Clinical Nutrition ESPEN 61 (2024) 274–280

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Low subcutaneous adipose tissue and myosteatosis are prognostic factors after allogeneic hematopoietic stem cell transplantation

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ARTICLE INFO

Article history:
Received 2 August 2023
Accepted 29 March 2024

Keywords:
Tomography
X-ray computed
Stem cell transplantation
Hematological neoplasms
Adipose tissue
Sarcopenia

SUMMARY

Objective: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents the only curative treatment option for several hematological neoplasms. This study aimed to assess the parameters of body composition as predictors of post-transplant overall survival (OS) and adverse events in patients with leukemia, myelodysplastic syndromes (MDS), and myeloproliferative neoplasms (MPN).
Methods: This was a retrospective study of 122 adult patients who underwent their first allo-HSCT. The CT-based semi-automated measurement of subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), visceral-to-subcutaneous fat ratio (VSR), sarcopenia in terms of skeletal muscle index (SMI), and myosteatosis based on the skeletal muscle radiation attenuation (SM-RA) was performed. Cox regression analysis was used to assess the association of body composition parameters with OS.
Results: In the univariate analysis, low SAT and myosteatosis were associated with lower OS (hazard ratio [HR] 2.02, 95% confidence interval [CI] 1.16–3.51, $p = 0.01$) and (HR 2.50, 95% CI 1.48–4.25, $p =< 0.001$), respectively. This association remained significant after adjusting for relevant covariates, with HR 2.32, 95% CI 1.23–4.38, $p = 0.01$ and HR 2.86, 95% CI 1.51–5.43, $p =< 0.001$, respectively. On the contrary, VAT, VSR, sarcopenia, and sarcopenic obesity were not statistically significant in OS. Severe post-transplant adverse events were more common in the low SAT group (odds ratio [OR] 3.12, 95% CI 1.32–7.40, $p = 0.01$) and OR 3.17, 95% CI 1.31–7.70, $p =< 0.01$ in the age- and sex-adjusted analysis.
Conclusion: Low SAT and myosteatosis may contribute to an increased risk of post-transplant mortality, while low SAT appears to increase the risk of severe post-transplant adverse events.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially life-saving procedure for several hematological malignancies [1]. Relevant indications for HSCT comprise acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myeloproliferative neoplasms (MPN), including chronic myeloid leukemia (CML), and myelodysplastic syndromes (MDS), depending on the stage of disease and risk factors [2–5]. Additionally, allo-HSCT remains a valuable therapeutic option for patients with multiply relapsed or poor-risk chronic lymphocytic leukemia (CLL) [6–8]. Allo-HSCT is associated with immediate and long-term complications, which can result in decreased quality of life and shortened life expectancy [1]. Studies on the influence of body composition parameters as predictors of overall survival (OS) and adverse events following allo-HSCT are scarce.

Obesity has been identified as a risk factor in hematological diseases [9,10]. According to a meta-analysis by Wallin et al., in

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https://doi.org/10.1016/j.clnesp.2024.03.032

2011, the risk of multiple myeloma (MM) was significantly elevated among obese patients (relative risk 1.21, 95% confidence interval [CI]: 1.08–1.35) [10]. Fuji et al., in 2014, reported that the risk of non-relapse mortality after allo-SCT was significantly higher in the overweight and obese group compared to the normal weight group (hazard ratio [HR] 1.19 and 1.43, respectively) [11].

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) can predict clinical outcomes in solid tumors [12,13]. In 2016, Takeoka et al. evaluated 56 patients with newly diagnosed MM. Their findings revealed a significant association between low SAT and poor 2-year OS (HR 4.05, 95%CI 1.24–13.19), p = 0.02) [14]. Moreover, a meta-analysis conducted by Aleixo et al., shed further light on the prognostic significance of adipose tissue in hematological malignancies. Patients categorized with low VAT demonstrated a twofold increase in mortality risk (HR 2.02, 95% CI 1.30–3.14, p = 0.004). Similarly, patients classified with low SAT exhibited an almost threefold greater mortality risk (HR 2.98, 95% CI 1.69–5.26, p = 0.0002) [15].

