Original Article

Association of adipose tissue and skeletal muscle metrics with overall survival and postoperative complications in soft tissue sarcoma patients: an opportunistic study using computed tomography

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Background: To determine the relationship between adipose tissue and skeletal muscle measurements on computed tomography (CT) and overall survival and major postoperative complications in patients with soft-tissue sarcoma (STS).

Methods: The retrospective study included 137 STS patients (75 men, 62 women; mean age, 53 years, SD 17.7; mean BMI, 28.5, SD 6.6) who had abdominal CT exams. On a single CT image, at the L4 pedicle level, measurements of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle area and attenuation were obtained using clinical PACS and specialized segmentation software. Clinical information was recorded, including STS characteristics (size, depth, grade, stage, and site), overall survival, and postoperative complications. The relationships between CT metrics and survival were analyzed using Cox proportional hazard models and those between CT metrics and postoperative complications using logistic regression models.

Results: There were 33 deaths and 41 major postoperative complications. Measured on clinical PACS, the psoas area (P=0.003), psoas index (P=0.006), psoas attenuation (P=0.011), and total muscle attenuation (P=0.023) were associated with overall survival. Using specialized software, psoas attenuation was also associated with overall survival (P=0.018). Adipose tissue metrics were not associated with survival or postoperative complications.

Conclusions: In STS patients, CT-derived muscle size and attenuation are associated with overall survival. These prognostic biomarkers can be obtained using specialized segmentation software or routine clinical PACS.

Keywords: Computed tomography (CT); muscle; myosteatosis; sarcopenia; soft-tissue sarcoma (STS)

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Introduction

The interpretation of CT examinations in patients with neoplasms routinely focuses on documenting the lesion site, size, and extent, as well as providing the differential diagnosis. Although body composition information is available on these CT exams, it is usually not reported.

Body composition can affect cancer development and cancer prognosis (1-4). Obesity, for example, is an important risk factor for developing 10 of 17 common cancers (5,6). CT measures of visceral adipose tissue (VAT) have been associated with survival with some types of cancers (e.g., colorectal and pancreatic cancers), but not with others (e.g., renal cell carcinoma) (4,7-9). In patients with soft-tissue sarcoma (STS), there is currently no compelling evidence about VAT influencing patient survival.

There is also accumulating evidence that skeletal muscle mass and attenuation are associated with health outcomes in many cancers, including those involving the abdominopelvic viscera (1,10-15). In a meta-analysis of 38 studies in 7,843 patients with solid tumors (1), low muscle mass measured on CT was associated with poorer overall survival (HR: 1.44, 95% CI: 1.32–1.56, P<0.001). Caution is warranted, however, because prognosis is influenced by many variables, including cancer type. With esophageal cancer, for example, most studies have found no association between CT-derived muscle mass and overall survival (16-20). In patients with STS, two studies seem to show conflicting results regarding the role of CT muscle metrics. In one study (21), low psoas muscle attenuation was associated with higher mortality, but in another study (22) low psoas muscle area showed no association with outcomes.

Although CT measures of adipose tissue and skeletal muscle outperform body mass index (BMI) in risk stratification for many cancers, there are several barriers to clinical implementation, including access to segmentation software used in most research studies (11-15). This specialized software requires considerable time and resources (e.g., data transfer and analysis on an independent workstation). A much easier alternative is to derive these CT metrics on clinical PACS workstations. While VAT and subcutaneous adipose tissue (SAT) measurements on CT are fairly standardized, there is continuing debate on the best methodology to characterize muscle on CT images (23,24). We are not aware of any studies using both specialized segmentation software and routine clinical PACS software to evaluate muscle in patients with STS. To address this gap, our aim was to use specialized and PACS software to investigate adipose tissue and skeletal muscle metrics as prognostic indicators for overall survival and major postoperative complications in STS patients.

