

Original Article

A comparison of CT-body composition measurements in non-cancer and cancer patients from a single UK centre

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Abstract

Objectives: Establish the prevalence of low skeletal muscle index and density in our population, by comparing age and sex matched cohorts of patients with and without cancer, using standardized methodology for CT-Body composition (CT-BC). **Methods:** A retrospective analysis of prospectively collected data. Patients admitted to our institution between 17th March 2020 - 1st May 2020, with confirmed coronavirus disease and imaging suitable for CT-BC (n=52), were age and sex matched with patients undergoing resection for colorectal cancer (n=52). **Results:** 104 patients were included in the final analysis. 43% (n=45) were male, 77% (n=80) were aged 65 years or older, 50% (n=50) were overweight (BMI \geq 25) and 53% (n=55) were systemically inflamed (mGPS \geq 1). The prevalence of a low SMI (56% vs. 65%) and low SMD (83% vs. 67%) was similar between cohorts. A low SMI and SMD were both associated with age (p<0.05 and p<0.01, respectively) on univariate analysis. On multivariate analysis, a low SMD was independently associated with age (OR 2.38 (1.34-4.22), p=0.003) and mGPS (OR 2.10 (1.20-3.68), p=0.01). **Conclusions:** In conclusion, the prevalence of a low SMI and low SMD was similar in non-cancer and cancer cohorts in our institution.

Keywords: Cancer, Obesity, Sarcopenia

Introduction

CT-Body composition (CT-BC) has been shown to be a reliable and objective measure of soft tissues including muscle, routinely available in clinical practice¹⁻³. The prognostic value of a low skeletal muscle index (SMI) and low radiodensity (SMD) in patients with cancer has been widely published^{4,5}. Furthermore, both have been found to be prevalent in patients with cancer, across a range of tumour types and disease stages⁶. This raises the issue of whether poor muscle status is constitutional in these patients and not a result of the cancer per se.

CT-imaging is a gold standard methodology for quantification of soft tissues including muscle³, with measurements of muscle mass shown to be consistent with other methods⁷. A range of pre-defined thresholds for stratifying patients with a low muscle mass (myopenia) and density (myosteatosis), adjusted for age and sex, exist within the current literature^{6,10}. However, to date, few CT-body composition studies have been carried out in non-cancer patients due to the potential harmful effects of the radiation exposure.

During the first wave of the coronavirus (COVID-19) global pandemic, an increase in CT imaging of non-cancer patients was observed, following guidance from the Royal College of Surgeons⁸. This facilitated immediate diagnosis, non-operative management and safe discharge of patients. As such, this cohort provides a rare and useful comparator of CT-body composition in patients without cancer. Therefore, the aim of the present study was to compare the CT-body composition (using a standardised methodology) of non-

The authors have no conflict of interest.

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Edited by: Yannis Dionyssiotis

