-event analyses were calculated using the Kaplan-Meier method, with differences between cohorts assessed using the log-rank test. Within certain subgroups, time to event survival data did not reach a median survival; therefore, to ensure consistency of reporting throughout, the mean (95% confidence interval [CI]) values are reported. The relationship between covariates and mortality was assessed using a cox proportional hazards model; covariates were initially interrogated in univariate analysis, and those with univariate $P < 0.10$ were included in a multivariate model. One-year survival and % standard error were calculated in CFS, CT-SS, and mGPS subgroups using censored survival data, and absolute differences were compared. The predictive value of covariates on CFS ($\leq 4/>4$) was assessed using a binary logistic regression model; covariates were initially interrogated in univariate analysis, and those with univariate $P < 0.10$ were included in a multivariate model. Correlations between continuous variables were assessed by Pearson correlation. P values < 0.05 were considered statistically significant. Analyses were performed using IBM SPSS 28.0 and RStudio 2022.02.01.

RESULTS

There were 190 patients included. Median (interquartile range) follow-up was 22 (6) months (range 15−32 months). CFS was recorded in all patients; 100 (53%) had a CFS >4. When compromised images were excluded on a parameter-by-parameter basis, there were 185 cases (VFI), 176 cases (SFI), 185 cases (SMI), and 185 cases (SMD) available for analysis. There were 79 deaths during the follow-

up period. Mean (95% CI) survival in the entire cohort was 21.1 (19.2−23.0) months. Thresholds of body composition parameters associated with survival that were used to subgroup patients and the number within each subgroup are shown in Supplemental Table 2. Scatter plots of body composition parameters subgrouped by CFS are shown in Supplemental Figure 1A and B, respectively.

The association between baseline clinicopathological characteristics, CT-derived body composition parameters, mGPS, and CFS >4 is shown in Table I. Age ≥75 ($P < 0.001$), female sex ($P < 0.05$), MUST ≥2 ($P < 0.05$), ASA >2 ($P < 0.001$), elevated CT-SS ($P < 0.001$), and elevated mGPS ($P < 0.01$) were all more prevalent in patients with CFS >4, while high VFI ($P < 0.01$) was less prevalent in patients with CFS >4. On multivariate analysis, age ≥75 (odds ratio [OR] 2.21, 95% CI 1.07−4.56, $P < 0.05$), ASA >2 (OR 6.83, 95% CI 2.10−22.22, $P < 0.01$), and CT-SS (OR 1.88, 95% CI 1.09−3.24, $P < 0.01$) were associated with CFS >4. mGPS (OR 1.35, 95% CI 0.89−2.03, $P = 0.16$) was not independently associated with CFS >4.

Mean (95% CI) survival in the CFS ≤4 versus CFS >4 subgroups was 25.8 (23.5−28.2) versus 16.8 (14.2−19.5) months ($P < 0.001$, Fig. 1). Mean (95% CI) survival in the high VFI versus low VFI subgroups was 22.1 (19.6−24.7) versus 19.9 (17.0−22.7) months ($P = 0.26$). Mean (95% CI) survival in the high SFI versus low SFI subgroups was 22.2 (18.6−25.8) versus 20.8 (18.5−23.1) months ($P = 0.48$). Mean (95% CI) survival in the CT-SS 0 versus CT-SS 1 versus CT-SS 2 subgroups was 25.4 (22.8−28.1) versus 18.4 (15.9−20.9) versus 18.4 (15.9−20.9) months ($P < 0.001$, Fig. 2). Mean (95% CI) survival in the mGPS 0 vs. 1 vs. 2 subgroups was 27.2 (24.7−29.8) months versus 24.4 (20.3−28.6) months versus 17.1 (14.5−19.8) months ($P < 0.001$, Fig. 3).

The relationship between baseline clinical characteristics, CT-derived body composition parameters, and mortality in the entire patient cohort is shown in Table II. On univariate analysis, age >75 ($P < 0.01$), CFS >4 ($P < 0.001$), CT-SS (<0.001), and mGPS (<0.001) were associated with increased mortality. On multivariate analysis, CFS >4 (hazard ratio [HR] 2.14, 95% CI 1.25−3.66, $P < 0.01$), CT-SS (HR 1.47, 95% CI 1.03−2.09, $P < 0.05$), and mGPS (HR 1.54, 95% CI 1.11−2.13, $P < 0.01$) were associated with increased mortality.

