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The relationship between clinical frailty score, CT-derived body composition, systemic inflammation, and survival in patients with chronic limb threatening ischaemia.

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Abstract

Introduction

Frailty is a chronic condition with complex aetiology and impaired functional performance, which has been associated altered body composition and chronic inflammation. Chronic Limb Threatening Ischaemia (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 centre with CLTI were included over a 12-month period. Frailty was diagnosed using the clinical frailty scale (CFS). Body composition was assessed using CT at the L3 vertebral level (CT-BC) to generate visceral and subcutaneous fat indices (VFI, SFI), skeletal muscle index (SMI), and skeletal muscle density (SMD). SMI and SMD 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 (IQR) follow-up of 22 (6) months (range 15-32 months), and 79 deaths during the follow-up period. 100 patients (53%) had a CFS > 4. CFS > 4 (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 independently associated with increased mortality. CT-SS (OR 1.88, 95% CI 1.09 – 3.24, p < 0.01) was independently associated with CFS > 4. Patients with CT-SS 0 & CFS ≤4 had 90% (SE 5%) 1-year survival, compared with 35% (SE 9%) in patients with CT-SS 2 & CFS >4 (p <0.001). Patients with

mGPS 0 & CFS ≤ 4 had 94% (SE 4%) 1-year survival compared with 44% (SE 6%) in the mGPS 2 & CFS > 4 subgroup (p <0.001).

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

Sarcopenia is characterised 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 CT-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][A]. The effect that body composition has on functional performance, including frailty, has been reported previously[7], though the evidence base in non-cancer patients is limited. The literature describing CT-BC in patients CLTI is limited to small series with heterogenous methodology[8–11], chief of which is a lack of standardised thresholds to determine abnormal CT-BC parameters. Validated CT-BC thresholds have been widely reported in patients with cancer[12], though these have not been widely described in non-cancer populations.

Activation of the systemic inflammatory response (SIR) is an aetiological factor in the development of sarcopenia[4], and has been associated with inferior prognosis in patients with and without cancer[13,14]. 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[15]. 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[16,17]. Furthermore, there appears to be an association between altered CT-BC parameters and activation of the SIR[18,19], though this association is poorly described in non-cancer populations. Finally, an association between clinical frailty and activation of the SIR has been reported[20].

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 & Methods

Patient Selection

This study was a retrospective analysis of a pre-existing prospectively maintained audit database. Consecutive patients presenting as unscheduled admissions with CLTI to a single tertiary vascular centre between January 2020 and June 2021 were prospectively recorded as part of ongoing institutional audit. West of Scotland Research Ethics Committee approval was obtained for the retrospective analysis of this database, which formed the cohort analysed in the present study (Reference 21/WS/0146; approval granted 23/11/2021). 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 (CHI) 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 ASA, which was recorded from operative records and sub-grouped (≤ 2 / > 2) in keeping with previous literature[21]. 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*[22]. CFS ≤4 (considered non-frail) and >4 (considered frail) was used to subgroup patients for comparison, in keeping with widely reported values from other studies, which are used in existing clinical practice[23]. 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)[15], based on the first blood sample taken on unscheduled admission. In order to control for the potentially confounding effect of tissue loss on mGPS, sub-group analyses on patients presenting with no tissue loss were performed. Nutritional state was assessed by Malnutrition Universal Screening Tool (MUST) score, which is routinely collected by nursing staff in NHS Health Boards as part of an admission proforma, with MUST ≥2 consider 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 (VFA), subcutaneous fat area (SFA), skeletal muscle area (SMA), and skeletal muscle density (SMD) were manually measured using the freeware program ImageJ v1.53[24] using muscle tissue thresholds of -29 to + 150 Hounsfield Units (HU), and adipose tissue thresholds of -190 to -30 HU. The areas obtained were normalised 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 normalised. To determine optimal thresholds for dichotomisation 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 selectively excluded if compromise deemed substantial. CT-Sarcopenia Score (CT-SS) was calculated as per McGovern *et al*[25], 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 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 sub-groups, time to event survival data did not reach a median survival, therefore to ensure consistency of reporting throughout, the mean (95% 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. 1-year survival and % standard error were calculated in CFS, CT-Sarcopenia Score, and mGPS subgroups using censored survival data, and absolute differences compared. The predictive value of covariates on CFS (≤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 (IQR) 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 which were used to sub-group patients, and the number within each sub-group, are shown in Supplemental Table 2. Scatter plots of body composition parameters sub-grouped by CFS are shown in Supplemental Figure 1a) and 1b) respectively.

