



**HAL**  
open science

## High prevalence of pre-existing sarcopenia in critically ill patients with hematologic malignancies admitted to the intensive care unit for sepsis or septic shock

Antoine Herault, Emilie Lévêque, Simon Draye-Carbonnier, Pierre Decazes, Alexandra Zduniak, Romain Modzelewski, Julie Libraire, Najate Achamrah, Anne-Lise Ménard, Pascal Lenain, et al.

### ► To cite this version:

Antoine Herault, Emilie Lévêque, Simon Draye-Carbonnier, Pierre Decazes, Alexandra Zduniak, et al.. High prevalence of pre-existing sarcopenia in critically ill patients with hematologic malignancies admitted to the intensive care unit for sepsis or septic shock. *Clinical Nutrition ESPEN*, 2023, 55, pp.373-383. 10.1016/j.clnesp.2023.04.007 . hal-04112173

**HAL Id: hal-04112173**

**<https://normandie-univ.hal.science/hal-04112173v1>**

Submitted on 30 May 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



Contents lists available at ScienceDirect

## Clinical Nutrition ESPEN

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

## Original article

# High prevalence of pre-existing sarcopenia in critically ill patients with hematologic malignancies admitted to the intensive care unit for sepsis or septic shock



Antoine Herault <sup>a, b</sup>, Emilie Lévêque <sup>c</sup>, Simon Draye-Carbonnier <sup>d, 1</sup>, Pierre Decazes <sup>d, e, h, 1</sup>, Alexandra Zduniak <sup>b</sup>, Romain Modzelewski <sup>e, h</sup>, Julie Libraire <sup>c</sup>, Najate Achamrah <sup>f</sup>, Anne-Lise Ménard <sup>b</sup>, Pascal Lenain <sup>b</sup>, Nathalie Contentin <sup>b</sup>, Maximilien Grall <sup>a</sup>, Stéphane Leprêtre <sup>b</sup>, Emilie Lemasle <sup>b</sup>, Hélène Lanic <sup>b</sup>, Mustafa Alani <sup>b</sup>, Aspasia Stamatoullas-Bastard <sup>b</sup>, Hervé Tilly <sup>b</sup>, Fabrice Jardin <sup>b</sup>, Fabienne Tamion <sup>a, g</sup>, Vincent Camus <sup>b, \*</sup>

<sup>a</sup> Intensive Care Unit, Charles Nicolle University Hospital, Rouen, France

<sup>b</sup> Department of Hematology and INSERM U1245, Centre Henri Becquerel, Rouen, France

<sup>c</sup> Clinical Research Unit, Centre Henri Becquerel, Rouen, France

<sup>d</sup> Department of Nuclear Medicine, Centre Henri Becquerel, Rouen, France

<sup>e</sup> Unité QuantIF LITIS EA 4108, Université de Rouen, Normandie, France

<sup>f</sup> Department of Nutrition, Charles Nicolle University Hospital, Rouen, France

<sup>g</sup> Normandie Univ, UNIROUEN, INSERM U1096, CHU Rouen, France

<sup>h</sup> Département D'imagerie, Centre Henri-Becquerel, Rouen, France

## ARTICLE INFO

## Article history:

Received 22 December 2022

Accepted 9 April 2023

## Keywords:

Hematologic malignancies

Sarcopenia

Adipopenia

Intensive care unit

Sepsis

Septic shock

## SUMMARY

**Background & aims:** We aimed to evaluate body composition (BC) by computed tomography (CT) in hematologic malignancy (HM) patients admitted to the intensive care unit (ICU) for sepsis or septic shock.

**Methods:** We retrospectively assessed BC and its impact on outcome of 186 patients at the 3rd lumbar (L3) and 12th thoracic vertebral levels (T12) using CT-scan performed before ICU admission.

**Results:** The median patient age was 58.0 [47; 69] years. Patients displayed adverse clinical characteristics at admission with median [q1; q3] SAPS II and SOFA scores of 52 [40; 66] and 8 [5; 12], respectively. The mortality rate in the ICU was 45.7%. Overall survival rates at 1 month after admission in the pre-existing sarcopenic vs. non pre-existing sarcopenic patients were 47.9% (95% CI [37.6; 61.0]) and 55.0% (95% CI [41.6; 72.8]),  $p = 0.99$ , respectively, at the L3 level and 48.4% (95% CI [40.4; 58.0]) vs. 66.7% (95% CI [51.1; 87.0]),  $p = 0.062$ , respectively, at the T12 level.

**Conclusions:** Sarcopenia is assessable by CT scan at both the T12 and L3 levels and is highly prevalent in HM patients admitted to the ICU for severe infections. Sarcopenia may contribute to the high mortality rate in the ICU in this population.

© 2023 The Author(s). Published by Elsevier Ltd on behalf of European Society for Clinical Nutrition and Metabolism. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Abbreviations:** intensive care unit, ICU; diffuse large B-cell lymphoma, DLBCL; acute myeloid leukemia, AML; computed tomography, CT; positron emission tomography-computed tomography, PET-CT; Charlson Comorbidity Index, CCI; Sequential Organ Failure Assessment, SOFA; Simplified Acute Physiology, SAPS II; body mass index, BMI; cross-sectional area, CSA; Hounsfield units, HU; the L3 skeletal muscle index, LSMI; the T12 skeletal muscle index, TSMI; theL3 subcutaneous adipose tissue index, LSAI; the T12 subcutaneous adipose tissue index, TSAI; the L3 visceral adipose tissue index, LVAI; overall survival, OS; performance status, ECOG-PS.

\* Corresponding author. Department of Hematology, Centre Henri Becquerel, Rouen, France

E-mail address: [vincent.camus@chb.unicancer.fr](mailto:vincent.camus@chb.unicancer.fr) (V. Camus).

<sup>1</sup> These authors contributed equally to this work.

<https://doi.org/10.1016/j.clnesp.2023.04.007>

2405-4577/© 2023 The Author(s). Published by Elsevier Ltd on behalf of European Society for Clinical Nutrition and Metabolism. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Patients with hematologic malignancies are at high risk of developing critical illness leading to admission to an intensive care unit (ICU) [1,2]. Historically, patients with hematologic malignancies who required ventilation or catecholamines had poor outcomes with nearly 90% mortality [3]. However, advancements in critical care and hematology management have led to reduced mortality rates (39.3%) [4]. Despite improvements in ICU mortality, the persistent overall unfavorable prognosis may be linked to severe infections, progressive disease or postintensive care syndrome. Several reports previously demonstrated that the catabolic state with severe protein degradation induced by septic shock leads to the rapid loss of muscle mass and impaired function, which is associated with increased hospital mortality [5–7]. Sarcopenia (loss of skeletal muscle mass and function [8]) may be a major complication in hematologic malignancies after ICU discharge [9]. Likewise, it may also contribute significantly to determining the poor prognosis of critically ill patients with hematologic malignancies. Sarcopenia is commonly quantified as a surrogate marker in hematologic malignancies with 2.39-fold mortality in diffuse large B-cell lymphoma (DLBCL), 1.82-fold mortality in leukemia [10] and increased mortality in hematopoietic stem cell transplant patients [11,12].