Table III displays 1-year survival in patients subgrouped by CT-SS, mGPS, and CFS. There were significant trends toward inferior 1-year survival with both increasing CT-SS and mGPS, irrespective of frailty. Patients with CT-SS 0 and CFS ≤4 had 90% (standard error [SE] 5%) 1-year survival, compared with 35% (SE 9%) in patients with CT-SS 2 and CFS >4 ($P < 0.001$). Patients with mGPS 0 and CFS ≤4 had 94% (SE 4%) 1-year survival compared with 44% (SE 6%) in the mGPS 2 and CFS >4 subgroup ($P < 0.001$).

144 patients (79%) underwent inpatient revascularization on the index admission included in the study period. The rate of intervention in patients with CFS ≤4 versus CFS >4 was 75 (86%) versus 69 (73%) ($P < 0.05$). The rate of intervention in patients with CT-SS 0 versus CT-SS 1 versus CT-SS 2 was 45 (80%) versus 69 (86%) versus 26 (62%) ($P < 0.05$). There was no difference in the rate of intervention between mGPS subgroups ($P = 0.81$).

Subgroup analyses were performed on patients presenting without tissue loss ($n = 33$, 18%). There were 15 deaths during the follow-up period in this subgroup. On univariate analyses, CT-SS (HR 2.99, 95% CI 1.40−6.37, $P < 0.01$) and mGPS (HR 2.19, 95% CI 1.10−4.35, $P < 0.05$) were associated with increased mortality, while CFS >4 (HR 2.52, 95% CI 0.85−7.42, $P = 0.09$) was not. The low number of events in this subgroup precluded meaningful multivariate analyses. There was no difference in CT-SS ($P = 0.83$) or mGPS ($P = 0.37$) between patients with tissue loss and those without tissue loss.

The overall 1-year major limb amputation rate in the entire study cohort was 28.4% ($n = 54$). The overall 1-year major limb amputation-free survival in the entire study cohort was 53.2% ($n = 100$). The rate of 1-year major limb amputation-free survival in patients with CFS ≤4 versus CFS >4 was 63.3% versus 32.0% ($P < 0.001$). The rate of 1-year major limb amputation-free survival in patients with CT-SS 0 versus CT-SS 1 versus CT-SS 2 was 69.0% versus 41.5% versus 28.9% ($P < 0.001$). The rate of 1-year major limb amputation-free survival in patients with mGPS 0 versus mGPS 1 versus mGPS was 82.0% versus 64.3% versus 25.7% ($P < 0.001$). On univariate analysis, tissue loss ($P < 0.05$), CFS >4 ($P < 0.001$), CT-SS ($P < 0.001$), and mGPS ($P < 0.001$) were associated with increased odds of limb loss or death at 1 year. On multivariate analysis, CFS >4 (OR 2.80, 95% CI 1.35−5.78, $P < 0.01$) and mGPS (OR 3.36, 95% CI 2.15−5.25, $P < 0.001$) were associated with increased odds of limb loss or death at 1 year.

DISCUSSION

The present study reports for the first time the prognostic value of frailty, CT-derived body composition, and systemic inflammation in a real-world cohort of

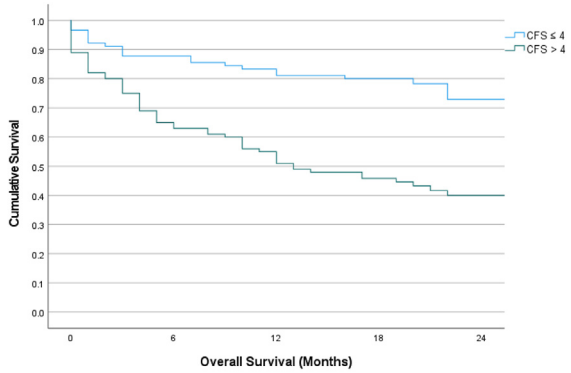
Table I. The association between baseline clinical characteristics, CT-BC parameters, systemic inflammation, and CFS in patients presenting acutely with chronic limb-threatening ischemia