As per the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is defined as a progressive and widespread skeletal muscle disorder, this condition is confirmed by the presence of low muscle quantity or quality [16]. Radiological sarcopenia has been explored as a biomarker utilizing the opportunistic measurement of skeletal muscle from routine cross-sectional cancer imaging via CT and MRI scans, widely regarded as the gold standard for non-invasive assessment of muscle quantity [17]. In a recent meta-analysis, sarcopenia identified on CT examinations was found to be associated with OS rates in hematological diseases, including Diffuse Large B-cell Lymphoma (DLBCL) and leukemias HR 3.05 (95% CI 2.30–4.05, p < 0.00001) and HR 1.57 (95% CI 1.07–2.31, p < 0.02), respectively [18]. In 2019, Armenian et al. showed that sarcopenia assessed by measuring the skeletal muscle index (SMI) was an independent predictor of higher post-transplant mortality in patients with acute leukemia and MDS HR 1.58, 95% CI 1.16–2.16, $p = 0.004$) [19]. Besides the loss of skeletal muscle tissue (SMT), qualitative structural changes, such as the presence of inter- and intramyocellular fat deposition, a condition known as myosteatosis, can potentially impact clinical outcomes in hematological diseases [20].

Our study aimed at assessing the body composition parameters: VAT, SAT, sarcopenia, and myosteatosis based on the skeletal muscle radiation attenuation (SM-RA) as predictors of OS and adverse events in patients with leukemia, MDS, or MPN undergoing allo-HSCT.

2. Methods

2.1. Participants

This retrospective cohort study was approved by the Institutional Review Board (Nr. 145/21, Ethics Committee, Otto-von-Guericke University of Magdeburg, Magdeburg, Germany). The requirement to obtain informed consent was waived.

Inclusion criteria were the following: (a) patients (≥18 years old) who underwent their first allo-HSCT for confirmed leukemia (acute or chronic, regardless of the phenotype), MDS, or MPN at the Department of Hematology and Oncology (University Hospital Magdeburg) between January 2015 and October 2021, (b) CT of the chest, abdomen, and pelvis before the transplant conducted within four weeks prior allo-HSCT. The exclusion criteria were as follows: (a) no available CT and (b) previous hematopoietic stem cell transplantation (HSCT). CT scans were performed to rule out occult infection before the initiation of conditioning therapy. Patients were identified in our internal clinical database (MEDICO KIS, CompuGroup Medical SE & Co. KGaA, Koblenz, Germany). Clinical information was extracted and comprised of gender, age, height, weight, body mass index (BMI), total serum protein (g/dL), total serum albumin (g/dL), and allo-HSCT donor source.

2.2. Overall survival and adverse events

OS was defined as the time from transplant to death or the date of the last contact in February 2023. Early post-transplant adverse events were retrieved from patients' medical records and graded according to the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) of the National Institutes of Health [21]. Early post-transplant adverse events were defined as those manifesting within the initial 30 days post-transplantation. After transplantation, patients were seen in our outpatient clinic every week and later every 4–8 weeks depending on their general condition and side–effect profile. Subsequently, follow-up intervals were extended.

2.3. CT technique and segmentation of body composition

CT scans were performed on a Canon Aquilion Prime (Canon Medical Systems, Otawara, Japan) or Siemens SOMATOM Definition AS+ (Siemens Healthcare, Erlangen, Germany) multidetector CT scanner. Patients were scanned in a supine position. The protocol was as follows: acquisition slices thickness of 1 mm with reconstructions of 5 mm, tube voltage of 120 kV, automated tube current modulation, pitch factor of 1.2., and collimation of 0.6 mm.

Our segmentation technique has been previously described [22,23]. In brief, we chose series with a 5 mm axial slice thickness and soft tissue kernel at the level of the third lumbar vertebra (L3). The cross-sectional areas of the SMT, SAT, VAT, and intermuscular adipose tissue (IMAT) were semiautomatically measured with the ImageJ software 1.48v (Wayne Rasband, National Institutes of Health, Maryland, USA). Furthermore, the mean SM-RA as an indicator of muscle density and myosteatosis was recorded in Hounsfield Units (HU). Skeletal muscle, was identified using threshold values of −29 and 150 HU. Fat areas were measured using HU threshold levels of −190 and −30 HU, as previously reported [23–26]. The software was operated by a researcher with four years of experience in the field of abdominal radiology, complex imaging analysis, and segmentation techniques, who was blinded to the patient's survival status (Fig. 1).