The association between baseline clinicopathological characteristics, CT-derived body composition parameters, mGPS, and CFS > 4 is shown in Table 1. Age ≥ 75 ($p < 0.001$), female sex ($p < 0.05$), MUST ≥ 2 ($p < 0.05$), ASA > 2 ($p < 0.001$), elevated CT-Sarcopenia Score ($p < 0.001$), and elevated mGPS ($p < 0.01$) were all more prevalent in patients with CFS > 4, whilst high VFI ($p < 0.01$) was less prevalent in patients with CFS > 4. On multivariate analysis, age ≥ 75 (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-Sarcopenia Score (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 vs. CFS > 4 subgroups was 25.8 (23.5 – 28.2) vs. 16.8 (14.2 – 19.5) months ($p < 0.001$, Figure 1). Mean (95% CI) survival in the high VFI vs. low VFI subgroups was 22.1 (19.6 – 24.7) vs. 19.9 (17.0 – 22.7) months ($p = 0.26$). Mean (95% CI) survival in the high SFI vs. low SFI subgroups was 22.2 (18.6 – 25.8) vs. 20.8 (18.5 – 23.1) months ($p = 0.48$). Mean (95% CI) survival in the CT-Sarcopenia Score 0 vs. CT-

Sarcopenia Score 1 vs. CT-Sarcopenia Score 2 subgroups was 25.4 (22.8 – 28.1) vs. 18.4 (15.9 – 20.9) vs. 18.4 (15.9 – 20.9) months (p <0.001, Figure 2). Mean (95% CI) survival in the mGPS 0 vs. 1 vs. 2 subgroups was 27.2 (24.7 – 29.8) months vs. 24.4 (20.3 – 28.6) months vs. 17.1 (14.5 – 19.8) months (p < 0.001, figure 3).

The relationship between baseline clinical characteristics, CT-derived body composition parameters, and mortality in the entire patient cohort is shown in Table 2. On univariate analysis, age > 75 (p <0.01), CFS > 4 (p <0.001), CT-Sarcopenia Score (<0.001), and mGPS (<0.001) were associated with increased mortality. On multivariate analysis, CFS > 4 (HR 2.14, 95% CI 1.25 – 3.66, p <0.01), CT-Sarcopenia Score (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 3 displays 1 year survival in patients sub-grouped by CT-Sarcopenia Score, mGPS, and CFS. There were significant trends towards inferior 1 year survival with both increasing CT-SS and mGPS irrespective of frailty. Patients with CT-Sarcopenia Score 0 & CFS ≤4 had 90% (SE 5%) 1-year survival, compared with 35% (SE 9%) in patients with CT-Sarcopenia Score 2 & CFS >4 (p <0.001). Patients with mGPS 0 & CFS ≤ 4 had 94% (SE 4%) 1-year survival compared with 44% (SE 6%) in the mGPS 2 & CFS > 4 subgroup (p <0.001).

144 patients (79%) underwent inpatient revascularisation on the index admission included in the study period. The rate of intervention in patients with CFS ≤ 4 vs. CFS > 4 was 75 (86%) vs. 69 (73%) (p < 0.05). The rate of intervention in patients with CT-Sarcopenia Score 0 vs. CT-Sarcopenia Score 1 vs. CT-Sarcopenia Score 2 was 45 (80%) vs. 69 (86%) vs. 26 (62%) (p < 0.05). There was no difference in the rate of intervention between mGPS sub-groups (p = 0.81).

Sub-group analyses were performed on patients presenting without tissue loss (n = 33, 18%). There were 15 deaths during the follow-up period in this sub-group. On univariate analyses CT-Sarcopenia Score (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, whilst CFS > 4 (HR 2.52, 95% CI 0.85 – 7.42, p =0.09) was not. The low number of events in this sub-group precluded meaningful multivariate analyses. There was no difference in CT-Sarcopenia Score (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 vs. CFS > 4 was 63.3% vs. 32.0% (p < 0.001). The rate of 1-year major limb amputation-free survival in patients with CT-Sarcopenia Score 0 vs. CT-Sarcopenia Score 1 vs. CT-Sarcopenia Score 2 was 69.0% vs. 41.5% vs. 28.9% (p < 0.001). The rate of 1-year major limb amputation-free survival in patients with mGPS 0 vs. mGPS 1 vs. mGPS was 82.0% vs. 64.3% vs. 25.7% (p < 0.001). On univariate analysis, tissue loss (p < 0.05), CFS > 4 (p < 0.001), CT-Sarcopenia Score (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 patients presenting with CLTI. Furthermore, we report an association between CFS and CT-Sarcopenia Score. CFS, CT-Sarcopenia Score, 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-Sarcopenia Score were less likely to undergo revascularisation. 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 systemic inflammatory response. 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[2,26]. However, the association with body composition, and the prognostic factors evaluated in the present study, is a novel finding. The multifactorial aetiology of frailty is incompletely understood, however the association between frailty and activation of the systemic inflammatory response is emerging as an important component[7,20,27]. The lack of association between mGPS and CFS observed in the present study may reflect an underpowered study, however further investigation is warranted. Whilst CT-Sarcopenia Score and mGPS are more resource demanding to quantify than CFS, the independent prognostic value observed suggests a potential role in clinical 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[28].

