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The prevalence and prognostic significance of Sarcopenia and Adipopenia in Pleural Mesothelioma

Andrew C. Kidd [a,b], Gordon W. Cowell [b,c], Geoffrey A. Martin [a], Jenny Ferguson [a], Dean A. Fennell [d], Matt Evison [e,f], Kevin G. Blyth [a,b,*]

[a] Glasgow Pleural Disease Unit, Queen Elizabeth University Hospital, Glasgow, UK
[b] School of Cancer Sciences, University of Glasgow, UK
[c] Department of Radiology, Queen Elizabeth University Hospital, Glasgow, UK
[d] University of Leicester, UK
[e] Wythenshawe Hospital, Manchester, UK
[f] Manchester Academic Health Science Centre (MAHSC), Faculty of Biology, Medicine & Health, University of Manchester, UK

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ABSTRACT

Introduction: Altered body composition is associated with adverse survival in multiple cancers. We determined the prevalence, prognostic significance and clinicopathological correlates of sarcopenia and adipopenia in Pleural Mesothelioma (PM) patients receiving chemotherapy.

Methods: We performed a multi-centre retrospective cohort study. Clinical data and CT images were retrieved for 111 patients from 4 UK centres. Skeletal muscle (at L3 and T4) and fat tissue areas (at L3 only) were measured on pre- and post-chemotherapy CT scans (ImageJ software) and normalised for height. Pre-chemotherapy sarcopenia and adipopenia were defined using validated thresholds, where available or indices <25th percentile. Muscle/fat loss were defined by < 0 % change (%Δ) between CT scans. Extreme muscle/fat loss were defined by <25th percentile of %Δ. Overall survival associations were evaluated using Kaplan–Meier methodology ± Cox proportional hazards models.

Results: T4 and L3 measurements were possible in 111/111 and 91/111 (82 %). L3 sarcopenia was observed at baseline in 35 % (32/91); all other features were observed in 25 % at baseline, as defined a priori. Body composition changes during chemotherapy were heterogeneous. Overall, 61.5 % and 53.1 % patients lost muscle at L3 and T4. 60.4 % lost fat (at L3 only). Extreme T4 muscle loss and total fat loss were independently prognostic (HR 2.99, $p < 0.001$; HR 1.92, $p = 0.014$). Pre-chemotherapy T4 muscle indices were inversely associated with age. No associations were observed with tumour volume, histology, weight, inflammatory markers.

Conclusion: T4 muscle indices were feasible in all cases and outperformed L3 values in prognostication. Extreme T4 muscle and total fat loss were independently prognostic.

Introduction

Pleural mesothelioma (PM) is an uncommon malignancy causally linked to prior asbestos exposure in most patients. The survival benefit from the available treatment options is limited, and most patients are offered palliative systemic therapy or symptom-directed treatment not involving cancer drugs. A small proportion are considered for radical surgery, while others may be offered a clinical trial, most frequently in the second-line setting. For nearly two decades, platinum/pemetrexed was the only licensed first-line systemic therapy [1], but <50 % of eligible patients received this in many regions, reflecting low activity (objective response being 21–24 % in large series) [2], the lack of a reliable predictive biomarker and resultant concerns regarding adverse quality of life and uncertain benefit. The recent licensing of first-line combination immune checkpoint inhibitor therapy (ipilimumab and nivolumab) [3] affords new opportunities for PM patients but treatment planning remains difficult, placing a premium on new predictive and prognostic biomarkers. These would be particularly valuable if associated with actionable mechanisms that might improve tolerance to cancer therapies or outcomes independently.

* Corresponding author at: Professor of Respiratory Medicine and Honorary Consultant Respiratory Physician, School of Cancer Sciences, University of Glasgow, Wolfson Wohl Cancer Research Centre, Switchback Rd, Glasgow, G61 1BD, UK.
E-mail address: kevin.blyth@glasgow.ac.uk (K.G. Blyth).

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Altered body composition is common in cancer, including sarcopenia and adipopenia [4,5], which are characterised by loss of skeletal muscle and adipose tissue mass, respectively. The 'cancer cachexia syndrome' also includes anorexia, weight loss and catabolism [6]. Sarcopenia has previously been associated with increased chemotherapy-related toxicity and poorer overall survival (OS) in non-PM cancers [7]. In PM, recent studies report an association between sarcopenia and adverse survival following surgical resection [8,9]. Muscle loss also appears prevalent at diagnosis in patients with poor performance status (PS) not receiving active therapy, in whom further muscle loss is associated with adverse survival [10,11]. However, these data were based on dual-energy X-ray absorptiometry (DEXA), precluding direct translation to the clinic, and it is unclear if similar associations apply to fitter patients receiving active therapy.

We performed the current study to establish the prevalence, associated features and prognostic significance of altered body composition in PM patients receiving chemotherapy. Our data are based on routinely collected Computed Tomography (CT) imaging, providing an opportunity for rapid translation to clinical practice. We measured skeletal muscle indices at two levels: the third lumbar vertebra (L3) and the fourth thoracic vertebra (T4). Although L3 measures are well validated in other cancers, and are strongly associated with adverse survival [12], L3 is not always included on thoracic CT for PM. T4 data were therefore computed as a universally available alternative. We also performed adiposity measurements at L3, but not at T4, where adipose tissue volumes are low, and interpretation is confounded by sex-specific differences related to breast tissue.

Methods

Study design and objectives

This was a multicentre retrospective cohort study. The primary objective was to determine the prevalence of sarcopenia at L3 and T4, and the prevalence of adipopenia at L3 only. Our secondary objectives were:

(1) to identify clinical or demographic features associated with sarcopenia or adipopenia, including primary tumour volume, histological subtype and measures of systemic inflammation.
(2) to identify any association between sarcopenia and adipopenia, either present at baseline or developing during chemotherapy, and subsequent overall survival (OS).
(3) to describe the reproducibility of the body composition measurements deployed.

The study protocol was granted ethical approval via the NHS Greater Glasgow and Clyde (NHSGGC) Safe Haven (Ref: GSH/18/ON/001).