2.4. Definitions of body composition groups and myosteatosis

BMI was calculated by using the formula [weight (kg)/height squared (m^2)] [27]. Patients were categorized according to their BMI, as follows: (a) underweight (<18.5 kg/m^2), (b) normal weight (18.5–24.9 kg/m^2), (c) overweight (25.0–29.9 kg/m^2), and (d) obese (≥30 kg/m^2) [28]. The cut-off value for the classification of SAT was 100 (cm^2); for VAT 100 (cm^2); and for VSR ratio 1.1 [22,29]. Sarcopenia was defined depending on the SMI. The latter was calculated by dividing SMT (cm^2) by height squared (m^2) [27]. In accordance with the criteria established by Prado et al., radiological sarcopenia was defined using SMI cut-off values, for male patients, the SMI cut-off value was 52.4 cm^2/m^2, while for female patients, it was 38.5 cm^2/m^2 [30]. Sarcopenic obesity was defined as the occurrence of sarcopenia and increased BMI (>25 kg/m^2) [31]. Myosteatosis was defined as SM-RA < 41 HU for patients with a BMI ≤24.9 kg/m^2 and <33 HU for patients with a BMI ≥25.0 kg/m^2 [32,33].

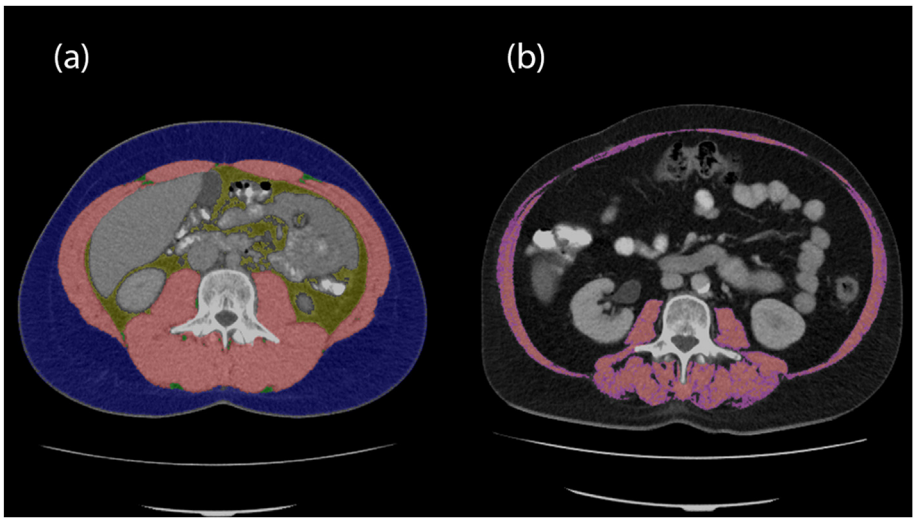

Fig. 1. CT-derived body composition at the third lumbar vertebral (L3) (a) blue, subcutaneous adipose tissue (SAT); pink, skeletal muscle tissue (SMT); green, intermuscular adipose tissue (IMAT); and yellow, visceral adipose tissue (VAT). (b) purple, skeletal muscle radiation attenuation (SM-RA). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.5. Statistical analysis

Data normality was assessed using the Kolmogorov–Smirnov test. Descriptive statistics were presented as the median and interquartile range (IQR) for data with non-parametric distributions and as the mean and standard deviation (SD) for parametric distributions. The correlation between BMI and body composition parameters was calculated by Spearman's rank correlation coefficient. Univariate and Cox regression analysis was used to assess the association of body composition parameters (based on dichotomous traits) with OS. Cox regression models adjusted for relevant covariates (age, sex, graft-versus-host disease, organ failure, renal failure, post-transplant adverse events, and severe adverse events graded according to CTCAE [≥4]) were also used to test this association. HRs are presented together with 95% CI. The Kaplan–Meier method was performed to estimate survival probabilities, which were compared between the groups of body composition using the log-rank test. Additionally, a binary logistic regression model (unadjusted and adjusted for age and sex) was performed to explore the association between the body composition groups as risk factors for specific early post-transplant adverse events and according to CTCAE (grade 3 or ≥ 4). Odds ratios (ORs) are presented together with 95% CI. A two-tailed p-value ≤0.05 was considered statistically significant. IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA) was used as analytic software.

3. Results

3.1. Participants

122 patients (68 males) were evaluated. The median age of the patients was 56.50 years (IQR: 44.00–64.00 years). The mean BMI was 26.16 ± 4.4 kg/m^2 51 (41.80%) and 23 (18.85%) patients were categorized as overweight and obese based on BMI, respectively. The most common diagnosis was AML in 59 patients (48.36%), followed by MDS in 20 patients (16.39%). The majority of the patients received their allo-HSCT from an unrelated donor [n = 101 (82.79%)], followed by a matched related donor in 17 cases (13.93%) (Table 1).

Table 1
Patient characteristics (n = 122).