The value of assessing skeletal muscle mass and function in ICU patients has recently emerged. Computed tomography (CT) scans may serve as a tool to quantitatively measure muscle and fat tissue [13–15].

Sarcopenia in ICU patients is associated with a poor prognosis, such as ventilator-free days, difficulty in weaning, and increased mortality in nonhematological critically ill patients [16,17]. Among patients with septic shock, sarcopenic patients have 1.7 times higher mortality [18].

However, the impact of pre-existing sarcopenia on clinical outcomes, especially mortality, in critically ill patients with hematologic malignancies is still poorly studied. In a previous study, we observed that the main reasons for ICU admission in diffuse large B-cell lymphoma (DLBCL) patients were acute respiratory failure (40.0%) and septic shock (33.3%), an event that clearly impacted the outcomes of this population with DLBCL (mortality rate 33.3%). We observed that ICU prognosis seemed mainly related to critical patient severity at admission rather than lymphoma-related prognostic factors [19]. The unfavorable prognostic impact of pre-existing sarcopenia was recently highlighted in critically ill patients with intra-abdominal sepsis [20]. However, the effect of pre-existing sarcopenia and/or adipopenia on the outcomes of critically ill patients with hematological malignancies remains unclear, especially in the context of septic shock, one of the major direct causes of death in this population [21].

In the present study, we aimed to evaluate the prevalence of pre-existing sarcopenia/adipopenia assessed by CT scans in hematology patients admitted to the ICU for sepsis or septic shock and the impact of pre-existing sarcopenia/adipopenia on patient outcomes.

## 2. Methods

### 2.1. Study design and setting

We conducted a retrospective cohort study screening all consecutive patients diagnosed with hematologic malignancies between 2013 and 2020 and who had a first ICU admission for sepsis or septic shock. This study was conducted in two centers: Centre Henri Becquerel (Department of Hematology) and Charles Nicolle University Hospital (ICU). This retrospective study was

approved by our internal review board (N°2006B) and by the Commission for the Qualification of Research Projects of Rouen University Hospital (N°595) and was conducted in accordance with the Declaration of Helsinki.

### 2.2. Study population

Patients with hematologic malignancies were included if they had available abdominal or thoracic CT scans or positron emission tomography-computed tomography (PET-CT) scans performed within 2 months prior to the first ICU admission for sepsis or septic shock between January 2013 and December 2020. Hematologic malignancies included acute leukemia, lymphoma, lymphoproliferative disorders, multiple myeloma, myelodysplastic syndromes and myeloproliferative syndromes.

According to international guidelines, sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection; septic shock is defined as hemodynamic failure secondary to infection despite adequate fluid resuscitation associated with a serum lactate level  $>2$  mmol/L [22–24].

### 2.3. Data collection

The following prognostic scores [25] were analyzed: CCI (Charlson Comorbidity Index) score on a scale of 0–6, excluding primary disease, to estimate a 10-year survival probability [26], SOFA (Sequential Organ Failure Assessment) score (during ICU stay, Days 1, 2, 3, 7, 14, 21, 28) [27] and SAPS II (Simplified Acute Physiology Score II) score [28].

The anthropometric nutritional parameters analyzed were weight and BMI (body mass index) at admission and at the end of the ICU stay and biological parameters at ICU admission (albuminemia and phosphoremia).

### 2.4. Body composition measurements

Computed tomography (CT) is regarded as one of the most accurate methods available for conducting a body composition analysis. As reported in other studies [15,29], muscle mass and fat tissue were measured by analyzing stored images from available imaging (CT, PET-CT) performed within two months before admission to the ICU for imaging number 1 (I1), during the ICU stay for imaging number 2 (I2) and within two months after the ICU stay for imaging number 3 (I3).

At the level of the third lumbar vertebra (L3), in axial sections, we assessed the skeletal muscle area and the visceral and subcutaneous fat areas [14,30]. At the level of the twelfth thoracic vertebra (T12), in axial sections, we assessed the skeletal muscles and subcutaneous fat areas [31].

Hounsfield unit-based image analysis was performed using dedicated macro ImageJ software [32] to segment fat and lean tissue and quantify the cross-sectional area (CSA) (cm<sup>2</sup>) of each tissue type by summing the given tissue pixels and multiplying the sum by the absolute unit pixel surface area [33,34]. CT CSA of tissues was identified through Hounsfield units (HU) measured from –29 to 150 for skeletal muscle and –190 to –30 and –50 to –150 for subcutaneous and visceral adipose tissue, respectively [35].

The quality criteria of the CT sections [36] had to be validated by the two readers (AH, PD and/or SDC); otherwise, the images were excluded from the analysis. Each tissue was examined and corrected manually by two readers (AH and PD or AH and SDC). But, only the index values of one reader were used for further statistical tests.

The following parameters were analyzed: skeletal muscle mass, including the mass of the psoas, quadratus lumborum, transversus abdominis, external and internal obliques, rectus abdominis and erector spinae muscles; subcutaneous fat mass, including the fat present in the subcutaneous tissue and the intramuscular fat contained in the intercostal muscles; and visceral fat mass. The fat present in the psoas was not taken into account for adiposity assessment. As fat and muscle pixels have no HU in common in these windows, no overlap between these tissues was observed. Moreover, subcutaneous fat pixels were obtained by subtracting visceral fat pixels from pixels estimated by whole-body fat extrapolation [35]. This value was normalized for stature (in  $m^2$ ) to calculate the L3 skeletal muscle index (LSMI), the T12 skeletal muscle index (TSMI), the L3 subcutaneous adipose tissue index (LSAI), the T12 subcutaneous adipose tissue index (TSAI) and the L3 visceral adipose tissue index (LVAI). All indices were expressed in  $cm^2/m^2$  (Supplemental Fig. 1).

Each index was calculated independently by the two readers. Given the good correlation (Spearman coefficient: 0.9) between the two readers for index calculations, only the index values of one reader were used for further statistical tests.

### 2.5. Definitions of sarcopenia and adipopenia

According to the EWGSOP2 guidelines, L3 sections should be the reference for defining sarcopenia status in cancer patients [30]. The gender-specific thresholds defining sarcopenia in L3 are based on the *Prado* study, which is the gold standard in the literature: for men, the cutoff is  $< 52.4 \text{ cm}^2/m^2$ , and for women, the cutoff is  $< 38.5 \text{ cm}^2/m^2$  [37]. Thoracic cutoff values for sarcopenia at the T12 level were  $42.6 \text{ cm}^2/m^2$  for men and  $30.6 \text{ cm}^2/m^2$  for women, as proposed by Nemeč et al. [31] In addition, due to a lack of published data, we defined adipopenic patients as those whose LVAI, LSAI and/or TSAI values were lower than the respective median of adiposity measurements from imaging I1 for men and women in our population.