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 BASIL trial[29], and subsequently supported by other authors. Moreover, the recent BEST-CLI study highlights inferior outcomes in a sub-group of patients, describing differences based on revascularisation strategy[30], complementing our hypothesis of patient-specific prognostic factors. Post-hoc analysis of systemic inflammation in the BEST-CLI 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-Sarcopenia Score, and mGPS are potentially useful clinical tools.

Whilst 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*[9] reported skeletal muscle area without normalisation, and Taniguchi *et al*[8] report psoas muscle index (normalised to height^2). Normalisation 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 [31]. The present study attempts to resolve these methodological concerns and provide a uniform framework for the future reporting of body composition related prognostication in this patient group. A benefit to the use of CT-Sarcopenia Score 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[32]. 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[33].

Chronic inflammation is increasingly being recognised as the key feature in the development of atherosclerosis, though the precise aetiopathological mechanisms remain undefined[34]. 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 CANTOS trial demonstrated a reduction in cardiovascular events following IL-1β blockade in patients with ischaemic heart disease compared with placebo[35]. IL-1β blockade in patients with PAD has been investigated, and an improvement in walking distance reported, however these data are derived from small patient groups and require validation[36]. A key limitation of this therapeutic strategy is the increased risk of significant infection, which was noted by the CANTOS 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 revascularisation has on systemic inflammation; if systemic inflammation were to persist despite successful revascularisation the rationale for immunomodulation may be strengthened.

Chronic activation of the SIR is associated with sarcopenia, which is also associated with the frailty syndrome[37]. Furthermore, systemic inflammation is also associated with increasing fatigue, reduced function, and reduced quality of life in older adults[38]. The majority of studies to date report CRP levels rather than using the parameters in this study which provide a more holistic representation of systemic inflammation[39]. 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 generalisability of our conclusions. The study is also limited by retrospective single centre design. Use of the Society for Vascular Surgery Wound Ischaemia and Foot Infection (WIfI[40]) Score may have allowed for 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 through the confounding effect of tissue damage or infection on the systemic inflammatory response. Despite this, the primary outcome of the present study was mortality, and whilst 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-Sarcopenia Score, 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 systemic inflammatory response and body composition. Multimodal prognostic assessment including CFS, CT-Sarcopenia Score, and mGPS is a potential novel clinical tool.

392 **Figure Legends**

393 Figure 1: Kaplan-Meier survival plots and life table in patients presenting acutely with
394 chronic limb threatening ischaemia when sub-grouped by CFS, $p < 0.001$(log-rank method).

395 Figure 2: Kaplan-Meier survival plots and life table in patients presenting acutely with
396 chronic limb threatening ischaemia when sub-grouped by CT-SS, $p < 0.001$(log-rank
397 method).

398 Figure 3: Kaplan-Meier survival plots and life table in patients presenting acutely with
399 chronic limb threatening ischaemia when sub-grouped by mGPS, $p < 0.001$(log-rank
400 method).

401 Supplemental Figure 1: Scatter plots of a). SFI (cm^2/m^2) vs. VFI (cm^2/m^2) and b). SMI
402 (cm^2/m^2) vs. SMD (HU) in patients presenting acutely with chronic limb threatening
403 ischaemia, sub-grouped by CFS.

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References

1. Xue QL. The Frailty Syndrome: Definition and Natural History. *Clin Geriatr Med* 2011; 27: 1.

2. Houghton JSM, Nickinson ATO, Morton AJ, et al. Frailty Factors and Outcomes in Vascular Surgery Patients: A Systematic Review and Meta-analysis. *Ann Surg* 2020; 272: 266–276.

3. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg* 2019; 69: 3S-125S.e40.

4. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: Revised European consensus on definition and diagnosis. *Age and Ageing*. Epub ahead of print 2019. DOI: 10.1093/ageing/afy169.

5. McGovern J, Dolan RD, Horgan PG, et al. Computed tomography-defined low skeletal muscle index and density in cancer patients: observations from a systematic review. *J Cachexia Sarcopenia Muscle* 2021; 12: 1408–1417.