Parameters	n, (%)
Female	54 (44.26)
Male	68 (55.73)
Age (years), median (IQR)	56.50 (44.00–64.00)
Body mass index (BMI) kg/m^2, mean ± SD	26.16 ± 4.4
Underweight (<18.5 kg/m^2)	3 (2.46)
Normal weight (18.5–24.9 kg/m^2)	45 (36.89)
Overweight (25.0–29.9 kg/m^2)	51 (41.80)
Obese (≥30 kg/m^2)	23 (18.85)
Total serum protein (g/dL)[a], mean ± SD	69.85 ± 6.8
Total serum albumin (g/dL)[b], mean ± SD	37.00 ± 0.87
Diagnosis	
Acute myeloid leukemia (AML)	59 (48.36)
Acute lymphoblastic leukemia (ALL)	8 (6.56)
Mixed-phenotype acute leukemia (MPAL)	4 (3.28)
Chronic lymphocytic leukemia (CLL)	12 (9.84)
Myeloproliferative neoplasms (MPN)	5 (4.10)
Myelodysplastic syndromes (MDS)	20 (16.39)
Others	14 (11.48)
Donor	
Matched-unrelated donor	101 (82.79)
Matched-related donor	17 (13.93)
HLA-haploidentical donor	4 (3.28)

Continuous variables are presented as mean (M) ± standard deviation (SD) or median and interquartile range (IQR).
[a] Information available for 120 patients.
[b] Information available for 82 patients.

3.2. Body composition parameters

Regarding the body composition parameters of our population, the mean SAT and VAT were 185.54 ± 102.2 cm^2 and VAT 140.97 ± 95.8 cm^2, respectively. The mean SM-RA density was 37.51 ± 9.2 HU. The median VSR was 0.66 [IQR 0.24–1.21]. 29 (23.77%) patients were classified in the group of low SAT, 75 (61.48%) in the group of high VAT, and 35 (28.7.%) in the group of high VSR. The median SMI was 43.55 cm^2/m^2 [IQR 37.9–52.35]. and Based on the sex-specific cutoffs, sarcopenia was identified in 69 patients (56.56 %), sarcopenic obesity in 30 (24.59%), and myosteatosis in 52 patients (43.62%) (Table 2).

Table 2
Body composition parameters of the patients ($n = 122$).

Body composition measurements (continuous variables)	*n*, (%)
SAT (cm^2), *m* ± SD	185.54 ± 102.2
VAT (cm^2), *m* ± SD	140.97 ± 95.8
VSR, *median, IQR*	0.66 [0.24–1.21]
SMT (cm^2), *median, IQR*	126.51 [106.92–157.73]
SMI (cm^2/m^2), *median, IQR*	43.66 [37.9–52.35]
IMAT (cm^2), *median, IQR*	7.83 [5.17–12.25]
SM-RA (HU), *m* ± SD	37.51 ± 9.2
Body composition groups (based on dichotomous traits)	
Low SAT	29 (23.77)
High VAT	75 (61.48)
High VSR	35 (28.69)
Myosteatosis	52 (42.62)
Sarcopenia	69 (56.56)
Sarcopenic obesity	30 (24.59)

Continuous variables are presented as mean (*m*) ± standard deviation (*SD*) or median and interquartile range (IQR).
SAT, subcutaneous adipose tissue, VAT visceral adipose tissue; VSR, visceral-to-subcutaneous fat ratio; SMT, skeletal muscle tissue; SMI, skeletal muscle index; IMAT, intermuscular adipose tissue; SM-RA, skeletal muscle radiation attenuation; HU, Hounsfield unit.

3.3. Association between body composition parameters and overall survival

Overall, 57 patients (46.7%) died during the evaluation period. The median OS time was 22.62 months (IQR: 7.07–58.01 months). In the univariate Cox regression analysis, low SAT and myosteatosis were associated with lower OS (HR 2.02, 95% CI 1.16–3.51, $p = 0.01$, adjusted: HR 2.32, 95% CI 1.23–4.38, $p = 0.01$) and (HR 2.50, 95% CI 1.48–4.25, p =<0.001, adjusted: HR 2.86, 95% CI 1.51–5.43, p=<0.001). On the contrary, high VAT, high VSR, sarcopenia, and sarcopenicobesity did not significantly influence OS (HR 0.93, 95% CI: 0.55–1.58, $p = 0.79$, adjusted: HR 0.79, 95% CI 0.47–1.78, $p = 0.91$) (HR 1.30, 95% CI 0.75–2.28, $p = 0.35$, adjusted: HR 1.88, 95% CI 0.89–3.98, $p = 0.10$) (HR 1.16, 95% CI 0.68–1.96, $p = 0.59$, adjusted: HR 1.19, 95% CI 0.68–2.08, p = 0.54), and (HR 0.82, 95% CI 0.43–1.55, $p = 0.54$, adjusted: HR 0.78, 95% CI 0.40–1.52, $p = 0.46$), respectively (Table 3). Similar results were observed in the Kaplan–Meier analysis (Fig. 2 and Suppl. Figure 1). There was a statistically significant difference between the groups of low SAT and high SAT and normal muscle density compared to myosteatosis regarding OS (log-rank test, $p = 0.01$ and p=<0.001, respectively).