### 2.6. Study outcomes

The primary objective was to assess the prevalence of L3 pre-existing sarcopenia at ICU admission and the impact on overall survival (OS) at 1 month in critically ill hematologic malignancy patients.

The secondary objectives were to analyze T12 pre-existing sarcopenia prevalence, the association between T12 pre-existing sarcopenia and OS, factors associated with 1-month ICU mortality, factors associated with L3 sarcopenia, 1-month OS according to pre-existing adipopenic status at the L3 and T12 levels, and 1-month OS according to pre-existing sarcopenic plus pre-existing adipopenic status at L3.

### 2.7. Statistical analysis

The study population was described using the mean ( $\pm$ SD) and median (1st quartile–3rd quartile) for quantitative characteristics and the number and percentage for qualitative ones. The normality of the distribution of the variables was verified by a Shapiro Wilk test.

To determine sarcopenia status in the study population, we used known cutoffs of skeletal muscle indices (LSMI and LSAI), which were different according to sex (*Prado* et al. [15], Nemeč et al. [31]). Regarding adipopenia status, we used the respective median subcutaneous adipose tissue indices (LVAI or TSAI) from imaging I1 in male patients (resp. female patients) to determine the corresponding status from L3 and T12.

The proportions of patients with sarcopenia from L3 and T12 and adipopenia from L3 and T12 were described according to sex and all ICU stays (for some patients with available I2 and/or I3).

For survival analysis, only the pre-existing L3 and T12 sarcopenia status at ICU admission was taken into account. Kaplan–Meier curves were estimated to evaluate overall survival according to pre-existing sarcopenia status from L3 at ICU admission. A log rank test was also performed to compare estimated overall survival curves. Similarly, we generated Kaplan–Meier overall survival curves according to pre-existing sarcopenia status from T12.

We determined a binary endpoint, namely, 1-month ICU mortality, which corresponds to the occurrence of death within 1 month after admission to the ICU and is of particular interest. Univariate logistic regression models were used to estimate the OR (and its 95% CI) for the association between potential factors and the occurrence of this endpoint. Finally, a multivariate logistic regression model was considered (R packages *stats* and *epiDisplay*). It was adjusted on factors retained as significant in the univariate analysis (determined by a p value below 0.01 from Wald test). Nevertheless, the variables age and gender were forced into the multivariate analysis.

To describe and potentially differentiate nonsarcopenic and sarcopenic patients, we compared both groups in terms of certain specified characteristics by using the chi-squared test for qualitative characteristics and the Mann–Whitney–Wilcoxon test for quantitative characteristics.

## 3. Results

### 3.1. Study population

During the study period, 643 patients were admitted to the ICU. Of these patients, 444 did not meet the inclusion criteria (76 had already been in the ICU since the diagnosis of the hematologic malignancy, and 368 had not had a first baseline scan within two months before the ICU stay). In addition, 13 patients were excluded due to the lack of quality criteria for the images evaluated by the two readers.

Finally, 186 patients were included in the present analysis. Details of the available CT scans analyzed in this population are presented in Fig. 1. The median number of days between I1 and ICU admission was 11.5 [3, 22]; 59.6% ( $n = 111/186$ ) of patients had performed their I1 within 15 days before ICU admission.

### 3.2. Patient characteristics

The baseline characteristics of the cohort are summarized in Table 1. The median (1st quartile–3rd quartile) age at ICU admission was 58.0 [47; 69] years. At admission, the median weight was 71.0 [61; 85] kg and the median BMI was 24.4 [22; 29]  $kg/m^2$ . The patients displayed several comorbidities (hypertension—38.6%, diabetes mellitus—14.5%, thromboembolic diseases—13%). Most of the patients presented with a good performance status (ECOG-PS 0–1: 69.3%).

The hematological diagnoses of the patients were mainly acute myeloid leukemia (AML:  $n = 63$  (35.4%)) and diffuse large B-cell lymphoma (DLBCL:  $n = 45$  (25.3%)), with a predominance of male patients ( $n = 122$  (65.6%)). The median ([q1; q3]) number of lines of anticancer therapy received prior to ICU admission was 1 [1; 2]. A total of 63.4% of patients presented with chemotherapy-induced bone marrow aplasia at ICU admission. The median time between hematologic malignancy diagnosis and ICU admission was 56 days [20; 382].

The median SAPSII score at admission was 52.0 [40; 66], the median SOFA score was 8.0 [5; 12], and the median age-adjusted