6. Bradley NA, Roxburgh CSD, McMillan DC, et al. The relationship between pre-operative psoas and skeletal muscle parameters and survival following endovascular aneurysm repair: a systematic review and meta-analysis. *Sci Reports 2022 121* 2022; 12: 1–10.

7. McGovern J, Al-Azzawi Y, Kemp O, et al. The relationship between frailty, nutritional status, co-morbidity, CT-body composition and systemic inflammation in patients with COVID-19. *J Transl Med*; 20. Epub ahead of print 1 December 2022. DOI: 10.1186/S12967-022-03300-2.

8. Taniguchi R, Deguchi J, Hashimoto T, et al. Sarcopenia as a Possible Negative Predictor of Limb Salvage in Patients with Chronic Limb-Threatening Ischemia. *Ann Vasc Dis* 2019; 12: 194–199.

9. Matsubara Y, T M, Y A, et al. Sarcopenia is a prognostic factor for overall survival in patients with critical limb ischemia. *J Vasc Surg* 2015; 61: 945–950.

10. Ferreira J, Carneiro A, Vila I, et al. Inflammation and Loss of Skeletal Muscle Mass in Chronic Limb Threatening Ischemia. *Ann Vasc Surg*. Epub ahead of print 2022. DOI: 10.1016/J.AVSG.2022.07.009.

11. Pizzimenti M, Charles AL, Riou M, et al. Usefulness of Platelet-to-Lymphocyte Ratio as a Marker of Sarcopenia for Critical Limb Threatening Ischemia. *Ann Vasc Surg* 2021; 72: 72–78.

12. Martin L, Birdsell L, MacDonald N, et al. Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013; 31: 1539–1547.

13. Golder AM, McMillan DC, Park JH, et al. The prognostic value of combined measures of the systemic inflammatory response in patients with colon cancer: an analysis of 1700 patients. *Br J Cancer* 2021; 124: 1828–1835.

14. Bradley NA, Walter A, Wilson A, et al. The prognostic value of pre-operative systemic inflammation-based scoring in patients undergoing endovascular repair of AAA. *J Vasc Surg*. Epub ahead of print April 2023. DOI: 10.1016/J.JVS.2023.04.018.

15. Proctor MJ, Morrison DS, Talwar D, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. *Br J Cancer* 2011; 104: 726.

16. Bath J, Smith JB, Kruse RL, et al. Neutrophil-lymphocyte ratio predicts disease severity and outcome after lower extremity procedures. *J Vasc Surg* 2020; 72: 622–631.

17. González-Fajardo JA, Brizuela-Sanz JA, Aguirre-Gervás B, et al. Prognostic significance of an elevated neutrophil-lymphocyte ratio in the amputation-free survival of patients with chronic critical limb ischemia. *Ann Vasc Surg* 2014; 28: 999–1004.

18. Dolan RD, Almasaudi AS, Dieu LB, et al. The relationship between computed tomography-derived body composition, systemic inflammatory response, and survival in patients undergoing surgery for colorectal cancer. *J Cachexia Sarcopenia Muscle* 2019; 10: 111–122.

19. Golder AM, Sin LKE, Alani F, et al. The relationship between the mode of presentation, CT-derived body composition, systemic inflammatory grade and survival in colon cancer. *J Cachexia Sarcopenia Muscle*. Epub ahead of print 2022. DOI: 10.1002/JCSM.13097.

20. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis. *Ageing Res Rev* 2016; 31: 1–8.

21. Hackett NJ, De Oliveira GS, Jain UK, et al. ASA class is a reliable independent predictor of medical complications and mortality following surgery. *Int J Surg* 2015; 18: 184–190.

22. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173: 489–495.

23. Church S, Rogers E, Rockwood K, et al. A scoping review of the Clinical Frailty Scale. *BMC Geriatr* 2020; 20: 1–18.

24. Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods 2012 97* 2012; 9: 671–675.

25. McGovern J, Golder AM, Dolan RD, et al. The combination of computed tomography-derived muscle mass and muscle density and relationship with clinicopathological characteristics and survival in patients undergoing potentially curative surgery for colorectal cancer. *JCSM Clin Reports* 2022; 7: 65–76.

26. Takeji Y, Yamaji K, Tomoi Y, et al. Impact of Frailty on Clinical Outcomes in Patients With Critical Limb Ischemia. *Circ Cardiovasc Interv*; 11. Epub ahead of print 2018. DOI: 10.1161/CIRCINTERVENTIONS.118.006778.