3.4. Association between body composition parameters and post-transplant adverse events

We identified graft versus host disease (GVHD) in 52 out of 122 patients (42.62%), sepsis in 21 out of 122 (17.21 %), and organ failure in 38 out of 122 (31.15 %) patients, as detailed in Table 4. Subsequently, we evaluated the occurrence of these adverse events across different body composition groups). The results are presented in Suppl. Tables 2a, 2b, and 2c, outline the OR of body composition groups in relation to sepsis, GVHD, and organ failure, respectively. While the univariate analysis did not reveal significant associations between specific adverse events and body composition groups, myosteatosis emerged in the multivariate analysis as a significant risk factor for GVHD, with OR 3.49, 95% CI 1.46–8.32. Furthermore, we observed, that post-transplant adverse events grade 3 were reported in 70 patients (57.38.%), grade 4 in 43 (35.2%), and grade 5 in 7 (5.74%) (Table 5). Notably, regarding the analysis of body composition groups as risk factors for post-transplant complications according to CTCAE, we found that adverse events grade ≥4 were more likely to occur in patients with low SAT with OR of 3.12, 95% CI 1.32–7.40, $p = 0.01$ and OR 3.17, 95% CI 1.31–7.70, p = 0.01, after adjusting for sex and age.

3.5. Correlation analysis

The correlation analysis revealed significant associations between BMI and various body composition parameters (Suppl. Table 1). Specifically, BMI exhibited a strong positive correlation with SAT (r = 0.82, p < 0.01) and VAT (r = 0.68, p < 0.01). Additionally, BMI demonstrated a statistically significant positive correlation with SMT (r = <0.01, p < 0.01). However, a negative correlation was observed between BMI and SM-RA (r = −0.37, p < 0.01), indicating that higher BMI values were associated with lower skeletal muscle attenuation.

4. Discussion

Allo-HSCT has broad applications in treating various hematological malignancies [4–6]. Our study examined the association between parameters of body mass composition and OS after transplantation in leukemia, MDS, and MPN. Our findings suggested that low SAT and myosteatosis may contribute to an increased risk of post-transplant mortality, while low SAT appears to increase the risk of severe post-transplant adverse events.

According to a recent meta-analysis sarcopenia is related to lower OS in patients with hematological diseases that did not undergo allo-HSCT [18]. In acute leukemias and MDS, sarcopenia was associated with lower OS in the simple regression analysis (HR 3.05, 95% CI 2.30–4.05; $p = 0.00001$ and HR 1.57, 95% CI 1.07–2.31, p=<0.02). Nevertheless, multiple regression analyses showed no association between sarcopenia and a lower OS (HR 1.82, 95% CI 1.07–3.58). In this meta-analysis, two studies evaluating patients with leukemias/MDS were included [18]. In one of these studies, Nakamura et al. analyzed the three-year OS in 90 patients with AML who received chemotherapy and showed an association between

Table 3
Association between body composition parameters (as dichotomous traits) and overall survival ($n = 122$).

Parameters	Unadjusted			Adjusted*		
	HR	CI 95%	p-value	HR	95% CI	p-value
SAT (low vs. high)	2.02	[1.16–3.51]	0.01	2.32	[1.23–4.38]	0.01
VAT (high vs. low)	0.93	[0.55–1.58]	0.79	0.79	[0.47–1.78]	0.91
VSR (high vs. low)	1.30	[0.75–2.28]	0.35	1.88	[0.89–3.98]	0.10
SM-RA (myosteatosis vs normal muscle)	2.50	[1.48–4.25]	<0.001	2.86	[1.51–5.43]	<0.001
Sarcopenia (yes vs. no)	1.16	[0.68–1.96]	0.59	1.19	[0.68–2.08]	0.54
Sarcopenic obesity (yes vs. no)	0.82	[0.43–1.55]	0.54	0.78	[0.40–1.52]	0.46

Cox regression models were adjusted for age, sex, graft-versus-host disease, organ failure, renal failure, sepsis, and severe adverse events graded according to CTCAE (≥4). HR, hazard ratio; CI, confidence interval; SAT, subcutaneous adipose tissue, VAT visceral adipose tissue; VSR, visceral-to-subcutaneous fat ratio, SM-RA, skeletal muscle radiation attenuation.