	CFS ≤4 (n = 90)	CFS >4 (n = 100)		Univariate	Multivariate
Covariate	n (%)	n (%)	P	CFS >4	CFS >4
Age ≥75	22 (24%)	56 (56%)	<**0.001**	3.93 2.11−7.33 ***P* < 0.001**	2.21 1.07−4.56 <**0.05**
Female sex	26 (29%)	46 (46%)	<**0.05**	2.10 1.15−3.83 <**0.05**	1.08 0.42−2.82 0.88
BMI ≥25	58 (64%)	57 (57%)	0.30	0.73 0.41−1.31 0.30	-
MUST ≥2	4 (5%)	15 (15%)	<**0.05**	3.80 1.12−11.91 <**0.05**	2.25 0.51−9.92 0.28
ASA >2	64 (74%)	93 (95%)	<**0.001**	6.39 2.30−17.76 <**0.001**	6.83 2.10−22.22 <**0.01**
Tissue loss	72 (81%)	83 (84%)	0.30	1.23 0.57−2.60 0.60	-
High VFI	58 (65%)	41 (42%)	<**0.01**	0.40 0.22−0.72 <**0.01**	0.47 0.19−1.19 0.11
High SFI	24 (28%)	28 (31%)	0.71	1.13 0.59−2.16 0.71	-
CT-SS			<**0.001**		
0	41 (46%)	17 (18%)		2.38	1.88
1	34 (38%)	48 (50%)		1.55−3.64	1.09−3.24
2	14 (16%)	31 (32%)		<**0.001**	<**0.05**
mGPS			<**0.01**		
0	31 (35%)	19 (19%)		1.68	1.35
1	16 (18%)	12 (12%)		1.19−2.36	0.89−2.03
2	41 (47%)	68 (69%)		<**0.01**	0.16

Comparisons between subgroups of CFS performed using linear-by-linear chi-squared analysis. Binary logistic regression results presented as OR; 95% CI; P value. For covariates with >2 subgroups, the first category was considered as the reference category. Bold text denotes statistical significance.

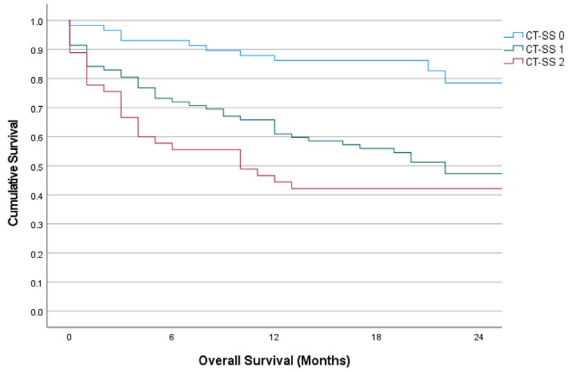
patients presenting with CLTI. Furthermore, we report an association between CFS and CT-SS. CFS, CT-SS, and mGPS were associated with poorer overall survival and limb salvage rates in patients presenting as unscheduled admissions with CLTI. Patients with elevated CFS or CT-SS were less likely to undergo revascularization. Moreover, these findings appear to be independent of disease severity, measured as presenting with or without tissue loss, an important potentially confounding factor in measuring the SIR. The addition of validated measures of tissue loss severity and presence of infection would improve the validity of the present conclusions and is an important area for further investigation.

Frailty assessment as a prognostic factor as well as the endemic nature of frailty in patients with CLTI has been previously reported.[2,27] However, the association with body composition and the prognostic factors evaluated in the present study is a novel finding. The multifactorial etiology of frailty is incompletely understood; however, the association between frailty and activation of the SIR is emerging as an important component.[8,21,28] The lack of association between mGPS and CFS observed in the present study may reflect an underpowered study; however, further investigation is warranted. While CT-SS and mGPS are more resource demanding to quantify than CFS, the independent prognostic value observed suggests a potential role in clinical



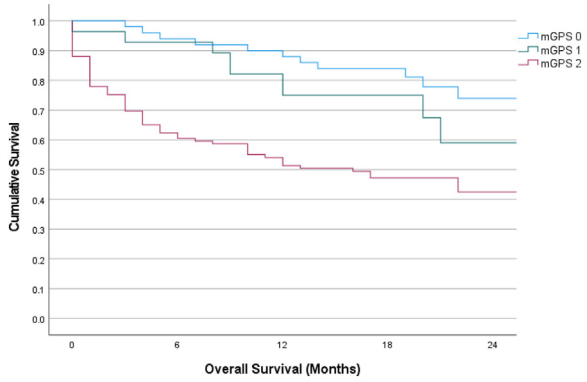
		Interval (Months)				
		0	6	12	18	24
Number at Risk	CFS ≤ 4	90	79	75	60	18
	CFS > 4	100	65	55	41	19

Fig. 1. Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb-threatening ischemia when subgrouped by CFS, $P < 0.001$ (log-rank method).