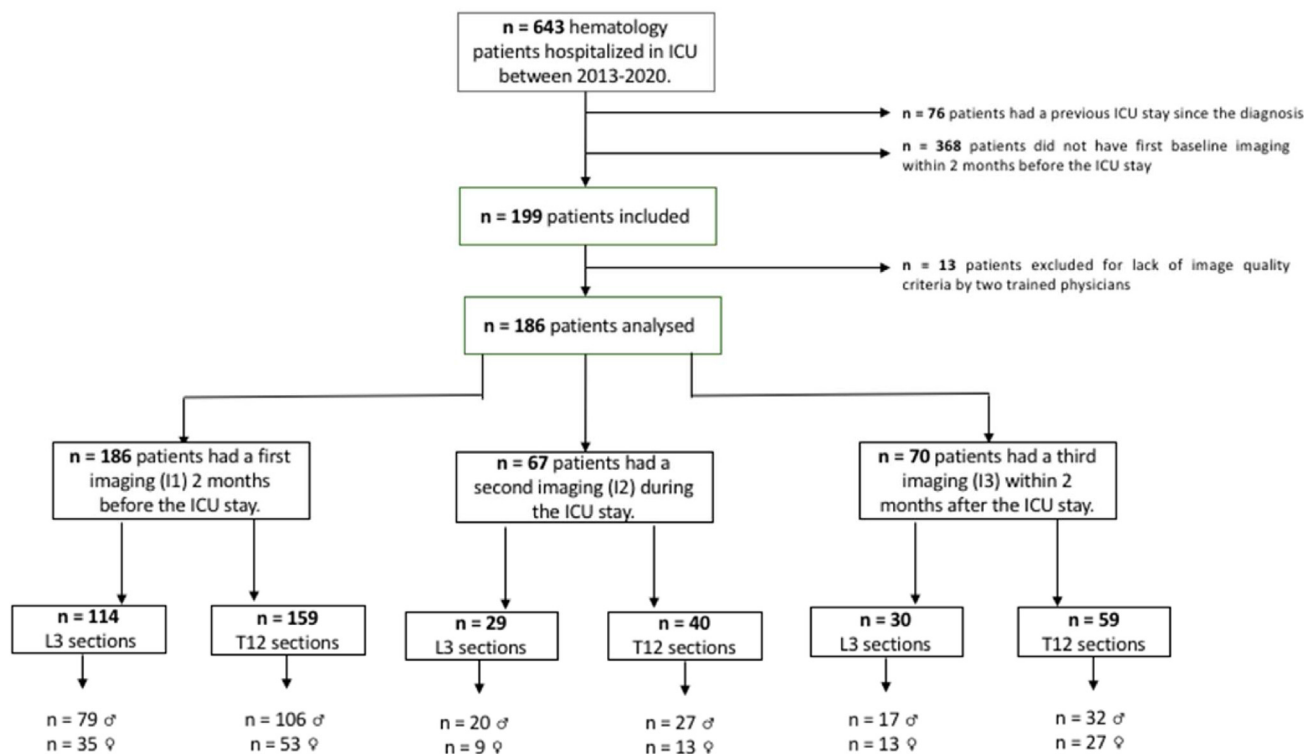


Fig. 1. Flow chart. ICU: intensive care unit; I1: first imaging of the study; I2: second imaging of the study; I3: third imaging of the study; ♂: men; ♀: women.

Charlson score was 4 [3; 6]. A total of 64.5% of patients required vasopressor amines, 71.1% required invasive ventilation, and 19.9% had renal replacement therapy. The median length of stay in the ICU was 5.0 [3; 12] days.

During the stay in the ICU, the median caloric intake was 11.7 [6; 16] Kcal/kg/day. 35.7% received enteral nutritional support (average duration 10.9 days (± 9.4)) and 15.7% parenteral nutritional support (average duration 8.8 days (± 7.4)). The median time to set up these nutritional supports was 2.0 days [2; 3].

### 3.3. Description of body composition

#### 3.3.1. Sarcopenia status

At baseline, the median LSMI [q1; q3] was 38.5 [34; 41] in women and 46.3 [41; 53] in men. The median TSMI was 25.8 [23 and 32] in women and 32.7 [28 and 38] in men (in cm<sup>2</sup>/m<sup>2</sup>) (Fig. 2 and Supplemental Table 1). CT-scan measures of sarcopenia at L3 (LSMI) and T12 (TSMI) were well correlated [r = 0.77; 95% confidence interval (CI): 0.687–0.838; P < 0.001], regardless of sex. According to the gender-specific cutoffs, at the L3 level, 64.9% of the patients were considered to have pre-existing sarcopenia at their ICU admission despite a normal BMI. At the T12 level, 83.0% of the patients were considered to have pre-existing sarcopenia despite a normal BMI. The proportion of sarcopenic patients was broadly stable during the ICU stay and after the ICU stay (Table 2). But few scans were performed during the ICU stay (29 for the LSMI evaluation and 30 for the TSMI evaluation) and after the ICU stay (30 for the LSMI evaluation and 59 for the TSMI evaluation). At ICU discharge, the median weight was 76.0 [65; 89] kg and the median BMI was 25.4 [22; 30] kg/m<sup>2</sup> or a median weight delta of 2.0 [–2; 11] kg (Table 1).

#### 3.3.2. Adipopenia status

At baseline, the median [q1; q3] LSAI was 61.9 [33; 89] in women and 53.2 [36; 76] in men; the median LVAI was 24.4 [13; 48]

in women and 56.0 [31; 81] in men; and the median TSAI was 38.8 [24; 62] in women and 28.7 [18; 42] in men (in cm<sup>2</sup>/m<sup>2</sup>) (Fig. 2 and Supplemental Table 1). The rate of patients with pre-existing subcutaneous adipopenia at baseline on L3 and T12 slices was similar (49.1% at the L3 level and 50.3% at the T12 level) (Table 2).

### 3.4. Outcomes in the ICU and after ICU discharge

Overall, 85 patients (45.7%) died in the ICU. The 1-month OS in patients admitted for sepsis was 24.5% (27/110) vs. 24.2% (17/70) for septic shock (Supplemental Fig. 2). The causes of death in ICU were hematologic malignancy for 46 of 85 (54.1%) patients, treatment-related toxicity for 35 of 85 (41.2%) patients; secondary malignancies for 3 (3.5%) patients and other cause for 1 (1.2%) patient.

Of the survivors, 29 (14.6) were readmitted to the ICU later in their disease course. Forty-six patients (24.7%) experienced limitations of life-sustaining care. After ICU discharge, 44 of 94 patients with available data (46.8%) relapsed from their hematologic malignancy. Among them, 39 of 43 patients (90.7%) were eligible for a new line of treatment.

At the time of the last follow-up (April 2021), 141 of 186 patients in the cohort had died (75.8%). The causes of death after ICU discharge were hematologic malignancy for 37 of 56 (66.1%) patients, treatment-related toxicity for 16 of 56 patients (28.6%), secondary malignancies for 1 (1.8%) patient, other cause for 1 (1.8%) patient and unknown cause for 1 (1.8%) patient. These causes of death after ICU discharge were not statistically different from causes of deaths during ICU stay (p = 0.316) (Supplemental Table 2). In univariate analysis, factors associated with 1-month mortality in the ICU were performance status 2–4, SAPS II score ≥53, SOFA score ≥9, use of vasopressor drugs, mechanical ventilation, presence of hyperlactatemia and presence of renal replacement therapy. In multivariate analysis, factors associated with 1-month ICU mortality were hyperlactatemia [OR = 3.14; 95% confidence interval