Study population

Study participants were identified retrospectively in 3 UK centres (Glasgow, Wythenshawe and Leicester). All had received chemotherapy for PM between January 2008 and December 2018 and met the following inclusion criteria: [1] histological diagnosis of PM [2] prior treatment with Cisplatin (or Carboplatin)-Pemetrexed [3] baseline CT images available [4] valid response assessment CT images available. The latter was defined as a venous-phase contrast-enhanced CT acquired ≥ 4 weeks after the first chemotherapy cycle. Cases were excluded if pre-chemotherapy height and weight were not available. Cases were excluded from L3 analyses if this level was not identifiable at both CT timepoints.

Clinical data

Clinical data were retrieved retrospectively from electronic hospital records (EHR), including demographics, histological subtype, ECOG PS, clinical disease stage (TNM v8 [13]), as recorded by specialist mesothelioma multi-disciplinary teams (MDTs) comprising Thoracic Surgeons, Thoracic Radiologists, Respiratory Physicians, Thoracic Oncologists and Palliative Care Physicians at each site, and pre-chemotherapy blood results (lymphocyte, neutrophil and platelet counts, C-reactive protein (CRP), albumin). Neutrophil:lymphocyte and platelet:lymphocyte ratios (NLR and PLR) were computed and recorded. Where PS was not recorded, this was retrieved or inferred from EHR data. Body mass index (BMI (m^2)) was calculated and categorised using standard definitions [14]. Pre-chemotherapy tumour volume was measured by ACK using manual annotation of CT images as previously reported [15]. Chemotherapy response was classified using modified Response Evaluation Criteria in Solid Tumours (mRECIST) version 1.1 criteria [16] by an expert PM thoracic radiologist (GWC).

Body Composition Analyses

Cases were included in L3 analyses if this level was visible in the CT data. ACK used a track-ball mouse and cursor to delineate skeletal muscle (L3 and T4) and adipose tissue areas (L3 only), both in cm^2, using ImageJ software (NIH, Bethesda, USA), see Fig. 1. This method used established Hounsfield unit (HU) thresholds for each compartment (skeletal muscle: -29 to +150 HU; adipose tissue: -190 to -30 HU) [17]. Outputs were normalised for height squared (m^2) and reported as indices in cm^2/m^2, i.e., L3 and T4 skeletal muscle index (L3SMI & T4SMI) and total fat index (TFI) at L3 only. TFI was subsequently dichotomised into subcutaneous fat index (SFI) and visceral fat index (VFI). SFI defines fat between the skin and external musculature, while VFI defines fat between external and internal muscle compartments. T4SMI was also dichotomised, either side of a straight line drawn between mid-vertebral body and mid-sternum, into ipsilateral SMI (iT4SMI; on the same side as the primary tumour) and contralateral T4SMI (cT4SMI).

Statistical analysis

Due to the exploratory design, no sample size calculation was performed. Data are reported as median [IQR], based on non-normal distribution. Fisher's exact test was used for categorical comparisons. For paired observations, the Wilcoxon signed rank test was used. For unpaired comparisons, the Mann–Whitney U test was used. Spearman's correlation was used, with Bonferroni's correction for multiple comparisons ($p < 0.003$ was considered significant in correlation matrix heatmaps ($p < 0.05/16$ comparisons)). OS was recorded from the date of pre-chemotherapy CT to death from any cause. Univariate survival associations were tested using Kaplan–Meier method and the log-rank test. Continuous baseline factors (e.g., age) were dichotomised based on the median value. Univariate p-values <0.1 were considered potentially associated with OS; but only $p < 0.05$ were included in subsequent Cox proportional hazards multivariable models, after testing for collinearity. Inter-/intra-observer reproducibility were quantified by intra-class correlation coefficient (ICC), based on review of 35 randomly selected cases by second investigators (GAM for L3; JF for T4) and re-annotation by ACK 3 weeks after first annotation.

Definition of Sarcopenia and Adipopenia

Baseline

Sarcopenia at L3 was defined using cut points established in other cancers [18]: L3SMI <41 cm^2/m^2 in females; < 53 cm^2/m^2 in males if BMI $\geq$ 25, or <43 cm^2/m^2 if BMI <25. In the absence of validated definitions for other measurements, sarcopenia or adipopenia were defined *a priori* as T4SMI, iT4SMI, TFI, SFI or VFI 1 standard deviation below the mean value, or <25th percentile, depending on distribution.