Accepted 8 March 2022

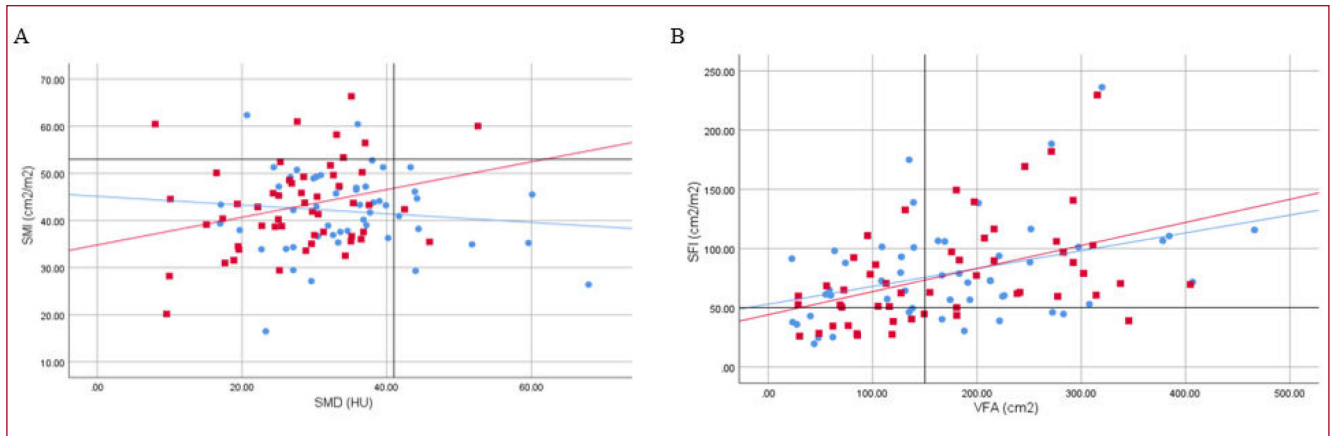


Figure 1. Correlations among CT-body composition measurements in patients with (blue circle) and without colorectal cancer (red square). The upper threshold for each measurement is shown: (A) SMI vs. SMD: Cancer (r_s : -0.03, $p=0.837$) vs. Non-cancer (r_s : 0.22, $p=0.117$); (B) SFI vs. VFA: Cancer (r_s : 0.368, $p=0.007$) vs. Non-cancer (r_s : 0.480, $p<0.001$).

cancer patients with an age and sex matched cohort of patients with colorectal cancer.

Material and Methods

Patients

This study was a retrospective analysis of prospectively collected data. Patients were identified from two prospectively maintained databases of those undergoing treatment within Glasgow Royal Infirmary (GRI). The first cohort was composed of those admitted to our unit between the 17th March 2020 - 1st May 2020, with radiological or polymerase chain reaction (PCR) confirmed COVID-19 infection and suitable CT-imaging for body composition analysis, performed within 3 months of the index admission⁹. Those with active cancer were then excluded ($n=11$), leaving a total of 52 patients. Of these patients, 6% ($n=3$) had an intensive care stay and 17% ($n=9$) died within thirty days of admission. The median length of stay was 14 days (IQR 7-23.5).

Patients were then randomly age and sex matched with those from a larger, prospectively maintained database of patients undergoing curative resections for colorectal cancer (TNM stage I-III disease) at our institution, with pre-treatment CT-imaging facilitating body composition analysis. As this was a retrospective analysis of existing clinical data, formal ethical committee review was not required (National Research Ethics Service guidance).

Routine demographic details including age, sex and BMI were recorded. Age categories were grouped into <64, 65-74 and >74 years. BMI was categorized as <25 and ≥ 25 . Systemic inflammation was determined using the modified Glasgow Prognostic score (mGPS)¹⁰ and Neutrophil:lymphocyte ratio (NLR)¹¹, derived as previously

described¹². Admission bloods were used in those non-cancer patients and pre-treatment bloods in patients with cancer. An autoanalyzer was used to measure serum CRP (mg/L) and albumin (g/L) concentrations (Architect; Abbot Diagnostics, Maidenhead, UK). For this study, thresholds of NLR <3, >3 - <5 and >5 were chosen and categorized as “mild”, “moderate” and “severe” systemic inflammatory response respectively. mGPS values were grouped into “non-inflamed” (i.e. mGPS=0) and “inflamed” (i.e. mGPS=1 or 2) cohorts.

CT-derived body composition

Each CT image was individually analysed using ImageJ - a free to download, Java-based program developed by NIH (NIH ImageJ version 1.47, <http://rsbweb.nih.gov/ij/>) shown to provide reliable measurements¹³. Body composition measurements derived from the CT image slice at L3 included total fat area (TFA), visceral fat area (VFA), and skeletal muscle area (SMA) using standardized methods from our institution. Attenuation thresholds were -190 to +30 Hounsfield units (HU) for fat and -29 to +150 HU for muscle.

The SMA was measured by manually delineating muscle areas including the quadratus lumborum, psoas, rectus abdominus, erector spinae muscles, internal transverse, and external oblique muscle groups. Skeletal muscle radiodensity (SMD, HU) was calculated as the mean of the measured muscle area used to calculate SMI. As with SMA, the TFA was quantified by depicting the outer contours of the abdominal wall, compared to the inner contour of the psoas and abdominal wall muscles for VFA. The subcutaneous fat area (SFA) was calculated by subtraction of the VFA from TFA. SFA and SMA measurements were normalized by division of the patient’s height in meter squared to generate

subcutaneous fat index (SFI, cm^2/m^2) and skeletal muscle index (SMI, cm^2/m^2). These indices were then compared with established thresholds for body composition status¹⁴⁻¹⁶.

Statistical Analysis

Correlations among body composition characteristics were explored using Spearman rank correlation. Demographic data, CT-BC measurements, mGPS and NLR were presented as categorical variables. Categorical variables were analysed using χ^2 test for linear-by-linear association. Univariate binary logistic regression with backward conditional method was performed separately for each of the body composition measurements. Covariates with a significance value of $p < 0.1$ in the univariate analysis were included in the multivariate analysis.