		Interval (Months)				
		0	6	12	18	24
Number at Risk	CT-SS 0	58	54	51	45	15
	CT-SS 1	82	60	54	40	16
	CT-SS 2	45	26	21	15	6

Fig. 2. Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb-threatening ischemia when subgrouped by CT-SS, $P < 0.001$ (log-rank method).



		Interval (Months)				
		0	6	12	18	24
Number at Risk	mGPS 0	50	47	45	29	11
	mGPS 1	28	26	23	13	5
	mGPS 2	109	68	59	31	8

Fig. 3. Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb-threatening ischemia when subgrouped by mGPS, $P < 0.001$ (log-rank method).

prognostication as part of multimodal assessment. The manual analysis methods used in the present study are time-intensive limiting their utility; instead, automated artificial intelligence-based systems show promise in their application to routine clinical practice.[29]

Identifying a subset of patients with CLTI who are more likely to experience poor prognosis is a key aspect of the management of CLTI; indeed, the recognition of tailored management strategy based on prognosis has been well described for almost 20 years since the landmark bypass versus angioplasty in severe ischaemia of the leg trial,[30] and subsequently supported by other authors. Moreover, the recent best endovascular versus best surgical therapy in patients with CLTI study highlights inferior outcomes in a subgroup of patients, describing differences based on revascularization strategy,[31] complementing our hypothesis of patient-specific prognostic factors. Post hoc analysis of systemic inflammation in the best endovascular versus best surgical therapy in patients with CLTI cohort would be of particular interest and may contribute to our understanding of assessing prognosis in patients with CLTI. Optimal prognostic assessments are likely to be multimodal, and the results of the present study suggest that CFS, CT-SS, and mGPS are potentially useful clinical tools.

While there are prior studies reporting inferior survival and limb salvage rates in sarcopenic patients, there was heterogeneity in the assessment of sarcopenia; Matsubara et al.[10] reported skeletal muscle area without normalization, and Taniguchi et al.[9] reported psoas muscle index (normalized to height^2). Normalization of CT-derived muscle parameters is widely accepted to be the superior technique in patients with cancer, with SMI considered to be the superior parameter for prognostication.[32] The present study attempts to resolve these methodological concerns and provide a uniform framework

Table II. The relationship between baseline clinical characteristics, CT-BC parameters, systemic inflammation, and mortality in patients presenting acutely with chronic limb-threatening ischemia described by cox proportional hazards models ($n = 190$)

		Univariate			Multivariate		
Covariate	*n*	HR	95% CI	*P*	HR	95% CI	*P*
Age (≤75/>75)	112 (59%)/78 (41%)	1.87	1.20−2.92	<**0.01**	1.25	0.78−2.03	0.36
Clinical Frailty Score >4	100 (53%)	3.12	1.89−5.15	<**0.001**	2.14	1.25−3.66	<**0.01**
Female sex	72 (38%)	1.11	0.71−1.75	0.65	-	-	-
BMI (<25/≥25 kg/m^2)	75 (40%)/115 (60%)	0.82	0.53−1.29	0.39	-	-	-
MUST (<2/≥2)	169 (90%)/19 (10%)	2.38	0.51−11.0	0.27	-	-	-
ASA (≤2/>2)	27 (15%)/157 (85%)	1.83	0.84−3.98	0.13	-	-	-
Tissue loss on presentation	155 (82%)	0.96	0.54−1.71	0.88	-	-	-
High VFI	99 (54%)	0.77	0.49−1.21	0.25	-	-	-
High SFI	52 (30%)	0.83	0.49−1.40	0.49	-	-	-
CT-SS (0/1/2)	58 (32%)/82 (44%)/45 (24%)	2.01	1.48−2.74	<**0.001**	1.47	1.03−2.09	<**0.05**
mGPS (0/1/2)	50 (27%)/28 (15%)/109 (58%)	1.92	1.40−2.62	<**0.001**	1.54	1.11−2.13	<**0.01**

HR: hazard ratio describing hazard of all-cause mortality during the follow-up period generated through cox proportional hazards analysis. For covariates with >2 subgroups, the first category was considered as the reference category.
Bold text denotes statistical significance.