Methods

Patients

After institutional review board approval with waiver of informed consent for this HIPAA-compliant retrospective study, a database of patients under the care of one subspecialty surgeon (RJC) at our tertiary care academic medical center was accessed. Inclusion criteria were: (I) available clinical data that included patient age at the time of presentation, sex, BMI, hemoglobin, creatinine, and C-reactive protein; (II) available neoplasm characteristics including maximal tumor dimension, depth, grade, stage, site, and histology; and (III) a baseline staging CT examination of the abdomen within three months of diagnosis, as per institutional protocol. This initial survey yielded 148 consecutive patients. Exclusion criteria were: (I) abdominal CT images were not available (n=6) or (II) abdominal CT images were of inadequate quality [e.g., due to tumor involvement (n=3) or postoperative change (n=2)], as determined by consensus of the two authors (RD Boutin, JR Katz) (n=11). This yielded 137 patients for the overall survival analysis. Nine patients were treated non-operatively, and therefore analysis of major postoperative complications included 128 patients.

Two major clinical outcomes were evaluated: overall survival and major postoperative complications. Overall survival was defined as the time from diagnosis to the time of death or to the study termination date. The latter were subsequently censored to the last date at which patients were documented to be alive. Major postoperative complications were defined as return to the operating room for wound repair, an invasive postoperative procedure (e.g., abscess drainage), hospital readmission for wound care (e.g., intravenous antibiotics), or prolonged wound packing (i.e., greater than 120 days from the date of operation) (25).

CT image analysis

Segmentation procedure

All radiologists were blinded to clinical data, including outcomes. The same axial CT image at the L4 pedicle level was used to obtain all fat and muscle measurements. Manual segmentation was performed by three radiologists (musculoskeletal fellow, third-year resident, second-year resident) who were trained to segment relevant tissue regions by a senior musculoskeletal radiologist with 20 years of research experience.

Adipose tissue metrics

VAT and SAT were measured on an independent workstation with a public-domain, Java-based, image-processing software (ImageJ, v1.42q; National Institutes of Health, http://rsb.info.nih.gov/ij). This method uses a "thresholding" technique, so that only pixels with CT numbers from −30 to −190 HU are analyzed as fat (26,27). Using this technique, the following were measured: (I) VAT area (cm^2); (II) VAT attenuation (HU); (III) SAT area (cm^2); and (IV) SAT attenuation (HU).

Muscle metrics

Muscle tissues were analyzed using two image-processing methods: (I) thresholded and (II) non-thresholded.

Thresholded

This method used the same software as the adipose tissue measurement (ImageJ). For muscle measurement, only pixels from −29 to 150 HU were analyzed for area and attenuation calculations. This method is commonly used in body composition research and is intended to capture only "lean muscle" by excluding intramuscular adipose tissue (26,27).

Non-thresholded

All muscle measurements were also made without thresholding, by drawing a region of interest around the individual muscles or muscle groups using the clinical PACS software (iSite, version 3.6, Philips Healthcare; Foster City, CA).

Both the thresholded and non-thresholded methods yielded muscle area and muscle attenuation metrics. For the psoas, the following muscle metrics were recorded: (I) psoas area (cm^2); (II) psoas area normalized for patient height, termed the psoas index (cm^2/m^2); and (III) psoas attenuation (HU). For the combination of all the psoas, paravertebral, and abdominal musculature, the following muscle metrics were recorded: (I) total muscle area (cm^2); (II) total muscle index (cm^2/m^2); and (III) total muscle attenuation (HU).

Statistical analysis

Descriptive statistics and analyses were obtained using Stata version 12 (StataCorp, College Station, TX). Because of the low number (n=12) of stage 4 patients, statistical analyses combined stages 3 and 4. Univariable and multivariable analyses for overall survival were performed using the Cox proportional hazards model to evaluate the covariate effects of each variable. Logistic regression models were used to evaluate the association of CT metrics with major postoperative complications. Age and sex adjustments were used to account for known normative differences in fat and muscle composition in these groups. Significant variables from the multivariable model were analyzed further using multiple hypothesis testing with the Sidak correction. The concordance C-statistic for each model was also calculated. A C-statistic of 0.5 has no discriminating ability for survival versus death, while a value of 1.0 has perfect discrimination. 95% confidence intervals were calculated. Results were considered significant at $P<0.05$. Intra-observer and inter-observer analysis were performed on a random subset of 14 patients (approximately 10% of the cohort) and the concordance correlation coefficients were calculated.