The present study was testing the hypothesis that patients with COVID-19 were similar to other patient groups and that the body composition measurements are constitutional in such disease groups. Therefore, the present analysis was exploratory in nature and no formal power calculation was carried out.

Missing data were excluded from analysis on a variable-by-variable basis. Two-tailed p values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS software version 25.0. (SPSS Inc., Chicago, IL, USA).

Results

A total of 52 patients admitted with COVID-19 and 52 patients with colorectal cancer were included in the final analysis. Of these patients, 43% ($n=45$) were male, 77% ($n=80$) were aged 65 years or older, 50% ($n=50$) were overweight ($\text{BMI} \geq 25$) and 53% ($n=55$) were systemically inflamed ($\text{mGPS} \geq 1$). The clinicopathological characteristics of the age and sex matched patient groups are shown in Table 1. The group characteristics were similar with the exception that the cancer group had less systemic inflammation (NLR and mGPS, both $p < 0.001$).

Relationship among CT body composition measurements

Relationships between CT derived muscle measurements in patients with and without cancer are displayed in Figures 1A and 1B. SFI was positively correlated with VFA in both the cancer and non-cancer groups ($r_s = 0.368$, $p = 0.007$ and $r_s = 0.480$, $p < 0.001$). SMI was positively correlated with SMD in the non-cancer group only ($r_s = 0.22$, $p = 0.117$).

Relationship between CT body composition parameters and clinicopathological characteristics

These relationship between CT body composition parameters and clinicopathological characteristics is shown in Table 2. A high SFI was significantly associated

	Non-cancer (n=52) n (%)	Colorectal Cancer (n=52) n (%)	p value
Age (years)			
<65	12 (23.1)	12 (23.1)	1.00
65-74	11 (21.2)	11 (21.2)	
>74	29 (55.7)	29 (55.7)	
Sex			
Male	22 (42.3)	23 (44.2)	0.843
Female	30 (57.7)	29 (55.8)	
NLR			
<3	9 (17.3)	28 (53.8)	<0.001
3-5	10 (10.2)	15 (28.8)	
>5	33 (63.5)	9 (17.3)	
mGPS			
0	9 (17.3)	40 (76.9)	<0.001
1	8 (15.4)	5 (9.6)	
2	35 (67.3)	7 (13.5)	
BMI (kg/m^2)			
<25	28 (53.8)	25 (48.1)	0.556
≥ 25	24 (46.2)	27 (51.9)	
High SFI			
No	11 (21.2)	11 (21.2)	1.00
Yes	41 (78.8)	41 (78.8)	
High VFA			
No	15 (28.8)	17 (32.7)	0.671
Yes	37 (71.2)	35 (67.3)	
Low SMI			
No	23 (44.2)	18 (34.6)	0.316
Yes	29 (55.8)	34 (65.4)	
Low SMD			
No	9 (34.6)	17 (32.7)	0.070
Yes	43 (82.7)	35 (67.3)	

Table 1. Relationship between clinicopathological variables and CT-body composition measurements in patients with and without cancer ($n=104$).

with age ($p < 0.01$) and sex ($p < 0.05$). A low SMI and SMD were both associated with age ($p < 0.05$ and $p < 0.01$, respectively). On multivariate analysis, high SFI remained significantly associated with age (0.47 (0.22-0.97), $p = 0.042$) and low SMD remained significantly associated with age (2.38 (1.34-4.22), $p = 0.003$) and mGPS (2.10 (1.20-3.68), $p = 0.01$).

	High SFI ¹⁴	High VFA ¹⁵	Low SMI ¹³	Low SMD ¹³
Age (<65/65-74/>74)	0.45 (0.22-0.93), p=0.03	0.58 (0.33-1.01), p=0.057	1.74 (1.07-2.83), p=0.024	2.31 (1.35-3.97), p=0.002
Sex (Male/Female)	0.35 (0.13-0.92), p=0.034	0.97 (0.42-2.25), p=0.947	0.96 (0.43-2.12), p=0.916	0.57 (0.23-1.38), p=0.211
Cancer (Yes/No)	1.00 (0.39-2.56), p=1.00	0.84 (0.30-1.92), p=0.671	1.50 (0.68-3.31), p=0.317	0.43 (0.17-1.09), p=0.074
NLR (<3/3-5/>5)	1.26 (0.73-2.17), p=0.40	1.16 (0.72-1.88), p=0.536	1.05 (0.67-1.66), p=0.823	1.34 (0.80-2.23), p=0.271
mGPS (0/1/2)	0.85 (0.51-1.41), p=0.524	0.85 (0.54-1.33), p=0.473	0.92 (0.61-1.41), p=0.705	2.06 (1.20-3.54), p=0.009

Odds ratio, 95%CI, p value.