Table III. One year survival and standard error in patients presenting acutely with chronic limb-threatening ischemia when subgrouped by CT-BC parameters, mGPS, and CFS

		CFS ≤4		CFS >4	
Covariate	*n*	1 yr OS (% SE)	*n*	1 yr OS (% SE)	*P*
CT-SS 0	41	90% (SE 5%)	17	82% (SE 9%)	0.08
CT-SS 1	34	79% (SE 7%)	48	56% (SE 7%)	<**0.05**
CT-SS 2	14	71% (SE 12%)	31	35% (SE 9%)	0.09
P		<**0.05**		<**0.05**	
mGPS 0	31	94% (SE 4%)	19	84% (SE 8%)	<**0.05**
mGPS 1	16	94% (SE 6%)	12	67% (SE 14%)	<**0.05**
mGPS 2	41	71% (SE 7%)	68	44% (SE 6%)	<**0.05**
P		<**0.05**		<**0.01**	

Bold text denotes statistical significance.
1 yr OS, 1 year overall survival; SE, standard error.

for the future reporting of body composition related prognostication in this patient group. A benefit to the use of CT-SS compared with either SMI or SMD in isolation is the more holistic assessment of sarcopenia, incorporating both muscle mass (SMI) and muscle function (SMD) as per the EWGSOP2 definition of sarcopenia.[4] Loss of skeletal muscle is a key feature of sarcopenia, which has a well-described association with poor prognosis.[33] Sarcopenia is predominantly described in patients with cancer; however, there is an increasing recognition of the prevalence of sarcopenia in a range of chronic conditions.[34]

Chronic inflammation is increasingly being recognized as the key feature in the development of atherosclerosis, though the precise etiopathological mechanisms remain undefined.[35] The present study demonstrated that, even in patients without tissue loss, a baseline elevated magnitude of systemic inflammation conferred inferior prognosis, highlighting a potential clinically relevant target for intervention. The Canakinumab Antiinflammatory Thrombosis Outcome Study trial demonstrated a reduction in cardiovascular events following IL-1β blockade in patients with ischemic heart disease compared with placebo.[36] IL-1β blockade in patients with PAD has been investigated, and an improvement in walking distance has been reported; however, these data are derived from small patient groups and require validation.[37] A key limitation of this therapeutic strategy is the increased risk of significant infection, which was

noted by the Canakinumab Antiinflammatory Thrombosis Outcome Study authors. Further prospective studies are required, in particular in a patient cohort presenting without tissue loss, to evaluate the effect on long-term prognosis as well as limb salvage rates. Moreover, serial inflammatory profiling in this patient cohort may help to clarify the effect that revascularization has on systemic inflammation; if systemic inflammation were to persist despite successful revascularization the rationale for immunomodulation may be strengthened.

Chronic activation of the SIR is associated with sarcopenia, which is also associated with the frailty syndrome.[38] Furthermore, systemic inflammation is also associated with increased fatigue, reduced function, and reduced quality of life in older adults.[39] The majority of studies to date report C-reactive protein levels rather than using the parameters in this study, which provide a more holistic representation of systemic inflammation.[21] Defining the specific relationship between frailty and SIR and the mechanism therein warrants further study and may contribute to the development of novel prognostic scoring systems assessing both frailty and systemic inflammation.

Limitations

In the present study, there were a number of limitations. A relatively small sample size was studied and therefore limits the generalizability of our conclusions. The study is also limited by retrospective single center design. Use of the Society for Vascular Surgery Wound Ischemia and Foot Infection (WIfI[40]) Score may have allowed us to more comprehensively describe the cohort; however, WIfI scores were not available for the majority of patients in the present study. Moreover, adjusting for WIfI scores may be useful in reducing the potential bias introduced by the confounding effect of tissue damage or infection on the SIR. Despite this, the primary outcome of the present study was mortality, and while the association between WIfI and limb salvage appears to be growing, there remain conflicting reports of the association between WIfI and mortality.[41,42] The thresholds of CT-derived body composition parameters were derived from the dataset reported in this study, introducing a potential source of bias, and these thresholds require external validation.

CONCLUSIONS

Frailty assessed by CFS was independently associated with CT-derived body composition. CFS, CT-SS, and mGPS were independently associated with poorer survival in patients presenting as unscheduled admissions with CLTI. Therefore, frailty assessment in these patients should include a measure of the SIR and body composition. Multimodal prognostic assessment including CFS, CT-SS, and mGPS is a potential novel clinical tool.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.avsg.2023.06.012.

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