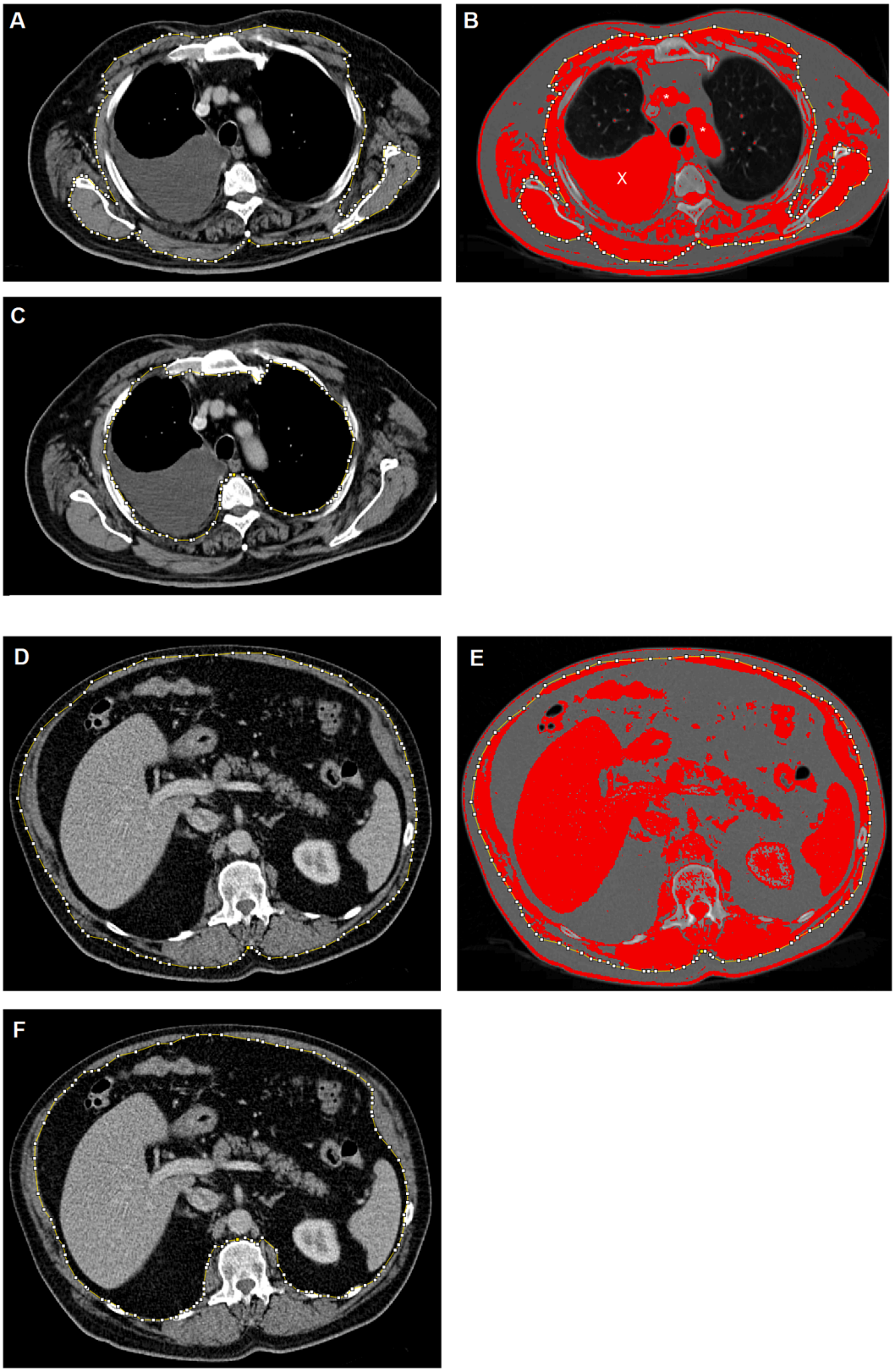

Fig. 1. Axial slices of CT scans demonstrating fourth thoracic vertebra (T4, Panels A-C) and third lumbar vertebra (L3, Panels D-F), on ImageJ software. Panels A and D show the anatomical CT images with the external skeletal muscle area delineated by the yellow dotted line. Panels B and E show the ImageJ output at the same level with tissues in the skeletal muscle threshold selection range (HU range, -29 to +150 HU) highlighted in red; note this includes non-muscle regions including pleural effusion (X) and vasculature (*). Panels C and F show the internal skeletal muscle area delineated by the green dashed line on the same anatomical CT images. The SMA (m^2) at each level was derived by measuring the area of tissue within the skeletal muscle HU thresholds located between the external (yellow) and internal (green) areas.

Muscle and fat loss during chemotherapy

The percentage change (%Δ) in L3SMI, T4SMI, iT4SM, TFI, SFI, VFI during chemotherapy were computed as: ([response assessment area-baseline area/baseline area] x 100[%]). This allowed cases to be classified into those exhibiting muscle and fat loss (TFI, SFI and VFI loss), each defined as %Δ <0 %. *Post hoc* analyses were also performed in cases with extreme muscle or fat loss (TFI, SFI and VFI loss), which was defined as %Δ 1 standard deviation below the mean %Δ value for normally distributed values, or %Δ ≤25th percentile of the cohort if non-normally distributed.

Results

Study population

111 cases met all eligibility criteria (see Supplementary Figure 1). All were included in T4 analyses; 91/111 (82 %) were included in L3 analyses, based on visible L3 on CT. Baseline clinical characteristics are summarised in Table 1 and were similar in the T4 subset (see Supplementary Table 1). Most cases had epithelioid histology (81 %), were male (82 %) with good PS (0–1 in 76 %). The median pre-chemotherapy tumour volume was 377 [IQR 279–524] cm^3. By mRECIST criteria, 32/111 (29 %) had a partial response (PR) to chemotherapy, 27/111 (24 %) had progressive disease (PD) and 45/111 (41 %) had stable disease (SD).

Skeletal muscle indices and prevalence of Sarcopenia

L3

The prevalence of L3 sarcopenia was 35 % (32/91) at baseline and 48 % (44/91) during chemotherapy, $p = 0.071$. L3SMI fell in 56/91 (61.5 %) patients, although there was marked heterogeneity between cases (see Fig. 2A). Despite this variation, baseline median L3SMI fell from 50.5 [44.0–57.8] to 47.0 [42.0–57.0] cm^2/m^2 during chemotherapy, $p = 0.0009$.

T4

T4 muscle indices were non-normally distributed, therefore T4 sarcopenia was defined a priori as T4SMI <25th percentile of the baseline and post-chemotherapy datasets. The prevalence of T4 sarcopenia was therefore 25 % at both timepoints. T4SMI fell in 59/111 (53.1 %) patients, also with significant heterogeneity between cases (see Fig. 2B). Overall, median T4SMI was not different at baseline versus during chemotherapy (54.3 [48.7–60.3] versus 53.1 [47.6–60.1] cm^2/m^2, $p = 0.131$).

Table 1
Clinical data regarding 111 study participants who received chemotherapy for Pleural Mesothelioma, in whom skeletal muscle and adipose measurements were made on routinely acquired CT Images. Values reported as mean (SD), median (IQR), n (%).