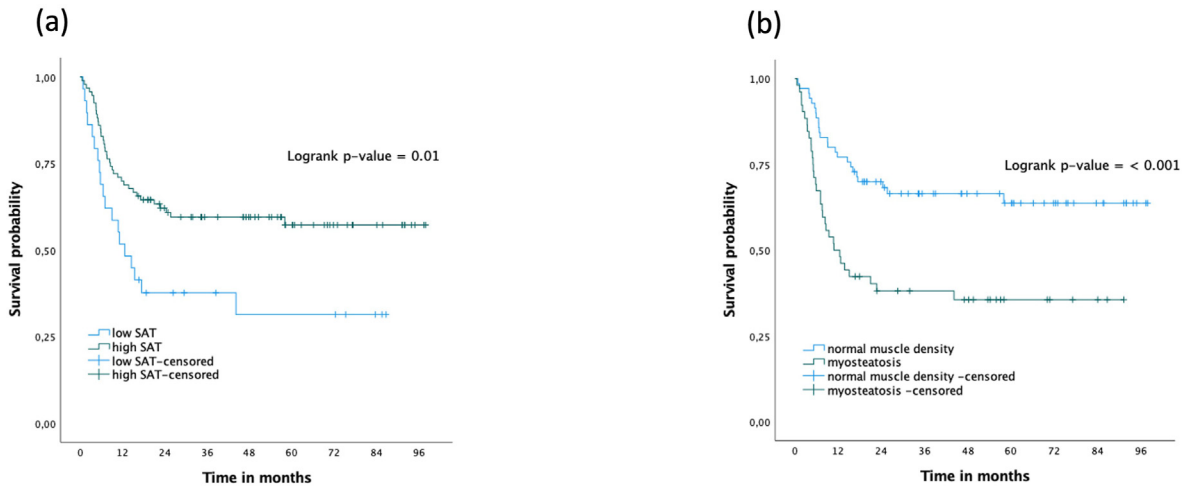

Fig. 2. Results of the Kaplan–Meier survival analysis for patients stratified according to (a) the subcutaneous adipose tissue (SAT) and (b) SM-RA, skeletal muscle radiation attenuation.

Table 4
Post-transplant adverse events (n = 122).

Adverse events after allo-HSCT	*n*, (%)
Fever	97 (79.51)
GvHD	52 (42.62)
Mucositis	42 (34.43)
Organ failure	38 (31.15)
Viral reactivation	37 (30.33)
Diarrhea	32 (26.23)
Renal failure	24 (19.67)
Sepsis	21 (17.21)
Thrush	19 (15.57)
Exanthema	17 (13.93)
Pneumonia	13 (10.66)
Urinary tract infection	13 (10.66)
Palmar-plantar-erythrodysesthesia	9 (7.38)

Allo-HSCT, Allogeneic Hematopoietic Stem Cell Transplantation, GvHD, Graft versus host disease.

sarcopenia and lower OS (HR 2.27, 95% CI 1.11–4.79, p=<0.005) [34]. In the other study, Armenian et al. conducted a retrospective observational analysis of sarcopenia as a prognostic factor in patients with AML, ALL, and MDS after transplantation [19]. They found that pre-transplant sarcopenia was an independent predictor of higher nonrelapse mortality during the first two years after transplantation (HR 1.58, 95% CI 1.16–2.16). In our study, sarcopenia and sarcopenicobesity did not significantly influence OS (HR 1.16, 95% CI 0.68–1.96, p = 0.59, adjusted: HR 1.19, 95% CI 0.68–2.08, p = 0.54), and (HR 0.82, 95% CI 0.43–1.55, p = 0.54, adjusted: HR 0.78, 95% CI 0.40–1.52, p = 0.46). The reason for this is not apparent ultimately, multi-centric studies are required to harmonize these discordant results regarding the role of pre-HSCT sarcopenia and OS.