**Table 1**  
Patient characteristics.

| Variable                                      | N (%)            |
|---|------------------|
|   | Mean ± SD        |
|   | Median [q1; q3]  |
| Number of patients                            | 186              |
| Gender  |                  |
| Female  | 64 (34.4)        |
| Male  | 122 (65.6)       |
| Age at admission (years)                      | 58.0 [47; 69]    |
| <u>Comorbidities</u>                          |                  |
| High blood pressure                           | 71 (38.6)        |
| Diabetic                                      | 27 (14.5)        |
| Chronic respiratory failure                   | 10 (5.4)         |
| Chronic renal failure                         | 11 (5.9)         |
| Liver diseases                                | 5 (2.7)          |
| Other cancers                                 |                  |
| Hematological malignancies                    | 25 (13.5)        |
| Solid tumors                                  | 21 (11.8)        |
| Thromboembolic diseases                       | 24 (13.0)        |
| Stroke  | 8 (4.3)          |
| HIV infection                                 | 1 (0.5)          |
| Solid organ transplantation                   | 3 (1.6)          |
| <u>Hematologic malignancies</u>               |                  |
| Type  |                  |
| Aplastic anemia                               | 6 (3.4)          |
| AML   | 63 (35.4)        |
| ALL   | 15 (8.4)         |
| MM  | 10 (5.6)         |
| HL  | 14 (7.9)         |
| NHL   | 70 (39.3)        |
| PTCL, NOS                                     | 12 (6.7)         |
| FL and other indolent lymphomas               | 13 (7.3)         |
| DLBCL, NOS                                    | 45 (25.3)        |
| Number of prior lines of anticancer therapies | 1.0 [1; 2]       |
| Allogenic stem cell transplant                | 20 (10.75)       |
| <u>At admission to ICU</u>                    |                  |
| ICU length of stay (days)                     | 5.0 [3; 12]      |
| Performance status 0–1 at admission           | 129 (69.3)       |
| Prognosis scores for ICU stay                 |                  |
| SAPS II                                       | 52.0 [40; 66]    |
| SOFA  |                  |
| J1  | 8.0 [5; 12]      |
| J3  | 8.0 [6; 14]      |
| CCI   | 3.0 [2; 4]       |
| Age-adjusted CCI                              | 4.0 [3; 6]       |
| CRP at admission (mg/L)                       | 105 [39; 234]    |
| Albuminemia at admission (g/L)                | 23.1 ± 5.04      |
| Lower than less albuminemia at admission      | 43 (100.0)       |
| Lower than less phosphoremia at admission     | 21 (18.1)        |
| <u>During ICU stay</u>                        |                  |
| Hemodynamic function                          |                  |
| Vasopressive drugs                            | 120 (64.5)       |
| Length vasopressive drugs (days)              | 2.0 [1; 6]       |
| Arterial lactate (mmol/L)                     | 2.6 [2; 6]       |
| Respiratory function                          |                  |
| Mechanical ventilation                        | 91 (71.1)        |
| Length of mechanical ventilation (days)       | 4.0 [2; 11]      |
| Acute kidney injury                           |                  |
| KDIGO 1-2                                     | 76 (62.3)        |
| KDIGO 3                                       | 46 (37.7)        |
| Renal replacement therapy                     | 37 (19.9)        |
| Hematology function                           |                  |
| Hemophagocytic lymphohistiocytosis            | 22 (11.8)        |
| Febrile neutropenia                           | 118 (63.4)       |
| Febrile neutropenia duration (days)           | 5.0 [3; 7]       |
| Hepatic function                              |                  |
| Total bilirubin (μmol/L)                      | 28.0 [14; 64]    |
| Documented infection                          | 140 (83.8)       |
| Nutritional function                          |                  |
| Weight at admission (kg)                      | 71.0 [61; 85]    |
| BMI at admission (kg/m <sup>2</sup> )         | 24.4 [22; 29]    |
| Weight at discharge (kg)                      | 76.0 [65; 89]    |
| BMI at discharge (kg/m <sup>2</sup> )         | 25.4 [22; 30]    |
| Weight delta during the stay (kg)             | 2.0 [-0.6; 11.4] |
| Limitation of Life-Sustaining Care            | 46 (24.7)        |

HIV: Human immunodeficiency Virus; AML: Acute Myeloid Leukemia; ALL: Acute Lymphoid Leukemia; MM: Multiple Myeloma; HL: Hodgkin Lymphoma; NHL: Non-Hodgkin Lymphoma; PTCL NOS: Peripheral T-Cell Lymphoma Not Otherwise Specified; FL: Follicular Lymphoma; DLBCL NOS: Diffuse Large B-Cell Lymphoma Not Otherwise Specified; ICU: Intensive Care Unit; CR: Complete Remission; SAPS II: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment; CCI: Charlson Comorbidity Index; CRP C-Reactive Protein; KDIGO Kidney Disease Improving Global Outcomes; BMI: Body Mass Index.

(CI): 1.06–9.33; P = 0.039] and use of mechanical ventilation [OR = 15.57; 95% confidence interval (CI): 4.18–58.02; P < 0.001]. (Table 3).

### 3.5. Relationship between outcomes and body composition

Regarding the main evaluation criteria of this study, with a median [q1; q3] follow-up of 25.5 [5–310] days, the 1-month OS rate in patients with no pre-existing sarcopenia at the L3 level was 55.0% (95% CI [41.6; 72.8]) vs. 47.9% (95% CI [37.6; 61.0]) in patients with pre-existing sarcopenia (not significantly different according to log-rank test, p = 0.99).

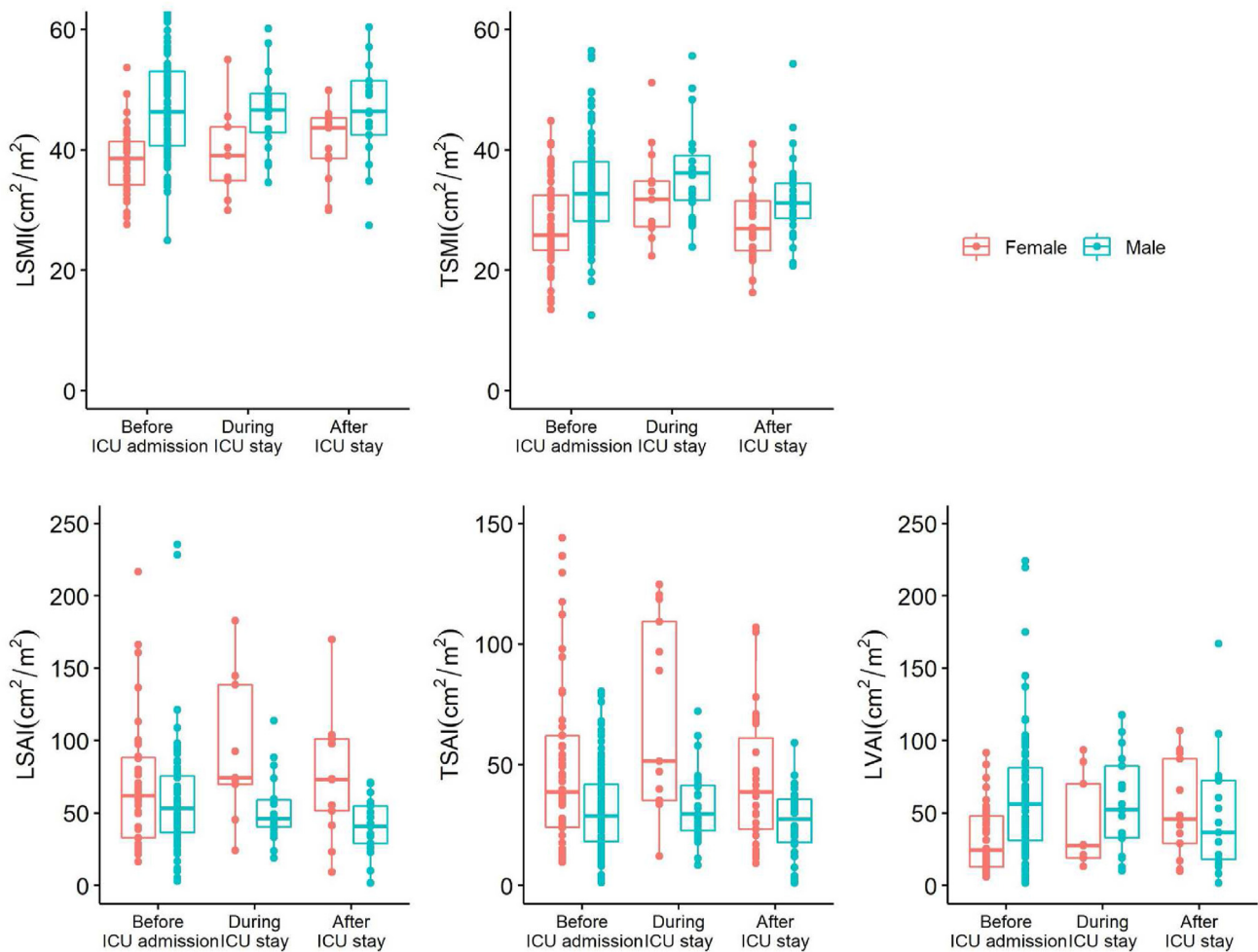
We observed a trend toward lower OS for patients with pre-existing sarcopenia at the T12 level: the 1-month OS rate in patients considered nonsarcopenic was 66.7% (95% CI [51.1; 87.0]) vs. 48.4% (95% CI [40.4; 58.0]) in patients with pre-existing T12 sarcopenia (p = 0.062, remaining insignificant) (Fig. 3). We identified male sex as a characteristic that could differentiate patients with L3 sarcopenia from patients without L3 sarcopenia (55% of patients were male in the nonsarcopenic group vs. 77% in the sarcopenic group, p = 0.015). The characteristics of the hematological disease and the characteristics during ICU stay did not differ between the sarcopenic group and the nonsarcopenic group (Table 4).