Age, years	69 [63–72]
Male sex	91 (82 %)
Performance Status	
0 / 1 / 2 / Not Available	30 (26 %) / 55 (50 %) / 8 (7 %) / 18 (16 %)
Histological Sub-type	
Epithelioid / Sarcomatoid /	90 (81 %) / 10 (8 %) / 8 (7 %)
Biphasic	3 (3 %)
Not specified	
Clinical Disease Stage	
I / II / III / IV	45 (41 %) / 22 (20 %) / 12 (11 %) / 19 (17 %)
Median number of cycles	4 [3–4]
Baseline Blood Results	
WCC $x10^9$/L	8.6 [7–11]
Neutrophils, $x10^9$/L	5.7 [5–8]
Lymphocytes, $x10^9$/L	1.5 [1–2]
Platelets, $x10^9$/L	344 [281–418]
NLR	4.1 [2.9–6]
PLR	234 [167–351]
Albumin, g/L	35 [30–39]
CRP, mg/L	25 [8–49]

WCC: White Cell Count; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; CRP: C-reactive Protein

Ipsilateral v Contralateral T4

At baseline, iT4SMI was significantly lower than cT4SMI although the magnitude of the difference was small (median 26.3 [23.6–29.8] versus 27.9 [25.1–31] cm^2/m^2, $p = 0.027$). iT4SMI fell in 49/111 (44.1 %) patients, again with marked heterogeneity between cases (see Fig. 2C). Overall, median iT4SMI was not different at baseline versus during chemotherapy (26.3 [23.6–29.8] versus 25.9 [23.1–29.4] cm^2/m^2, $p = 0.5728$).

Adiposity indices and prevalence of Adipopenia

Adiposity indices were non-normally distributed, therefore adipopenia was defined a priori as T4SMI <25th percentile of the baseline and post-chemotherapy datasets. The prevalence of adiposity was therefore 25 % at both timepoints. Median TFI was similar at baseline and during chemotherapy (124.0 [88.0–163.4] versus 116.4 [72.9–158.8], $p = 0.0764$). TFI fell in 55/91 (60.4 %) patients.

Median VFI was lower during chemotherapy (baseline 55.9 [36.7–86.8] versus 50.2 [29.5–78.3] cm^2/m^2, $p = 0.0019$). VFI fell in 56/91 (61.5 %) patients. Median SFI at baseline and during chemotherapy were similar (59.9 [44.9–75.9] versus 63.0 [37.7–83.2] cm^2/m^2, $p = 0.930$). SFI fell in 46/91 (50.5 %) patients.

Muscle associations

Muscle at baseline

These data are summarised in Supplementary Figure 2A, where adjusted significance ($p < 0.003$) is shown by red cells. L3SMI was positively associated with body weight ($r = 0.505$, $p < 0.001$) and BMI ($r = 0.533$, $p < 0.001$). There was a non-significant trend towards lower L3SMI in older patients (age: $r = -0.244$, $p = 0.017$). T4SMI and iT4SMI were also inversely associated with age ($r = -0.294$, $p = 0.002$ and $r = -0.247$, $p = 0.009$, respectively) but were not associated with body weight nor BMI. No significant associations were observed between baseline SMI at L3 or T4 and blood results or tumour volume.

Changes in muscle during chemotherapy

No associations were observed between extreme %ΔSMI at L3 or T4 and age, body weight, BMI, or baseline haemoglobin, inflammatory markers, or tumour volume (see Supplementary Figure 3A).

Adiposity associations

Adiposity at baseline

These data are summarised in Supplementary Figure 2B where adjusted significance ($p < 0.003$) is shown by red cells. TFI was positively associated with body weight ($r = 0.657$, $p < 0.001$) and BMI ($r = 0.842$, $p < 0.001$). Similar relationships with body weight and BMI were observed with VFI ($r = 0.661$, $p < 0.001$ and $r = 0.770$, $p<0.001$, respectively) and SFI ($r = 0.481$, $p < 0.001$ and $r = 0.671$, $p < 0.001$, respectively). Consistent but non-significant associations with platelets and PLR were observed (TFI: platelets $r = -0.300$, $p = 0.006$, PLR $r = -0.286$, $p = 0.008$; VFI platelets $r = -0.232$, $p = 0.034$, PLR $r = -0.243$, $p = 0.026$; SFI: platelets $r = -0.340$, $p = 0.002$, PLR $r = -0.294$, $p = 0.007$). SFI was non-significantly associated with albumin ($r = 0.309$, $p = 0.005$).

Change in Adiposity during chemotherapy

These data are summarised in Supplementary Figure 3B %ΔTFI was inversely associated with body weight ($r = -0.367$, $p < 0.001$) and BMI ($r = -0.413$, $p < 0.001$). %ΔVFI was inversely associated with body weight