Regarding the post-transplant complications, in our study, sarcopenia and sarcopenic obesity were not identified as risk factors for post-transplant adverse events grade ≥4 (OR = 0.96, 95% CI:0.46–1.99, p = 0.92, age and sex-adjusted: OR 0.95, 95% CI 0.42–2.15, p = 0.90) and (OR 0.53, 95% CI 0.22–1.29, p = 0.16, age and sex-adjusted: OR 0.55, 95% CI 0.23–1.34, p = 0.19), respectively. Suzuki et al. retrospectively assessed sarcopenia in 47 patients with ALL who underwent induction therapy. In their study, adverse events of grade 3 or greater were more likely to occur in sarcopenic patients than in non-sarcopenic (50.1% and 12.1%, p = 0.009) [35]. In their study, sarcopenia was measured by evaluating the psoas muscle area manually. Since the SMI is broadly considered a more complete and robust measurement of the skeletal muscle status and a strength of our study is the use of a semi-automated tool for

Table 5
Odds ratio of body composition groups and post-transplant adverse events (n = 122).

CTCAE grade 3 (n = 70)	Univariate analysis			Age and sex-adjusted		
	OR	CI	*p*-value	OR	CI	p-value
SAT (high vs. low SAT)	2.84	[1.20–6.71]	0.02	0.35	[0.15–0.85]	0.02
VAT (high vs. low VAT)	1.75	[0.84–3.67]	0.14	0.58	[0.25–1.35]	0.21
VSR (high vs. low VSR)	0.99	[0.45–2.18]	0.97	1.23	[0.48–3.17]	0.57
Myosteatosis vs normal muscle density	1.02	[0.49–2.11]	0.95	0.71	[0.25–2.06]	0.53
Sarcopenic vs. non-sarcopenic	1.06	[0.51–2.18]	0.88	1.04	[0.50–2.15]	0.92
Sarcopenic obesity vs non-sarcopenic obesity	2.05	[0.85–4.95]	0.11	0.35	[0.11–1.11]	0.07
CTCAE grade ≥ 4 (n = 50)	**OR**	**CI**	***p*-value**	**OR**	**CI**	**p-value**
SAT (low vs. high)	3.12	[1.32–7.40]	0.01	3.17	[1.31–7.70]	0.01
VAT (high vs. low VAT)	0.51	[0.24–1.07]	0.07	0.53	[0.23–1.23]	0.14
VSR (high vs. low VSR)	0.94	[0.42–2.10]	0.89	0.82	[0.31–2.12]	0.67
Myosteatosis vs normal muscle density	0.96	[0.46–1.99]	0.91	0.95	[0.42–2.15]	0.90
Sarcopenic vs. non-sarcopenic	0.96	[0.46–1.99]	0.92	1.02	[0.49–2.12]	0.96
Sarcopenic obesity vs non-sarcopenic obesity	0.53	[0.22–1.29]	0.16	0.55	[0.23–1.34]	0.19

OR, odds ratio; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events. SAT, subcutaneous adipose tissue; VAT visceral adipose tissue; VSR, visceral-to-subcutaneous fat ratio.

the assessment of body composition parameters, we cannot confirm these previous findings [35].

Our results suggest that myosteatosis as a surrogate of muscle quality may be a predictor of OS in leukemia, MDS, and MPN following allo-HSCT. In 2019, Mueske et al. conducted a prospective study of the presence and degree of chemotherapy-associated altered body composition parameters in 12 adolescents and young adults treated for ALL [36]. In their study, tissue volumes for adipose muscle and bone along the entire length of both tibias were calculated. Additionally, muscle-associated fat was assessed by quantitative CT and utilized as a marker of myosteatosis. They showed a significant decrease in muscle tissue volume during the pre-maintenance ALL therapy ($p = 0.001$) and increased muscle-associated fat volume, primarily during the delayed intensification period ($p = 0.001$). According to a meta-analysis by Aleixo et al., cancer patients classified with myosteatosis had a lower OS compared to non-myosteatosis patients (HR 1.75 95% CI 1.60–1.92, p=<0.00001) [37]. In this meta-analysis, 40 studies of solid tumors were included, and the effect of myosteatosis in leukemia, MDS, or MPN was not evaluated. Our study suggests that the clinical significance of myosteatosis can be broadened as a risk factor to hematological malignancies.