Results

Overall survival

Patient characteristics are shown in *Table 1*. Of the 137 patients included in the study, there were 33 (24%) deaths, with a mean survival time of 33.1 months in those patients. Mean follow-up time for the 104 (76%) survivors was 28.3 months. There was no significant association of age, sex, ethnicity, hemoglobin, creatinine, C-reactive protein, or tumor size, depth, and site with overall survival. However, there was a significant association of STS grade ($P=0.001$) and stage ($P<0.001$) with overall survival.

At presentation, patients varied widely in their BMI, adipose tissue, and muscle metrics. BMI had no significant association with overall survival ($P=0.210$). *Table 2* shows adipose tissue and muscle metrics analyzed using univariable models. *Table 3* shows the same CT metrics analyzed using a multivariable Cox proportional hazards model, adjusted for age (dichotomized at age 65), sex, tumor grade, and tumor stage.

Adipose tissue metrics

Visceral fat, subcutaneous fat, or total fat metrics showed no significant association with overall survival using univariable or multivariable analyses.

Muscle metrics

Thresholded

Using the thresholded (specialized software) method, two metrics were significantly associated with survival: the

Table 1 Initial clinicopathologic characteristics of soft-tissue sarcoma patients, with univariable analysis for overall survival (n=137[†])

Clinical variables	Overall (n=137)	Deceased (n=33)	Survived (n=104)	Univariable P value[&]
Age, mean (SD) (years)	53.0 (17.7)	57.0 (20.3)	51.7 (16.8)	0.149
Sex, n [%]				0.349
Female	62 [45]	13 [39]	49 [47]	
Male	75 [55]	20 [61]	55 [53]	
Ethnicity, n [%]				0.963
Caucasian	91 [66]	23 [70]	68 [65]	
Hispanic	20 [15]	5 [15]	15 [14]	
Asian	14 [10]	4 [12]	10 [10]	
Black	8 [6]	1 [3]	7 [7]	
Unknown	4 [3]	0 [0]	4 [4]	
Body mass index (kg/m^2), mean (SD)	28.5 (6.6)	27.4 (5.5)	28.9 (7.0)	0.210
Hemoglobin (g/dL), mean (SD)	13.3 (2.2)	12.6 (2.7)	13.5 (2.0)	0.058
Creatinine (mg/dL), mean (SD)	0.9 (0.4)	1.0 (0.6)	0.9 (0.3)	0.214
C-reactive protein (mg/L), mean (SD)	1.8 (4.7)	1.8 (3.1)	1.8 (5.0)	0.886
Maximal sarcoma dimension (cm), mean (SD)	12 (9.0)	13.8 (10.6)	12.3 (10.8)	0.987
Depth of Sarcoma, n [%]				0.120
Deep (subfascial)	125 [91]	29 [88]	96 [92]	
Superficial	12 [9]	4 [12]	8 [8]	
Grade of sarcoma, n [%]				0.001*
Low	51 [37]	4 [12]	47 [45]	
Intermediate & high	86 [63]	29 [88]	57 [55]	
Stage at presentation, n [%]				<0.001*
I	47 [34]	4 [12]	43 [41]	
II	23 [17]	3 [9]	20 [19]	
III	55 [40]	18 [55]	37 [36]	
IV	12 [9]	8 [24]	4 [4]	
Site, n [%]				0.415
Extremity	67 [49]	18 [55]	49 [47]	
Retroperitoneal	37 [27]	9 [27]	28 [27]	
Trunk	21 [15]	4 [12]	17 [16]	
Abdominal	12 [9]	2 [6]	10 [10]	

Table 1 (*continued*)

Table 1 (*continued*)

Clinical variables	Overall (n=137)	Deceased (n=33)	Survived (n=104)	Univariable P value[&]
Histology, n [%]				0.290
High-grade UPS	18 [13]	7 [21]	11 [11]	
Well-differentiated LS	18 [13]	2 [6]	16 [15]	
Myxoid LS	15 [11]	2 [6]	13 [13]	
Leiomyosarcoma	11 [8]	4 [12]	7 [7]	
Dedifferentiated LS	10 [7]	1 [3]	9 [9]	
Synovial sarcoma	9 [7]	2 [6]	7 [7]	
Other	56 [41]	15 [45]	41 [39]	

Treatments included surgery (87.6%), as well as radiation therapy before surgery (25.2%), pre-operative chemotherapy (8.7%), and administration of a tyrosine kinase inhibitor (1.6%). †, only 128 patients underwent surgical resection with curative intent, of whom 104 were living at last follow up and 24 who died; &, the P value is based on a Cox proportional hazards univariable model or the log rank test; *, significant values (P<0.05) are highlighted. UPS, undifferentiated pleomorphic sarcoma; LS, liposarcoma.