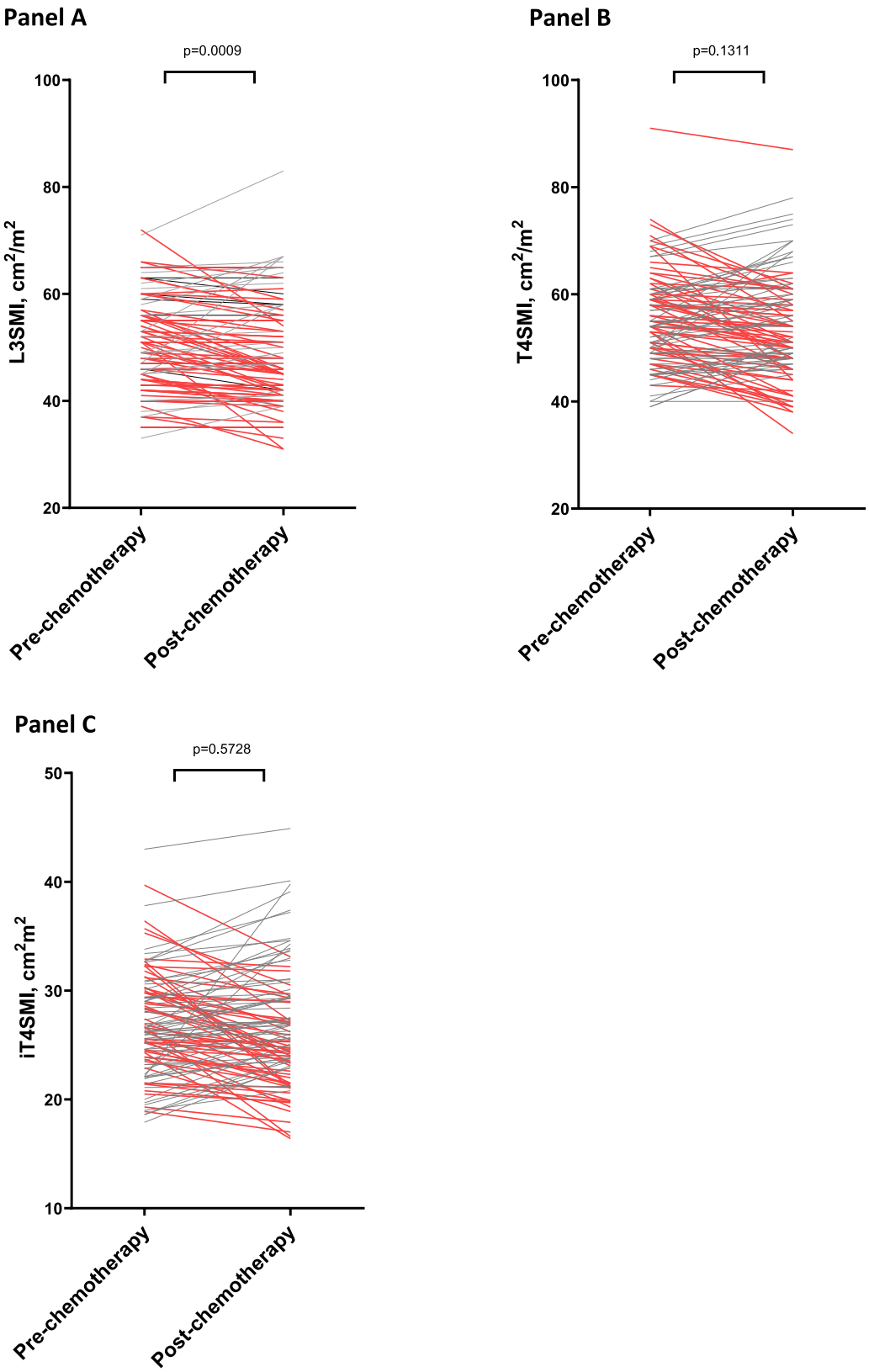

Fig. 2. Panel A, B and C illustrate the heterogeneous changes observed in skeletal muscle indices (SMIs) pre- and post-chemotherapy at L3 (Panel A) and T4 (Panel B and C, with the latter showing ipsilateral T4 only). Indices that fell are shown by red lines, with stable or rising values shown in grey. All indices fell in a significant number of individuals but the median value was statistically significantly lower only for L3.

(r = -0.482, $p < 0.001$) and BMI (r = -0.435, $p < 0.001$). In contrast, %Δ SFI was positively associated with BMI ($r = 0.362$, $p < 0.001$) and body weight ($r = 0.306$, $p = 0.003$).

Interaction between body composition measures and clinical features

L3SMI was positively correlated with T4SMI (r = 0.419, $p < 0.001$), TFI ($r = 0.385$, $p < 0.001$) and VFI ($r = 0.510$, $p < 0.001$) but was not associated with SFI ($r = 0.132$, $p = 0.214$). T4SMI was not associated with adiposity indices. Higher baseline tumour volume was non-significantly associated with lower lymphocytes (r = -0.286, p = 0.015) and higher NLR ($r = 0.289$, $p = 0.014$), PLR ($r = 0.307$, p = 0.009) and CRP ($r = 0.321$, $p = 0.018$).

Survival analyses

Univariate survival and extreme fat and muscle loss phenotypes

Median OS was 389 [IQR 255–603] days over a median follow-up of 389 [255–603] days. Univariate survival analyses are summarised in Table 2. At baseline, only lower baseline SFI was associated with shorter OS (HR 1.82, 95 % CI 1.02–3.26, $p = 0.011$, see Fig. 3A). During chemotherapy, TFI loss and SFI loss were also associated with shorter OS (HR 1.79, 95 % CI 1.17–2.75), $p = 0.005$, see Fig. 3B, and HR 2.12, 95 % CI 1.34–3.29, $p = 0.0003$, see Fig. 3C, respectively.

Table 2
Univariate analyses of factors associated with overall survival in 111 patients with Pleural Mesothelioma. Factors associated with a p-value < 0.1 are highlighted in bold. Only those with $p < 0.05$ (in bold italics) were included in subsequent multivariable survival models evaluating the potential independent association observed with CT measures of altered body composition.

Variables	HR (95 % CI)	*p*-value
Age ≥69 years	1.026 (0.694–1.516)	0.899
Male gender	1.439 (0.858–2.414)	0.168
Performance status 1/2 v 0	1.039 (0.648–1.667)	0.874
Epithelioid v non-epithelioid subtype	0.611 (0.373–1.004)	0.052
Stage 2, 3 or 4 v 1	1.480 (0.971–2.256)	0.069
Primary tumour volume ≥377 cm^3	1.563 (0.978–2.498)	0.062
Baseline body composition indices		
L3SMI	1.485 (0.919–2.401)	0.077
T4SMI	1.102 (0.716–1.694)	0.649
T4SMI	1.021 (0.656–1.589)	0.925
TFI	1.560 (0.776–3.134)	0.129
VFI	1.686 (0.878–3.237)	0.051
SFI	***1.825 (1.023–3.258)***	***0.011***
Change in body composition during chemotherapy (%Δ <0 %)		
%ΔL3SMI	1.015 (0.640–1.610)	0.949
%ΔT4SMI	***1.474 (1.00–2.174)***	***0.050***
%ΔiT4SMI	0.761 (0.512–1.128)	0.164
%ΔTFI	***1.795 (1.170–2.754)***	***0.005***
%ΔVFI	1.255 (0.8154–1.932)	0.289
%ΔSFI	***2.123 (1.368–3.294***	***0.0003***
Extreme change in body composition during chemotherapy (%Δ <25th centile)		
%ΔL3SMI	1.203 (0.723–2.003)	0.445
%ΔT4SMI	***2.794 (1.219–6.403)***	***<0.0001***
%ΔiT4SMI	***2.913 (1.287–6.594)***	***<0.0001***
%ΔTFI	1.538 (0.879–2.691)	0.079
%ΔVFI	***1.957 (1.048–3.617)***	***0.007***
%ΔSFI	1.409 (0.752–2.641	0.218
Weight ≤75.9 kg	1.188 (0.803–1.757)	0.389
BMI ≥30 kg/m^2	0.639 (0.397–1.028)	0.065
BMI ≤18.5 kg/m^2	1.353 (0.425–1.431)	0.609
Inflammatory indices		
WCC ≥8.6 × 10^9/L	***1.637 (1.079–2.484)***	***0.021***
Neutrophils ≥5.7 × 10^9/L	***1.841 (1.190–2.847)***	***0.006***
Lymphocytes ≥1.5 × 10^9/L	0.967 (0.643–1.454)	0.872
Platelets ≥244 × 10^9/L	1.493 (0.993–2.246)	0.054
NLR ≥4.1	1.380 (0.902–2.110)	0.138
PLR ≥234	1.258 (0.828–1.912)	0.283
Albumin ≤35 g/L	1.263 (0.834–1.914)	0.270
CRP ≥25 mg/L	***1.849 (1.119–3.057)***	***0.017***