27. McKechnie DGJ, AO P, LT L, et al. Associations between inflammation, cardiovascular biomarkers and incident frailty: the British Regional Heart Study. *Age Ageing*. Epub ahead of print 10 July 2021. DOI: 10.1093/AGEING/AFAB143.

28. Bates DDB, Pickhardt PJ. CT-Derived Body Composition Assessment as a Prognostic Tool in Oncologic Patients: From Opportunistic Research to Artificial Intelligence-Based Clinical Implementation. *AJR Am J Roentgenol* 2022; 219: 671–680.

29. Bradbury AW, Adam DJ, Beard JD, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet (London, England)* 2005; 366: 1925–1934.

30. Farber A, Menard MT, Conte MS, et al. Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia. *N Engl J Med* 2022; 387: 2305–2316.

31. Abbass T, Dolan RD, McMillan DC. Computed tomography-derived body composition analysis in patients with advanced cancer: clinical utility and future research. *Current opinion in supportive and palliative care*. Epub ahead of print 2020.

DOI: 10.1097/SPC.0000000000000529.

32. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011; 12: 489–495.

33. Muscaritoli M, Anker SD, Argilés J, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) 'cachexia-anorexia in chronic wasting diseases' and 'nutrition in geriatrics'. *Clin Nutr* 2010; 29: 154–159.

34. Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol*; 47. Epub ahead of print 18 April 2006. DOI: 10.1016/J.JACC.2005.09.068.

35. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2017; 377: 1119–1131.

36. Russell KS, Yates DP, Kramer CM, et al. A randomized, placebo-controlled trial of canakinumab in patients with peripheral artery disease. *Vasc Med* 2019; 24: 414–421.

37. Schaap LA, Pluijm SMF, Deeg DJH, et al. Inflammatory Markers and Loss of Muscle Mass (Sarcopenia) and Strength. *Am J Med* 2006; 119: 526.e9-526.e17.

38. De Almeida Roediger M, De Fátima Nunes Marucci M, Duim EL, et al. Inflammation and quality of life in later life: findings from the health, well-being and aging study (SABE). *Health Qual Life Outcomes*; 17. Epub ahead of print 6 February 2019. DOI: 10.1186/S12955-019-1092-2.

39. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis. *Ageing Res Rev* 2016; 31: 1–8.

40. Mills JL, Conte MS, Armstrong DG, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound,

ischemia, and foot infection (WIfI). *J Vasc Surg*; 59. Epub ahead of print 2014. DOI: 10.1016/J.JVS.2013.08.003.

41. Darling JD, McCallum JC, Soden PA, et al. Predictive Ability of the SVS WIfI Classification System Following Infrapopliteal Endovascular Interventions for CLI. *J Vasc Surg* 2016; 64: 616.

42. Robinson WP, Loretz L, Hanesian C, et al. Society for Vascular Surgery Wound, Ischemia, foot Infection (WIfI) score correlates with the intensity of multimodal limb treatment and patient-centered outcomes in patients with threatened limbs managed in a limb preservation center. *J Vasc Surg* 2017; 66: 488-498.e2.

References in press

A. Evaluation of the prognostic value of CT-derived body composition in patients undergoing endovascular aneurysm repair. Bradley et al, 2023 (ahead of print; accepted by Journal Cachexia Sarcopenia & Muscle 24/04/23).

551 **Table 1:** The association between baseline clinical characteristics, CT-BC parameters, systemic

552 inflammation, and CFS in patients presenting acutely with chronic limb threatening ischaemia.

	CFS ≤4 (n = 90)	**CFS >4 (n = 100)**		**Univariate**	**Multivariate**
	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	41 (46%)	17 (18%)	**<0.001**	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	31 (35%)	19 (19%)	**<0.01**	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 sub-groups 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.					

564 **Table 2:** The relationship between baseline clinical characteristics, CT-BC parameters, systemic
565 inflammation, and mortality in patients presenting acutely with chronic limb threatening ischaemia
566 described by cox proportional hazards models (n=190).

		Univariate			Multivariate		
	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.

583 **Table 3:** 1 year survival and standard error in patients presenting acutely with chronic limb
584 threatening ischaemia when sub-grouped by CT-BC parameters, mGPS, and CFS.