Table 2 Adipose tissue and muscle metrics for entire cohort of soft-tissue sarcoma patients, with univariable analysis for overall survival

Body composition metric	Overall (n=137)	Deceased (n=33)	Survived (n=104)	P value[†]
Fat, mean (SD)				
Visceral fat area	271.4 (132.1)	261.7 (126.4)	274.5 (134.3)	0.493
Visceral fat attenuation	–85.9 (10.6)	–86.7 (10.3)	–85.6 (10.7)	0.509
Subcutaneous fat area	263.2 (132.4)	265.2 (134.8)	262.5 (132.2)	0.942
Subcutaneous fat attenuation	–101.8 (29.0)	–105.2 (20.8)	–100.7 (31.1)	0.394
Total fat area	712.2 (236.3)	695.1 (251.5)	717.7 (232.3)	0.511
Total fat attenuation	–90.6 (10.2)	–91 (10.5)	–90.5 (10.1)	0.637
Thresholded muscle, mean (SD)				
Psoas area	24.3 (9.3)	22.6 (7.6)	24.9 (9.8)	0.288
Psoas index	9 (6.8)	10 (12.6)	8.7 (3.5)	0.114
Psoas attenuation	48.8 (10)	45.5 (12.7)	49.8 (8.8)	0.007*
Total muscle area	139.9 (42.8)	132.5 (41.7)	142.2 (43.1)	0.548
Total muscle index	52.3 (45.5)	61 (90.2)	49.5 (12.6)	0.015*
Total muscle attenuation	39 (11.8)	36 (12.9)	39.9 (11.4)	0.088
Non-thresholded muscle, mean (SD)				
Psoas area	20.5 (7.8)	17.6 (6.6)	21.4 (7.9)	0.019*
Psoas index	7.1 (2.3)	6.2 (1.9)	7.4 (2.3)	0.024*
Psoas attenuation	50.4 (12.6)	46.6 (17.6)	51.7 (10.3)	0.005*
Total muscle area	124.3 (42.4)	122.5 (41.3)	124.9 (42.9)	0.987
Total muscle index	43.1 (12.4)	43.2 (11.6)	43.1 (12.6)	0.687
Total muscle attenuation	35.2 (16.9)	29.2 (18.9)	37.1 (15.8)	0.011*

†, the P value is based on a Cox proportional hazards univariable model; *, significant values (P<0.05) are highlighted.

Table 3 Association of CT metrics and overall survival

CT metrics	Univariable analysis†		Multivariable analysis‡		Multivariable analysis with Sidak correction^	
	Unadjusted HR	P value	Adjusted HR	P value	Adjusted HR (95% CI)	Adjusted Sidak P value
Adipose tissue						
Visceral fat area	0.999	0.493	0.998	0.234	–	–
Visceral fat attenuation	0.988	0.509	0.997	0.875	–	–
Subcutaneous fat area	1.000	0.942	1.001	0.446	–	–
Subcutaneous fat attenuation	0.991	0.394	0.976	0.09	–	–
Thresholded muscle						
Psoas area	0.977	0.288	0.942	0.078	0.928 (0.86–1.003)	0.261
Psoas index	1.033	0.114	1.026	0.211	0.794 (0.632–0.998)	0.218
Psoas attenuation	0.955	0.007*	0.948	0.004*	0.947 (0.913–0.982)	0.018*
Total muscle area	0.998	0.548	0.994	0.271	–	–
Total muscle index	1.006	0.015*	1.004	0.079	–	–
Total muscle attenuation	0.972	0.088	0.963	0.049*	0.966 (0.929–1.004)	0.342
Non-thresholded muscle						
Psoas area	0.938	0.019	0.893	<0.001*	0.874 (0.81–0.944)	0.003*
Psoas index	0.811	0.024	0.664	<0.001*	0.684 (0.544–0.86)	0.006*
Psoas attenuation	0.969	0.005	0.963	0.002*	0.963 (0.939–0.986)	0.011*
Total muscle area	1.000	0.987	0.996	0.411	–	–
Total muscle index	1.006	0.687	0.989	0.546	–	–
Total muscle attenuation	0.973	0.011	0.967	0.004*	0.966 (0.944–0.99)	0.023*