L3: Measurement at 3rd Lumbar Vertebra; T4: Measurement at 4th Thoracic Vertebra; SMI: Skeletal Muscle Index; TFI: Total Fat Index; VFI: Visceral Fat Index; SFI: Subcutaneous Fat Index; %Δ: Percentage Change; BMI: Body Mass Index: WCC: White Cell Count; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; CRP: C-reactive Protein

None of the *a priori* defined muscle loss indices reached statistical significance. This prompted a *post hoc* analysis focused on extreme muscle and fat loss phenotypes (as defined earlier). Extreme T4 muscle loss was observed in 15/111 (13.5 %), with extreme ipsilateral T4 muscle loss observed in 16/111 (14.4 %). Extreme TFI, VFI and SFI loss were observed in 13/91 (14.3 %), 17/91 (18.7 %) and 17/91 (18.7 %), respectively.

Extreme T4 muscle loss and extreme ipsilateral T4 muscle loss were both associated with shorter OS (215 days versus 420 days, HR 2.79, 95 % CI 1.22–6.40, $p < 0.0001$ (see Fig. 3D), and 255 versus 433 days, HR 2.91, 95 % CI 1.28–6.59, $p < 0.0001$ (see Fig. 3E)). Extreme VFI loss was also associated with OS (272 versus 401 days, HR 1.95, 95 % CI 1.05–3.62, $p = 0.006$, see Fig. 3F).

Higher stage, tumour volume and systemic inflammation (as WCC, neutrophils, platelets, and CRP) were all potentially associated (as defined by p<0.1) with shorter OS. Epithelioid histology and obesity (BMI ≥30) were associated with longer OS. Only WCC, neutrophils and CRP were significant at $p < 0.05$ and therefore eligible for inclusion in subsequent multivariable models.

Multivariable survival model

The following 6 candidate variables were eligible for inclusion, based on a univariate p-value < 0.05: baseline subcutaneous fat index (SFI), total fat index loss during chemotherapy (%ΔTFI), subcutaneous fat loss during chemotherapy (%ΔSFI), extreme thoracic muscle loss (%Δ T4SMI), extreme ipsilateral thoracic muscle loss (%ΔiT4SMI) and extreme visceral fat loss (%ΔVFI). The following potential confounders were also eligible: WCC, neutrophils and CRP. Of these variables, co-linearity was observed between extreme thoracic muscle loss and extreme ipsilateral thoracic muscle loss ($r = 0.947$, p<0.01), total fat index loss and extreme visceral fat loss ($r = 0.805$; $p < 0.0001$), total fat index loss and CRP: (r = -0.268; $p = 0.046$), subcutaneous fat loss and extreme thoracic muscle loss ($r = 0.219$; $p = 0.037$), subcutaneous fat loss and extreme ipsilateral thoracic muscle loss ($r = 0.234$; $p = 0.025$), subcutaneous fat loss and total fat loss ($r = 0.586$; $p < 0.0001$), subcutaneous fat loss and extreme visceral fat loss ($r = 0.584$; p<0.0001), WCC and neutrophils ($r = 0.933$, $p < 0.0001$) and between CRP and WCC ($r = 0.306$, $p = 0.0096$), neutrophils ($r = 0.313$, $p = 0.008$) and extreme visceral fat loss (r = -0.282, $p = 0.035$). WCC was selected over neutrophils and CRP due its performance in other survival models [19, 20]. Due to co-linearity being observed with %ΔSFI and all the other body composition indices, %ΔSFI was not examined in either of the two multivariable models constructed.

Model 1 included extreme T4 muscle loss, baseline SFI, extreme VFI loss and WCC. In this model, only extreme T4 muscle loss retained independent statistical significance (HR 2.84, 95 % CI 1.52–5.31, p = 0.001, see Table 3).

Model 2 included extreme T4 muscle loss, total fat loss, baseline low SFI and baseline WCC. In this model, extreme T4 muscle loss and total fat loss retaining independent statistical significance (HR 2.99, 95 % CI 1.60–5.59, $p < 0.001$, and HR 1.92, 95 % CI 1.14–3.22, $p = 0.014$, respectively; see Table 3).

Reproducibility

L3SMI intra- and inter-observer agreement was excellent (ICC 0.987, $p < 0.001$ and 0.985, $p < 0.001$, respectively). Similar results were observed for T4SMI (ICC 0.988, $p < 0.001$ and 0.831, $p< 0.001$, respectively), VFI (ICC 0.998, $p < 0.0001$ and 0.962, $p< 0.001$, respectively) and SFI (ICC 0.996, $p < 0.0001$ and 0.969, $p < 0.001$, respectively).