		CFS ≤ 4		**CFS > 4**	
	n	1yr OS (%SE)	n	1yr OS (%SE)	
CT-SS 0	41	90% (SE 5%)	17	82% (SE 9%)	$p = 0.08$
CT-SS 1	34	79% (SE 7%)	48	56% (SE 7%)	$\mathbf{p < 0.05}$
CT-SS 2	14	71% (SE 12%)	31	35% (SE 9%)	$p = 0.09$
		$\mathbf{p < 0.05}$		$\mathbf{p < 0.05}$	
mGPS 0	31	94% (SE 4%)	19	84% (SE 8%)	$\mathbf{p < 0.05}$
mGPS 1	16	94% (SE 6%)	12	67% (SE 14%)	$\mathbf{p < 0.05}$
mGPS 2	41	71% (SE 7%)	68	44% (SE 6%)	$\mathbf{p < 0.05}$
		$\mathbf{p < 0.05}$		$\mathbf{p < 0.01}$	
*1yr OS; 1 year overall survival. SE; standard error.					

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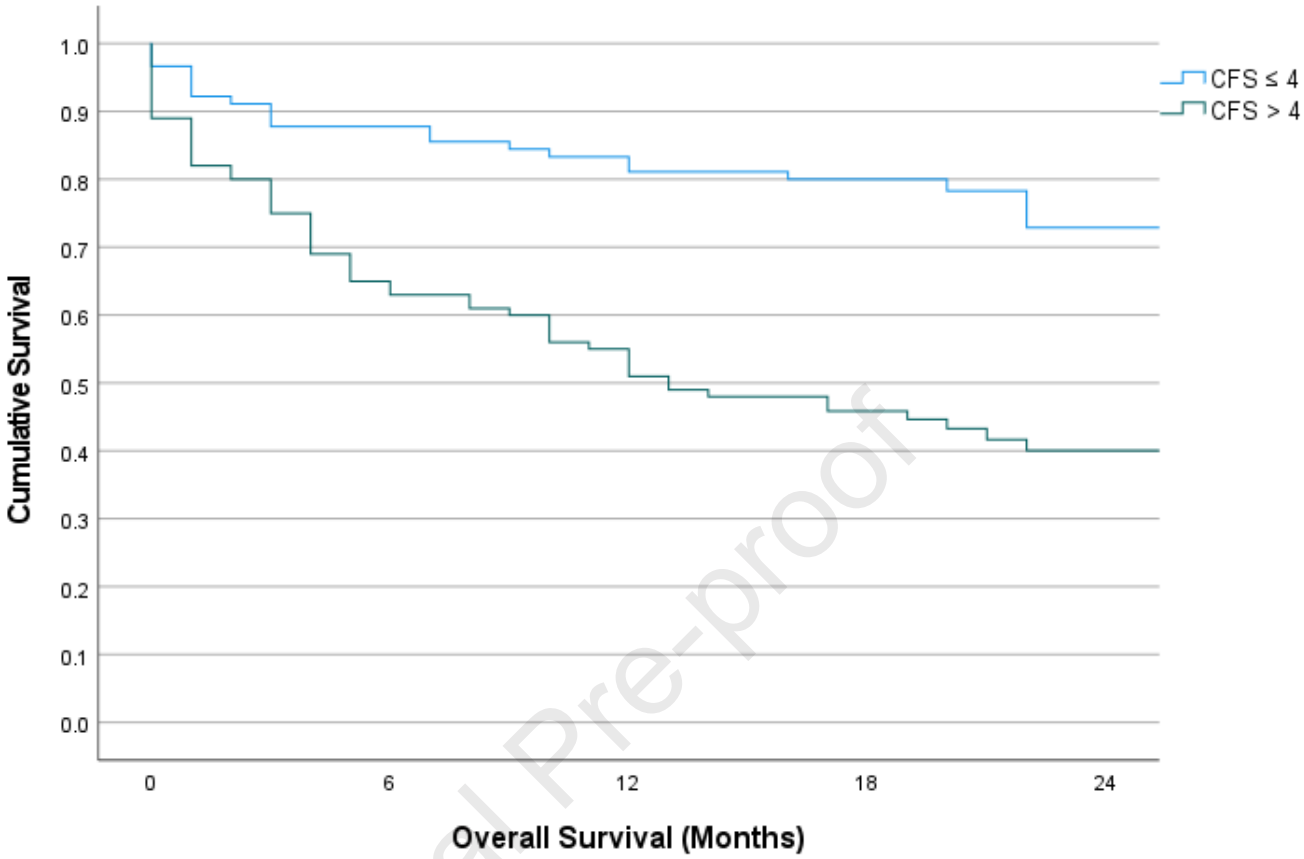
Supplemental Table 1: Calculation of the modified Glasgow Prognostic Score

Modified Glasgow Prognostic Score (mGPS)		
CRP ≤ 10 mg/L	Albumin ≥ 35 g/L	mGPS 0
CRP ≤ 10 mg/L	Albumin < 35 g/L	mGPS 0
CRP > 10 mg/L	Albumin ≥ 35 g/L	mGPS 1
CRP > 10 mg/L	Albumin < 35 g/L	mGPS 2