Pre-existing adipopenia had no significant impact on overall survival (Supplemental Fig. 3). Patients who displayed both pre-existing sarcopenia and adipopenia at the T12 level had a trend toward lower overall survival: 1-month OS rate: 41.4% (95% CI [31.4; 54.7]) for sarcopenic + adipopenic patients vs. 61.9% (95% CI [51.0; 75.1]) for sarcopenic or adipopenic patients vs. 55% (95% CI [37.0; 81.8]) for nonsarcopenic and nonadipopenic patients (p = 0.083), but this difference remained nonsignificant (Supplemental Fig. 4).

## 4. Discussion

In this retrospective study, we evaluated the association between body composition derived from CT scans and outcomes in critically ill patients with hematologic malignancies admitted to the ICU for the first time for sepsis or septic shock.

Most of these patients presented with pre-existing sarcopenia in the two months preceding ICU admission (64.9% at the L3 level and 83.0% at the T12 level), and sarcopenia may have contributed to the high ICU mortality rate (45.7%) observed in our cohort. The mortality rate in our cohort appears to be higher than rates previously reported in other studies (33.3–39.3%) [19],[4] Cox et al. have also demonstrated that patients with pre-existing sarcopenia and abdominal sepsis had greater acute physiologic derangement (APACHE II, 18 vs. 12.5), higher incidence of multiple organ failure (57% vs. 17%), longer lengths of stay in hospital (21 vs. 12 days) and intensive care unit (13 vs. 4 days), and higher inpatient mortality (17% vs. 0%; all P < 0.05) [20]. In addition, the loss of muscle mass in hematologic malignancy patients is multifactorial (undernutrition, low physical activity, comorbid health conditions, chronic inflammation, or treatment such as chemotherapy), which explains the high prevalence of pre-existing sarcopenia in our cohort. We hypothesize that hematologic malignancy patients with sarcopenia may be at higher risk of developing sepsis or septic shock leading to ICU admission. However, patients suffering



**Fig. 2.** Boxplots showing LSMI (A), LSAI (B), TSMI (C), TSAI (D), and LVAI (E) repartition at baseline (before ICU admission), during the ICU stay and after the end of the ICU stay, when available. LSMI: L3 skeletal muscle index; LSAI: L3 subcutaneous adipose tissue index; TSMI: T12 skeletal muscle index; TSAI: T12 subcutaneous adipose tissue index; LVAI: L3 visceral adipose tissue index.

**Table 2**  
Proportions of sarcopenia and adipopenia according to ICU stay.

| N (%)                         | At baseline                               |                      | During ICU stay                         |                      | After ICU discharge                     |                      |
|-------------------------------|---|----------------------|---|----------------------|---|----------------------|
|                               | Woman                                     | Male                 | Woman                                   | Male                 | Woman                                   | Male                 |
| Sarcopenia (L3)               | 17 (48.6)<br>NA = 29<br><b>74 (64.9)</b>  | 57 (72.2)<br>NA = 43 | 4 (44.4)<br>NA = 15<br><b>20 (68.9)</b> | 16 (80.0)<br>NA = 23 | 3 (23.1)<br>NA = 17<br><b>16 (53.3)</b> | 13 (76.5)<br>NA = 23 |
| Sarcopenia (T12)              | 37 (69.8)<br>NA = 11<br><b>132 (83.0)</b> | 95 (89.6)<br>NA = 16 | 6 (46.2)<br>NA = 11<br><b>30 (75.0)</b> | 24 (88.9)<br>NA = 16 | 19 (70.4)<br>NA = 3<br><b>49 (83.0)</b> | 30 (93.8)<br>NA = 8  |
| Subcutaneous adipopenia (L3)  | 17 (48.6)<br>NA = 29<br><b>56 (49.1)</b>  | 39 (49.4)<br>NA = 43 | 2 (22.2)<br>NA = 15<br><b>14 (48.2)</b> | 12 (60.0)<br>NA = 23 | 6 (46.2)<br>NA = 17<br><b>18 (60.0)</b> | 12 (70.6)<br>NA = 23 |
| Subcutaneous adipopenia (T12) | 27 (50.9)<br>NA = 11<br><b>80 (50.3)</b>  | 53 (50.0)<br>NA = 16 | 4 (30.8)<br>NA = 11<br><b>17 (42.5)</b> | 13 (48.1)<br>NA = 16 | 14 (51.9)<br>NA = 3<br><b>30 (50.8)</b> | 16 (50.0)<br>NA = 8  |
| Visceral adipopenia (L3)      | 18 (51.4)<br>NA = 23<br><b>57 (52.3)</b>  | 39 (49.4)<br>NA = 43 | 4 (44.4)<br>NA = 15<br><b>15 (53.5)</b> | 11 (55)<br>NA = 23   | 3 (23.1)<br>NA = 17<br><b>14 (46.6)</b> | 11 (64.7)<br>NA = 23 |

NA: missing data (body composition not evaluated).