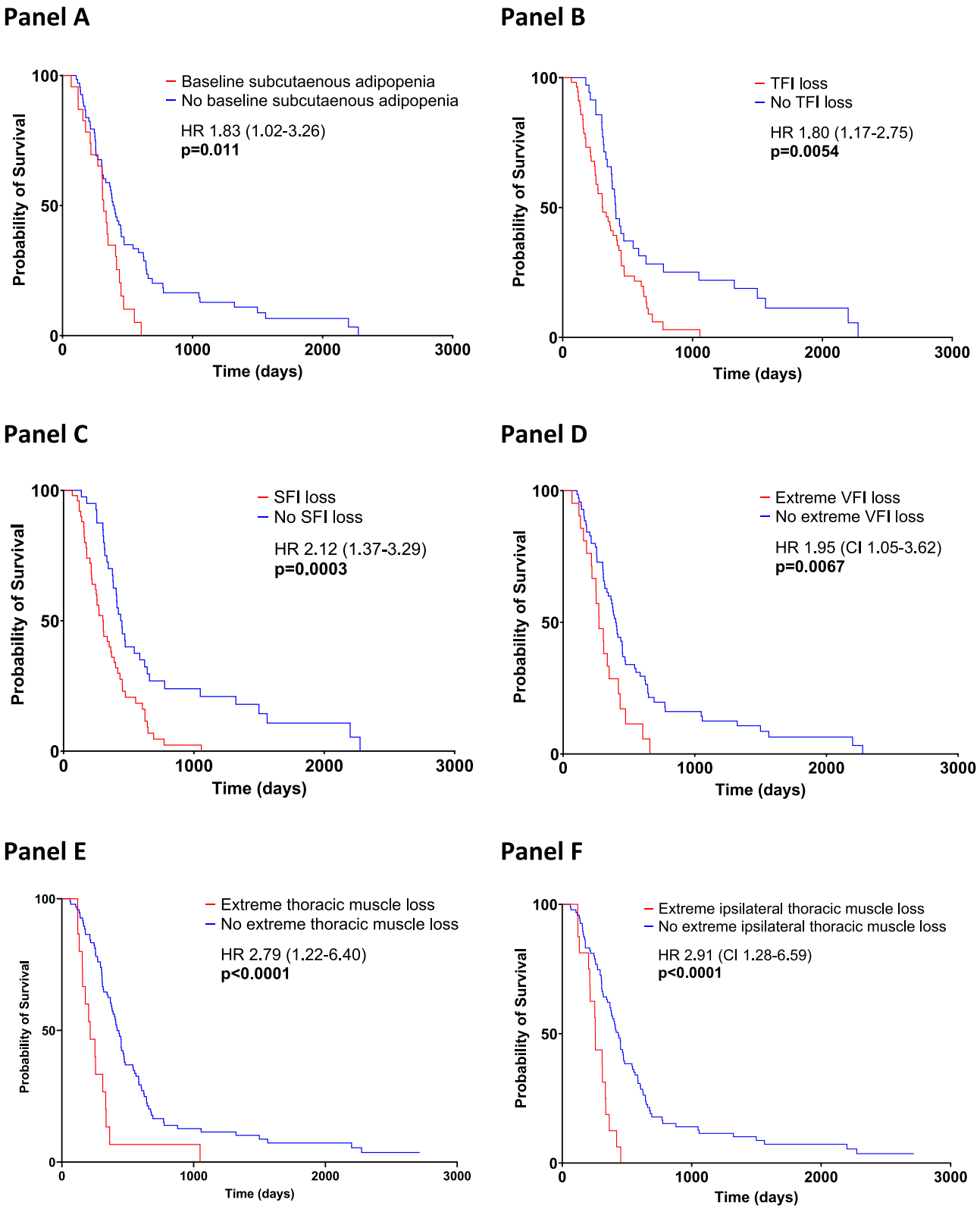

Fig. 3. Overall survival (days) was calculated from the date of pre-chemotherapy CT scan to death from any cause. Univariate survival analysis was performed using the Kaplan-Meier method for (A) baseline subcutaneous adipopenia (SFI, 317 versus 394 days, $n = 91$) (B) total fat index loss during chemotherapy (%ΔTFI, 306 versus 408 days, $n = 91$) (C) subcutaneous fat index loss during chemotherapy (%ΔSFI, 303 versus 443 days, $n = 91$) (D) extreme visceral fat index loss during chemotherapy (extreme %ΔVFI, 272 versus 401 days, $n = 91$) (E) extreme T4 skeletal muscle index loss during chemotherapy (%ΔT4SMI, 215 versus 420 days, $n = 111$) and (F) extreme ipsilateral (to tumour) T4 skeletal muscle index loss during chemotherapy (%ΔiT4SMI, 297 versus 433 days, $n = 111$).

Table 3
Multivariable analyses of factors associated with overall survival in 111 patients with Pleural Mesothelioma.

Model 1		
Variables	HR (95 % CI)	*p*-value
Extreme %ΔT4SMI	2.843 (1.521–5.314)	0.001
Baseline SFI	1.635 (0.949–2.818)	0.077
Extreme %ΔVFI	1.593 (0.881–2.881)	0.123
Baseline WCC	1.331 (0.834–2.125)	0.231
%ΔT4SMI=T4 skeletal muscle index percentage change; SFI=subcutaneous fat index; %ΔVFI=visceral fat index percentage change; WCC=white cell count		
Model 2		
Variables	HR (95 % CI)	*p*-value
Extreme %ΔT4SMI	2.994 (1.603–5.592)	<0.001
%ΔTFI	1.915 (1.139–3.222)	0.014
Baseline SFI	1.562 (0.913–2.675)	0.104
Baseline WCC	1.215 (0.755–1.957)	0.422
%ΔT4SMI=T4 skeletal muscle index percentage change; SFI=subcutaneous fat index; %ΔTFI=total fat index percentage change; WCC=white cell count		

Discussion

In this study, we assessed body composition at L3 and T4 using routine CT imaging in patients receiving chemotherapy for PM. Using a previously validated threshold, we found that 35 % of patients had sarcopenia at L3 prior to chemotherapy. In the absence of validated thresholds for other values, the prevalence of T4 sarcopenia and adipopenia were defined arbitrarily, but a priori, at 25 %, precluding comparison with other studies. In non-pleural cancers the reported prevalence of L3 sarcopenia varies from 22 % to 83 %, depending on tumour type and whether the patients involved were inpatients or outpatients [21]. In previous studies focusing on PM patients, sarcopenia prevalence has varied considerably. Pre-sarcopenia, defined as low appendicular skeletal muscle mass on DEXA scanning was reported in one series as 54 % [10], while 66 % of surgically-treated patients had sarcopenia in another study [9]. These values are higher than the 35 % prevalence observed here, which may reflect differences in the imaging methods used (e.g. DEXA [10] versus CT here) and differences in the muscles used to make the measurements (the surgical study used CT as we did here, but measured only paravertebral muscles at T12) [9].