†, the P value is based on a Cox proportional hazards univariable model; ‡, the P value is based on a Cox proportion hazards multivariable model adjusting for age (dichotomized at 65 years), sex, grade, and stage; ^, the P value is based on a Cox proportional hazards multivariable model adjusting for age (dichotomized at 65 years), sex, grade, and stage, and it is adjusted using the Sidak correction; *, significant values (P<0.05) are highlighted.

psoas attenuation (P=0.004) and total muscle attenuation (P=0.049). When the Sidak correction to the multivariable model was applied, only psoas attenuation remained significant (P=0.018), with an adjusted HR of 0.947 (95% CI, 0.913–0.982). For every 1 HU increase in the attenuation of the psoas muscle, the hazard of death decreased by 5.3%.

Non-thresholded

Using the non-thresholded (PACS) method, four muscle metrics were significantly associated with mortality: psoas area (P<0.001), psoas index (P<0.001), psoas attenuation (P=0.002), and total muscle attenuation (P=0.004). With Sidak correction, the adjusted P values were still significant, ranging from 0.003 to 0.023. The adjusted C-statistics ranged from 0.78 to 0.81, demonstrating moderate ability to discriminate between patients who survived and died. With Sidak correction, the HR of psoas attenuation was 0.963 (95% CI, 0.939–0.986). For every 1 HU increase in attenuation the hazard of death decreased by 3.7%. Similarly, the HR of psoas area was 0.874 (95% CI, 0.81–0.944). For every 1 cm^2 increase in area, the hazard of death decreased by 12.6%.

Total muscle area and total muscle index were not significantly associated with mortality in univariable or multivariable analysis.

Major postoperative complications

Of 128 patients who had surgery, 41 patients (32%) had

Table 4 Association of CT metrics and major postoperative complications

CT Metrics	Univariable analysis†		Multivariable analysis‡		Multivariable analysis with Sidak correction^	
	Unadjusted OR	P value	Adjusted OR	P value	Adjusted OR (95% CI)	Adjusted Sidak P value
Adipose tissue						
Visceral fat area	1.003	0.022*	1.003	0.135	–	–
Visceral fat attenuation	1.002	0.920	0.983	0.443	–	–
Subcutaneous fat area	1.000	0.806	1.000	0.834	–	–
Subcutaneous fat attenuation	1.004	0.569	1.007	0.326	–	–
Thresholded muscle						
Psoas area	0.992	0.697	0.997	0.913	0.987	0.998
Psoas index	0.971	0.492	0.974	0.587	0.999	>0.999
Psoas attenuation	0.957	0.048*	0.956	0.059	0.958	0.322
Total muscle area	0.999	0.844	0.997	0.625	–	–
Total muscle index	0.997	0.598	0.996	0.618	–	–
Total muscle attenuation	0.961	0.031*	0.965	0.104	0.965	0.451
Non-thresholded muscle						
Psoas area	0.982	0.457	0.997	0.93	0.976	0.984
Psoas index	0.945	0.52	1.007	0.955	0.978	>0.999
Psoas attenuation	0.957	0.030*	0.954	0.039*	0.956	0.216
Total muscle area	0.996	0.386	0.994	0.355	–	–
Total muscle index	0.991	0.604	0.987	0.528	–	–
Total muscle attenuation	0.971	0.019*	0.973	0.054	0.974	0.295

†, the P value is based on a logistic univariable model; ‡, the P value is based on a logistic multivariable model adjusting for age (dichotomized at 65 years), sex, grade, and stage. ^, the P value is based on a logistic multivariable model adjusting for age (dichotomized at 65 years), sex, grade, and stage, and it is adjusted using the Sidak correction; *, Significant values (P<0.05) are highlighted.

a major postoperative complication. Major postoperative complications were more common in patients who died (9/24, 38%) compared to those still living at last follow up (32/104, 31%). BMI had no significant association with major postoperative complications. *Table 4* shows univariable and multivariable analyses of major postoperative complications and CT metrics, adjusting for age (dichotomized at age 65), sex, tumor site, and tumor size (*Table 4*).