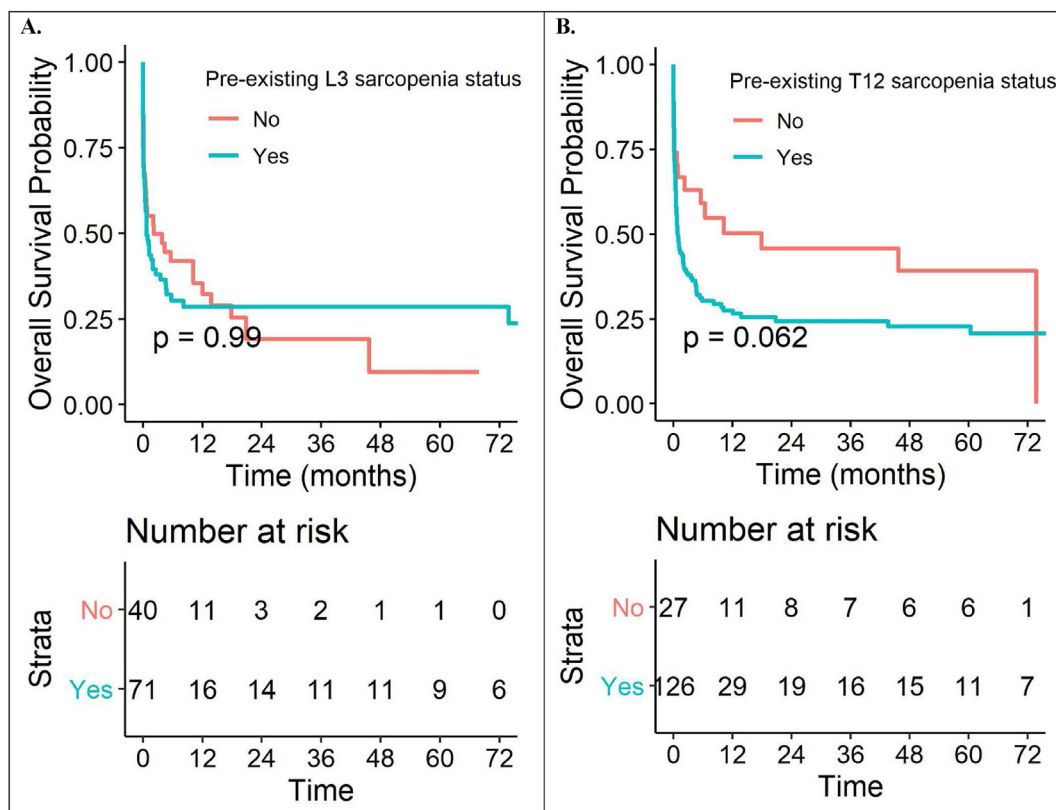
from sepsis are also overexposed to the risk of sarcopenia after ICU stay [17], and sepsis might act as a second hit, exacerbating muscle weakness in this population. Sarcopenia in septic patients increases mortality by a factor of 2.14 according to meta-analysis

by Liu et al. [38] The risk factors associated with ICU mortality observed in our study are similar to those described in the literature and are correlated with the severity of the different organ failures [4,39].

**Table 3**  
Factors associated with 1-month ICU mortality (logistic regression).

|                                | Odds Ratio (OR) [95% confidence interval] | p value          |
|--------------------------------|---|------------------|
| <b>Univariate analysis</b>     |   |                  |
| Age >60 years                  | 1.92 [1.05, 3.54]                         | 0.036            |
| Gender (reference woman)       | 1.54 [0.83, 2.86]                         | 0.17             |
| Performance status 2-4         | 2.56 [1.32, 4.97]                         | <b>0.005</b>     |
| Allogenic stem cell transplant | 0.82 [0.35, 1.91]                         | 0.649            |
| CCI ≥3                         | 1.18 [0.65, 2.16]                         | 0.587            |
| SAPS II score ≥53              | 2.78 [1.50, 5.14]                         | <b>0.001</b>     |
| SOFA score ≥9                  | 3.47 [1.82, 6.6]                          | <b>&lt;0.001</b> |
| Vasopressive drugs             | 5.21 [2.65, 10.23]                        | <b>&lt;0.001</b> |
| Lactates > normal              | 2.81 [1.46, 5.39]                         | <b>0.002</b>     |
| Mechanical ventilation         | 9.22 [4.22, 20.12]                        | <b>&lt;0.001</b> |
| Acute kidney injury (KDIGO 3)  | 2.64 [1.19, 5.83]                         | 0.017            |
| Renal replacement therapy      | 3.27 [1.43, 7.47]                         | <b>0.005</b>     |
| LSMI sarcopenia                | 1.33 [0.61, 2.89]                         | 0.472            |
| TSMI sarcopenia                | 2.13 [0.89, 5.1]                          | 0.089            |
| <b>Multivariate analysis</b>   |   |                  |
| Age >60 years                  | 2.63 [0.92, 7.50]                         | 0.07             |
| Gender (reference woman)       | 1.67 [0.58, 4.78]                         | 0.342            |
| Performance status 2-4         | 2.32 [0.71, 7.54]                         | 0.163            |
| SAPS II score ≥53              | 0.92 [0.34, 2.47]                         | 0.869            |
| SOFA score ≥9                  | 1.72 [0.57, 5.27]                         | 0.338            |
| Vasopressive drugs             | 2.25 [0.69, 7.29]                         | 0.177            |
| Lactates > normal              | 3.14 [1.06, 9.33]                         | <b>0.039</b>     |
| Mechanical ventilation         | 15.57 [4.18, 58.02]                       | <b>&lt;0.001</b> |
| Renal replacement therapy      | 1.76 [0.49, 6.37]                         | 0.389            |

CCI: Charlson Comorbidity Index; SAPS II: Simplified Acute Physiology Score II; SOFA: Sequential Organ Safety Assessment; KDIGO Kidney Disease Improving Global Outcomes; LSMI: L3 Skeletal Muscle Index; TSMI: T12 Skeletal Muscle Index.



**Fig. 3.** Kaplan–Meier curve estimates of overall survival according to pre-existing L3 sarcopenia (A); overall survival according to pre-existing T12 sarcopenia (B).

We observed a trend toward lower OS for patients who displayed T12 pre-existing sarcopenia and T12 pre-existing sarcopenia plus adipopenia.