Browne et al. reported that the percentage of overweight/obese children with ALL increased from 25.5% at diagnosis to approximately 50% during the off-therapy period. In our study, 51 (41.80%) and 23 (18.85%) were categorized as overweight and obese, respectively [38]. Notably, only 3 (2.46%) of the patients were classified as underweight. In agreement with Yu Yan et al., we consider that the evaluation of changes in fat content in cancer patients is clinically relevant [39]. In our cohort, a marked increase in severe adverse events with a corresponding decrease in OS was noted in patients with low SAT. One possible explanation for the heightened risk observed in patients categorized as having low SAT, leading to a higher occurrence of severe adverse effects (CTCAE $\geq$4, irrespective of type), is rooted in the role of tissue-derived mesenchymal cells. It has been reported that these cells can inhibit cell growth in hematologic malignancies and induce T-cell inhibition in patients undergoing allo-HSCT [15]. Our results align with previous studies by Takeoka et al., who evaluated 56 patients with MM and reported a low SAT index being linked to a poorer 2-year OS (HR 4.05, 95%CI 1.24–13.19), $p = 0.02$) [14], and with the findings of Ebadi et al., who indicated that low SAT is associated with increased cancer mortality (HR 1.26, 95% CI 1.26–1.43; p =<0.001) [14,40]. Ebadi et al. analyzed the parameters of body composition, including total adipose tissue index, subcutaneous adipose tissue (SATI) index, and visceral adipose tissue (VATI) in 1437 gastrointestinal and respiratory tract cancer patients and 273 metastatic renal cell carcinoma [40].

In our study, high VAT and high VSR did not significantly influence OS (HR 0.93, 95% CI 0.55–1.58, $p = 0.79$, adjusted: HR 0.79, 95% CI 0.47–1.78, $p = 0.91$) (HR 1.30, 95% CI 0.75–2.28, $p = 0.35$, adjusted: HR 1.88, 95% CI 0.89–3.98, $p = 0.10$). Our results are in line with Surov et al., who conducted an observational study of body composition parameters as prognostic factors for OS in MM after transplant [25]. In their study, regarding VAT, no significant association with OS was detected [HR 1.0 (CI 0.99–1.01), $p = 0.62$]. Multi-center studies with larger study populations should further explore the role of altered visceral adipose tissue in individual myeloid and lymphoid neoplasms.

Our study supports previous evidence by Alhomoud et al., in 2023, who asseverated that screening CT prior to transplantation is a beneficial tool to prevent potentially post-transplantation complications. In their descriptive analysis of 551 patients with leukemia, lymphoma, or MDS, abnormal clinical CT findings (such as consolidation and ground-glass opacification) were significantly associated with worse OS ($p = 0.032$) [41]. Our results suggest that the assessment of pretransplant CT scans has clinical significance beyond the evaluation of occult infection. The CT-based evaluation of body composition parameters, particularly SAT and SM-RA as an indicator of myosteatosis, is not only clinically significant but also feasible and reproducible in hematological malignancies, particularly with the help of semi-automated segmentation methods.

Our study has several limitations; firstly the study population encompassed a broad spectrum of hematological malignancies, potentially introducing heterogenicity into the analysis. The role of comorbidities or previous treatments, or adjuvant therapy as confounders was not explored. Additionally, the retrospective methodology and the monocentric setting limit the generalizability of our findings. One possible solution to address these limitations is to conduct multi-center studies with larger and more homogeneous study populations. Such studies would enable robust multivariate analyses exploring disease-modifying factors specific to individual neoplasms, which was not feasible in our study. Additionally, future research should aim to explore the role of altered body composition parameters in distinct myeloid and lymphoid neoplasms and evaluate the impact of multidisciplinary interventions of altered body composition parameters on clinical outcomes, including non-relapse mortality and progression-free survival and incorporating disease-modifying factors into our multivariate analysis to further refine our understanding of the complex interplay between body composition and disease outcomes.

In conclusion, low SAT and myosteatosis may contribute to an increased risk of post-tranplant mortality, while low SAT appears to increase the risk of severe post-transplant adverse events in patients with leukemia, MDS, or MPN after allo-HSCT. Integrating CT-based assessment of body composition parameters (particularly SAT and myosteatosis) into clinical protocols before allo-HSCT could aid in the identification of high-risk patients.

Source of funding

The authors have no support or funding to report.

Author contributions

A.S. and D.W. conceived and designed the study; Y.Z. A.A., H.K., and M.M. contributed to the collection of the clinical data, and M.H. performed the segmentation of the CT scans. F.B, Y.Z., and P.R. contributed to the manuscript writing. F.B., Y.Z., and P.R. contributed to the statistical analysis. D.M., D.W., and J.B. contributed to the critical revision of the manuscript. All authors approved the final manuscript for publication.

Declaration of competing interest

The authors have declared that no competing interests exist.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2024.03.032.

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