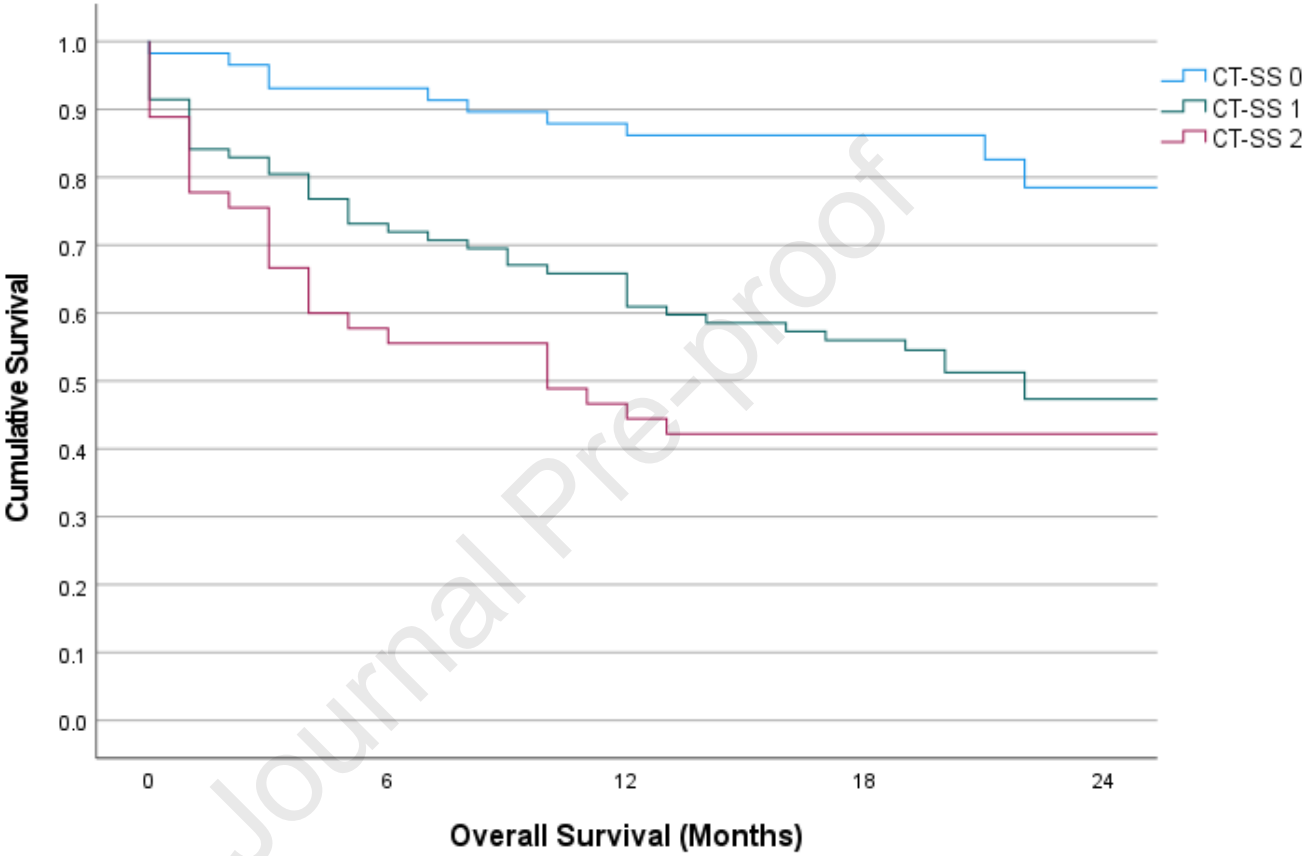
Supplemental Table 2: Classification of abnormal CT-derived body composition and number in each sub-group in a cohort of patients presenting acutely with chronic limb threatening ischaemia.