In the current study, L3SMI fell in 61.5 % of patients and L3 sarcopenia therefore became more prevalent during chemotherapy. However, this was not independently associated with shorter survival. As expected, it was not possible to conduct L3 measurements in a significant proportion of cases (20/111, 18 %) because L3 was not included in the CT acquisition. Similar attrition due to L3 availability has been reported in previous studies [22,23]. T4 muscle indices were universally available but fell slightly less frequently during chemotherapy. T4 muscle loss occurred in 59/111 (53.1 %) patients, with no overall change in the prevalence of T4 sarcopenia and no apparent association with OS. However, in a *post hoc* analysis, extreme T4 muscle loss and extreme ipsilateral T4 muscle loss, which were observed in 13.5 % and 14.4 % of the patients, respectively, were both associated with adverse survival on univariate analysis. In a subsequent multivariable survival analysis, extreme ipsilateral T4 muscle loss retained independent prognostic value, with a near 3-fold increase in the risk of death in patients who experienced this event.

The association reported here between ipsilateral thoracic muscle loss and OS is of uncertain significance and mechanism. Percentage change in T4 muscle was not associated with age, sex, stage, tumour volume or chemotherapy response (see Supplementary Figure 4). Although the magnitude of the difference between ipsilateral and contralateral T4 muscle was small, preferential loss on the ipsilateral side might be explained by loco-regional changes in chest wall mechanics and resulting thoracic muscle wasting. Similar findings have been observed bilaterally in patients with chronic obstructive pulmonary disease [24]. Chemotherapy may also directly promote muscle loss [25], via protein catabolism [18] and direct cytotoxic effects [26]. Cisplatin has been shown to induce sarcopenia in other human cancer cohorts [27,28] and carboplatin in murine models [29]. However, this ipsilateral nature of the changes observed would not be obviously explicable by this mechanism.

In our univariate analyses, pre-chemotherapy obesity (BMI $\geq$30 mg/m^2) was associated with superior survival. This 'obesity paradox' has been reported in other cancers [30] and emphasises the importance of fat distribution on outcome. All adiposity measures (TFI, VFI, SFI) tended to be elevated at baseline in patients with increased body weight and BMI. Patients with increased weight or BMI tended to lose more subcutaneous fat and less visceral and total fat during chemotherapy. A higher subcutaneous to visceral fat ratio has also been associated with poorer survival in other solid organ cancers [31]. In the current study, loss of total fat and subcutaneous fat during chemotherapy, and extreme loss of visceral fat during chemotherapy, were associated with adverse survival on univariate analysis, as was low baseline subcutaneous fat. Total fat loss retained independent prognostic significance in a subsequent multivariable model (HR 1.92, $p = 0.014$).

In the current study, higher tumour volume correlated with higher inflammatory indices such as NLR and PLR. This is concordant with previous associations between PM tumour volume and the inflammatory activin A [32] and complement component 4d [33]. Patients in the present study who had greater VFI loss during chemotherapy had higher pre-chemotherapy platelets. Pre-treatment thrombocytosis is known to be an adverse prognostic indicator in PM [34]. Moreover, thrombocytosis is positively associated with elevated BMI and total fat mass percentage [35] and visceral adipose tissue [36]. Further exploration of these biological associations is warranted.

Strengths and limitations

This is the first study to assess thoracic sarcopenia in PM and the first to investigate the potential impact of locoregional muscle changes ipsilateral to the primary pleural tumour. Three study centres contributed cases, maximising the generalisability of our findings. The body composition measurement techniques also demonstrated good-to-excellent intra- and inter-observer reproducibility. The full definition of sarcopenia should ideally include measures of muscle strength and performance not just muscle quantity as measured here [37]. Unfortunately, the retrospective nature of the study, precluded inclusion of these data.

Clinical implications

Sarcopenia and adipopenia are central components of the cancer cachexia syndrome. The simplicity in measuring these indices on routine CT makes them attractive biomarkers for prediction of worse outcomes or direct intervention using multimodality approaches [38] or simpler exercise interventions [39]. The EXTRA-Meso (EXercise TheRApy in Mesothelioma) feasibility study is an example of the latter and will open during 2023 in comparing the CT measurements reported here. Unfortunately, no baseline features were independently associated with shorter survival, limiting predictive utility. However, extreme loss of T4 muscle was detectable on early response CT imaging. This marker may therefore prove suitable in the future as an early warning marker, identifying patients for more intensive monitoring or cachexia-directed interventions.

Conclusion

Extreme thoracic skeletal muscle loss and total fat loss during chemotherapy for PM were associated with shorter survival. These may prove to be useful adverse early response, and potentially actionable,

biomarkers. Further studies are warranted.

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Ethical guidelines statement

The study protocol was granted ethical approval via the NHS Greater Glasgow and Clyde (NHSGGC) Safe Haven (Ref: GSH/18/ON/001). It has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

CRediT authorship contribution statement

Andrew C. Kidd: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Gordon W. Cowell:** Writing – review & editing, Supervision, Data curation. **Geoffrey A. Martin:** Writing – review & editing, Data curation. **Jenny Ferguson:** Writing – review & editing, Data curation. **Dean A. Fennell:** Writing – review & editing. **Matt Evison:** Writing – review & editing. **Kevin G. Blyth:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

None of the authors have conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2024.100856.

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