Adipose tissue metrics

Using the thresholded method, 1 of 6 adipose tissue metrics was significant: visceral fat area (P=0.022). Other adipose tissue metrics were not significantly associated with major postoperative complications.

Muscle metrics

Thresholded

Using the thresholded method, 2 of 6 muscle metrics were significantly associated with major postoperative complications in a univariable analyses: psoas attenuation (P=0.048) and total muscle attenuation (0.031).

Non-thresholded

Using the non-thresholded method, the same metrics were significant in a univariable analyses: psoas attenuation (P=0.030) and total muscle attenuation (P=0.019).

In multivariable analyses, only psoas attenuation remained significant (P=0.039, C-statistic =0.70), but with Sidak correction it was no longer significant (P=0.216). None of the other muscle metrics (thresholded and non-thresholded) were significant.

Concordance analysis

There was excellent intra-observer and inter-observer agreement among the three readers: all correlation coefficients were >0.9 for all variables and methods, with one exception. A single inter-observer coefficient (0.74) for the thresholded method of SAT attenuation was attributed to SAT attenuation measurement on a single patient performed by one reader.

Discussion

Our study shows that shorter survival is significantly associated with low CT measures of psoas muscle area, psoas index, and psoas attenuation in STS patients. These findings remained significant independent of commonly used prognostic factors in patients with cancer, including patient age and BMI.

Prior studies of patients with STS have also analyzed the relationship between CT-derived muscle metrics and survival. Our results on muscle attenuation compare favorably to Veld *et al.* (21) who studied 116 patients with extremity STS, and reported that psoas muscle attenuation at the L4 level was associated with mortality in fully adjusted models. However, unlike our study, they did not evaluate muscle cross-sectional area or muscle index (21).

Different results were reported by Wilson *et al.* (22) in 137 patients with STS undergoing a preoperative staging abdominal CT. They used a free-hand (non-thresholded) technique to measure the psoas area at the L3 level (indexed for patient height), and found no association with overall survival or wound complications. In contrast, our study found that a higher psoas index was associated with longer survival, even after adjusting for covariates. This difference may be related to differences in their study population compared to ours: percentage of superficial sarcomas (20% *vs.* 9%), undifferentiated pleomorphic sarcoma (42% *vs.* 13%), and intermediate/high grade sarcoma (82% *vs.* 63%).

In a prior study of adipose tissue metrics in patients with STS, Veld *et al.* (21) reported higher attenuation of SAT (but not VAT) was associated with mortality. In our study, we found no association between VAT and SAT metrics and mortality. Another study (28) of 60 patients with extremity STS undergoing non-contrast CTs reported that the attenuation of SAT at the L4 level was associated with post-operative wound infections. This is different from our study, where VAT area was associated with major postoperative complications in unadjusted models, but not significant after adjusting for covariates. Thus, in our cohort, the combination of four covariates (age, sex, grade, and stage) was a stronger determinant of clinical outcomes than VAT cross-sectional area.

A prospective, multi-institutional study is needed to reconcile the differences among STS studies and determine the value of CT-derived adipose and muscle metrics for patient management and prognosis.

Our study has several limitations that are similar to prior single-center studies, including retrospective study design, lack of non-cancer control subjects, heterogeneous histologic subtypes of sarcomas included in analyses, and lack of histologic correlation for the muscle and fat measurements made by CT. However, our study also has several strengths, including the quantitative evaluation of both cross-sectional area and attenuation metrics for adipose tissue and skeletal muscle, with rigorous statistical analysis of important clinical outcomes: overall survival and major postoperative complications.

Conclusions

In conclusion, muscle area and attenuation are associated with overall survival in patients with STS. These prognostic biomarkers can be quantitated on independent workstations that use thresholding software or measured using routine clinical PACS.

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Footnote

Provenance and Peer Review: With the arrangement by the Guest Editors and the editorial office, this article has been reviewed by external peers.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims.2020.02.09). The special issue "Body Composition Imaging" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study obtained ethics approval from our Institutional Review Board, with waiver of informed consent for this retrospective study.

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