NLR-neutrophil: lymphocyte ratio, mGPS- modified Glasgow Prognostic Score.

Table 2. Univariate regression analysis of predictors of CT-based abdominal body composition characteristics.

Discussion

The results of the present study found that despite their disparate presentations, CT- derived body composition measures were similar in age and sex matched non-cancer and cancer cohorts. This would suggest that sarcopenia (a low SMI and low SMD), is endemic and consistent with the hypothesis that poor muscle status is largely constitutional and not the result of the disease state per se⁶. Therefore, it may be that both COVID-19 and cancer diagnosis commonly occur on a background of a low skeletal muscle mass and that sarcopenia is constitutional in many of these patients. Furthermore, the present results may have implications for improving patient fitness.

The present observations are in keeping with a recent cohort study by Dolan and co-workers, including 804 patients with colorectal cancer, that showed SMI remained relatively stable over a 12-month period. Furthermore, that the majority of losses in SMI occur before the diagnosis of cancer^{17,18}. As such, many cancer patients are likely to start their treatment journey at a disadvantage if sarcopenia is constitutional, given the association with poor pre-treatment physical function^{19,20} and reduced oncological response to anti-cancer therapy¹⁸. Therefore, the die may be cast for patients at an early stage of their cancer journey.

Cachexia and sarcopenia have both been associated with clinical outcomes in patients with cancer and COVID-19²¹⁻²³. The Global Leadership Initiative on Malnutrition (GLIM) has defined cachexia as disease-related malnutrition with inflammation²⁴. Sarcopenia on the other hand has been defined by the second European Working Group on Sarcopenia in Older People (EWGSOP2) as a disease of skeletal muscle (muscle failure), associated with low a low muscle mass and strength²⁵. Cachexia and sarcopenia can be considered as related pathological entities, since a low

skeletal muscle mass is considered a diagnostic criterion for cachexia²⁴ and inflammation is a recognised aetiology in the pathogenesis of both^{23,26,27}. The importance of modulating the systemic inflammatory response to improve outcomes in patients with cancer has been highlighted by Roxburgh and co-workers and Diakos and co-workers^{28,29}. Therefore, modification of muscle mass alone in patients with cancer who are systemically inflamed may be futile. Indeed, clinical trials of patients with cancer cachexia, such as ROMANA 1 and 2, have shown while muscle mass could be increased, it did not correlate with improved physical function³⁰. This highlights the need for more meaningful patient-centred outcomes such as quality of life and other therapeutic endpoints, such as systemic inflammation, in future clinical trials of patients with cancer³¹. Furthermore, the inclusion of anti-inflammatory medications as part of multi-modal approach for treating patients with cancer cachexia³².

There are a number of limitations to the present study. Firstly, there was a relatively small sample size and therefore the study may be subject to sample bias. Secondly, while patients were age and sex matched, the majority of patients were over 65 years old in both cohorts. Indeed, age is a confounding variable in the present study and has implications given the association between sarcopenia and advanced age^{33,34}. While thresholds for a low SMI and SMD have been adjusted for sex and BMI^{14,35-37}, to date there are no recognised thresholds adjusted for age. As such, further study investigating these relationships in a younger age range would be of interest. Lastly, COVID-19 has been associated with cases of severe respiratory illness, often requiring intensive care admission³⁸. ESPEN have proposed that long intensive care stays may directly worsen or cause malnutrition, with a resultant severe loss of skeletal muscle mass and function²². Since only 6% (n=3) of patients with COVID-19 had an ITU admission a low muscle mass

was unlikely to be due the COVID-19 admission itself. Furthermore, when the patients from the non-cancer cohort who had CT-imaging used for body composition analysis performed before/during their admission with COVID-19 (31%, n=16) were compared with patients who underwent CT-imaging after discharge (69%, n=36), there were no significant differences in age ($p=0.186$), sex ($p=0.796$), NLR ($p=0.196$), mGPS ($p=0.808$), high SFI (0.079), high VFA ($p=0.433$), low SMI ($p=0.755$) or low SMD ($p=0.412$). Taken together these observations support the hypothesis that poor muscle status is largely constitutional and that COVID-19 and cancer diagnosis commonly occur on a background of a low skeletal muscle mass.

In conclusion, CT-based body composition measurements, in particular low SMI and low SMD, were found to be similar in non-cancer and cancer cohorts. This is consistent with the hypothesis that poor muscle status is largely constitutional and not the result of the cancer per se.

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