High visceral fat index (VFI)		**N (%)**
Males	>40cm^2/m^2	91 (78%)
Females	>114cm^2/m^2	8 (12%)
	Total	99 (54%)
High subcutaneous fat index (SFI)		
Males	>80cm^2/m^2	22 (20%)
Females	>103cm^2/m^2	30 (46%)
	Total	52 (30%)
Low skeletal muscle index (SMI)		
Males	<40cm^2/m^2	26 (22%)
Females	<41cm^2/m^2	31 (45%)
	Total	57 (31%)
Low skeletal muscle density (SMD)		
Males	<37 HU	69 (60%)
Females	<37 HU	46 (67%)
	Total	115 (62%)
CT-Sarcopenia Score (CT-SS)		
CT-SS 0	High SMI & High SMD	58 (32%)
CT-SS 1	Low SMI & High SMD OR High SMI & Low SMD	82 (44%)
CT-SS 2	Low SMI & Low SMD	45 (24%)



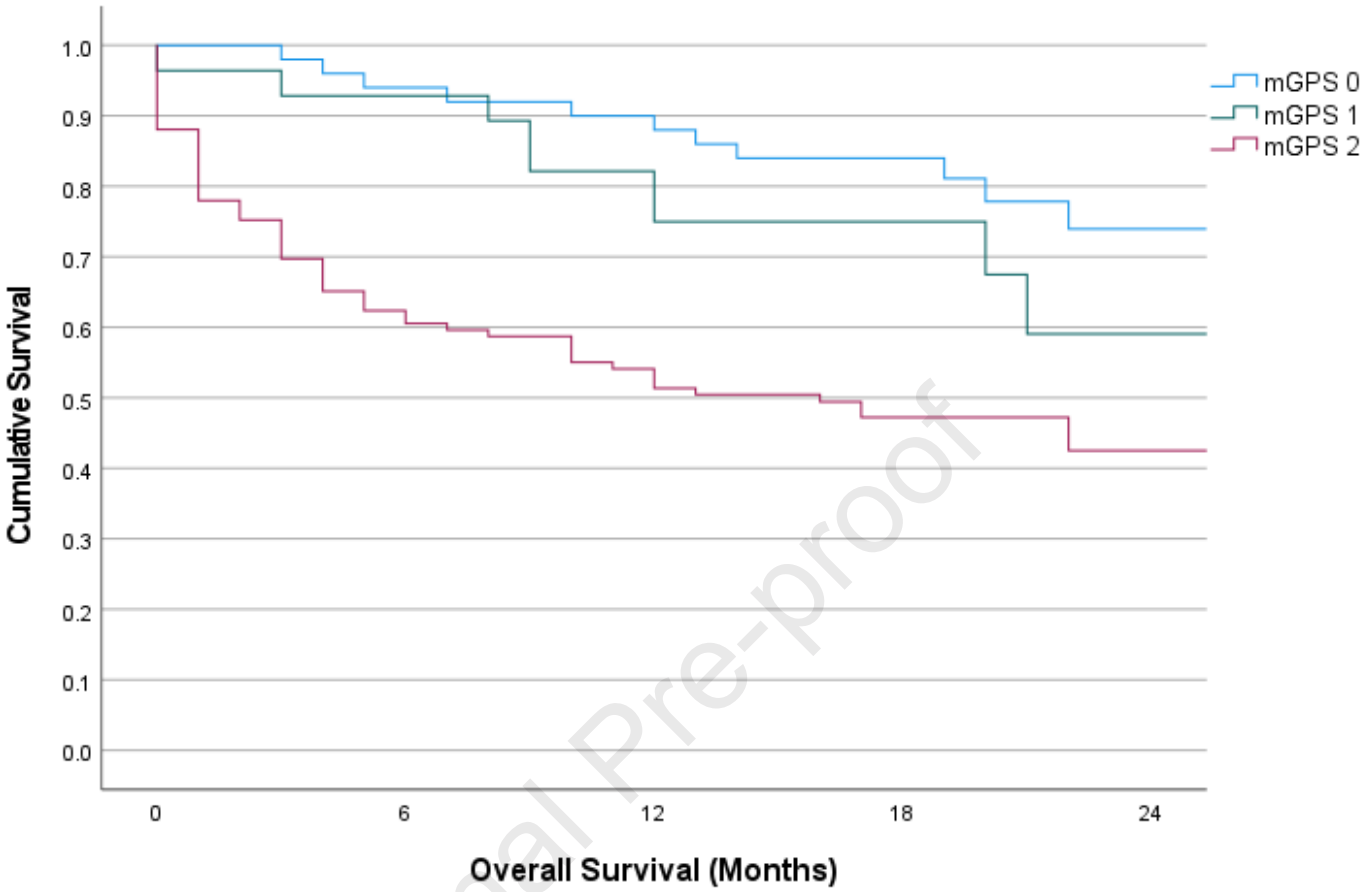
		Interval (Months)				
		0	**6**	**12**	**18**	**24**
Number at Risk	**CFS ≤ 4**	90	79	75	60	18
	CFS > 4	100	65	55	41	19

Figure 1: Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped 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

Figure 2: Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped 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

Figure 3: Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped by mGPS, $p < 0.001$(log-rank method).