Although the gold standard for body composition measurement is currently L3 [30], studies suggest alternatives with segmentations at T12 [31]. Data from T12 sections also show an impact of



**Table 4**  
Comparison of clinical and biological factors that could potentially differ between patients with or without L3 sarcopenia.

|  | Nonsarcopenic patients (n = 40)<br>N (%)<br>Median [IQR] | Sarcopenic patients (n = 74)<br>N (%)<br>Median [IQR] | p value      |
|--|--|---|--------------|
| <b>Basic characteristics</b>                               |  |   |              |
| Age, years   | 58.0 [51, 67]  | 58.0 [42, 68]   | 0.465        |
| Male gender  | 22 (55.0)  | 57 (77.0)   | <b>0.015</b> |
| Performance status 2-4                                     | 11 (27.5)  | 30 (40.5)   | <b>0.66</b>  |
| <b>Hematological malignancies</b>                          |  |   |              |
| Ann Arbor stage III-IV                                     | 18 (94.7)  | 30 (81.1)   | 0.243        |
| B symptoms   | 12 (30.8)  | 31 (41.9)   | 0.247        |
| LDH rate   | 422.0 [175, 652]   | 405.0 [291, 695]                                      | 0.965        |
| Prior lines of anticancer therapies >1                     | 14 (35.0)  | 27 (36.5)   | 0.875        |
| <b>Severity of illness score at ICU admission</b>          |  |   |              |
| SOFA day 1   | 7 [5, 11]  | 9 [5, 12]   | 0.766        |
| <b>Characteristics of ICU stay</b>                         |  |   |              |
| Delay in ICU transfer from diagnosis lower than the median | 18 (45.0)  | 40 (45.9)   | 0.356        |
| CCI ≥3   | 21 (56.8)  | 38 (53.5)   | 0.749        |
| Aplasia at admission                                       | 19 (54.3)  | 31 (50.8)   | 0.744        |
| <b>Biological parameters at diagnosis</b>                  |  |   |              |
| Albuminemia <30 g/L  | 16 (43.2)  | 34 (48.6)   | 0.599        |
| Phosphoremia lower than normal                             | 11 (28.2)  | 16 (22.2)   | 0.639        |

CCI: Charlson Comorbidity Index; SOFA: Sequential Organ Safety Assessment.

skeletal muscle mass on the prognosis of ICU patients [40]. In our study, 159 I1 images were analyzed at the T12 level, whereas only 114 I1 images were analyzed at the L3 level. The preponderance of T12 slices can be explained by the greater frequency of thoracic scans than abdominal-pelvic scans in the ICU. Typically, the primary reason (62.5%) for hospitalization of patients with hematologic malignancy in the ICU is acute respiratory distress, which explains the wider use of thoracic scans [4]. Our study showed a good correlation ( $r = 0.77$ ) of sarcopenia measurements between L3 and T12 methods, which encourages the complimentary use of the T12 method for body composition assessment, although the data to date in the literature are poor and T12 segmentation is a little trickier than L3. Furthermore, the use of T12 slices has advantages in image interpretation compared to L3 slices, namely, less impact of hydrosodic inflation [41,42] and fewer difficulties related to the presence of a tumor syndrome. Our hypothesis is that the analysis of the quantity of skeletal muscles in T12 in this population of severe patients in septic shock with edematous syndrome would be more efficient for the diagnosis of sarcopenia than similar analysis in L3, which seems to be suggested by our results of an unfavorable prognostic impact, although not statistically significant, of T12 sarcopenia on the outcome of these patients. Our results suggest that we might more widely use T12 assessment as a complement to L3 assessment, especially for patients who do not benefit from abdominal scans as part of routine care or with severe edematous syndrome.

Surprisingly, we did not find any impact of pre-existing sarcopenia, pre-existing adipopenia or the combination of both in L3 on ICU overall survival, contrary to the data in the literature [13],[43-45] In addition to the strong impact on mortality, sarcopenia is associated with an increase in the length of stay in the ICU [46] and an increase in the duration of mechanical ventilation [47] in hematologic malignancy patients [48].

This association between sarcopenia and mortality has been described in multiple pathologies, including cancers [49,50]. For example, an association was described in diffuse large-cell B lymphoma, where sarcopenia was more frequent in patients with a high IPI score [51], was associated with a poorer response to treatment [52], was a predicting risk factor for relapse [53] and was associated with a longer time to liberation from ventilation [48].

The lack of data that is consistent with the literature can be explained mainly by positive fluid balance related to ICU stage

altering the quality of interpretation of CT scans [41],[42] This tissue edema may have been less severe at T12 than at L3. In addition, the new definition of sarcopenia, according to the 2018 EWGSOP2 guidelines [30], should include the clinical features of muscle strength alteration and function. However, these clinical elements are associated with the quantification of muscle mass loss. In our study, only the quantification of skeletal surfaces (LSMI and TSMI) was performed, and there was no functional assessment due to the retrospective design of the study. The study reported by Yanagi et al. [16] shows that physical disability, which is a reflection of impaired muscle strength and, thus, sarcopenia indirectly, increases the risk of mortality by a factor of 4.19 even away from ICU stay.

Emerging evidence suggests that fat mass loss by adipocyte lysis may reflect adipopenia and ultimately cachexia. The main players in the regulation of adipocyte lysis are the catecholaminergic and natriuretic systems, which are particularly active in the ICU [54]. Adipolysis is a provider of weight loss and itself a provider of cachexia. In the literature, cachexia is a major risk factor for mortality in patients with chronic diseases [55]. For cancer diseases, the prognostic role of adipopenia goes further: the detection of adipopenia marks a prognostic turning point of the disease because it appears approximately 7 months before death [56]. However, not all fatty masses are equal, and the presence of subcutaneous adipopenia may be associated with worse prognosis [57]. However, in our study, adipopenic status had no impact on outcomes. The reasons for this finding may be insufficient statistical power and the presence of many confounding factors (severity of sepsis, organ failures and severity of underlying hematologic malignancy).

Current approaches for assessing prognosis in critically ill patients with hematologic malignancies frequently involve consideration of information on the underlying disease (ECOG-PS, type of leukemia), patients' baseline morbidity (functional status, comorbidities), and severity of illness per ICU admission (severity scores). Our findings may suggest the utility of body composition measurements as an objective evaluation of sarcopenia at the time of critical illness. Patients with hematologic malignancies lose a significant amount of skeletal muscle mass depending on disease progression, chemotherapy or anorexia, and ICU admission worsens only the underlying sarcopenia.

Undernutrition in physical frailty before critical illness has been increasingly recognized as an important predictor of ICU outcomes,

including length of stay, mortality, and long-term disability [58]. It refers to the concept of pre-existing sarcopenia. A review by *McKendry* et al. focuses on this concept and shows that strategies to combat muscle wasting need to be established; notably, loading exercise and protein provision are the most compelling [58].

Our study has several limitations to be highlighted. First, hematologic malignancies represent a heterogeneous population with different prognoses and disease courses. It is therefore possible that among these patients, there exist different phenotypes where the association between body composition measurement and clinical outcome differs. Indeed, our negative findings could be explained by this heterogeneity of the population. We did not have sufficient statistical power to perform all of the sub-analyses for each of the hematological malignancy subtypes included in the study.

Second, we chose to use CT scans performed up to 2 months before ICU admission to evaluate body composition, but 59.6% CT scans were performed within 15 days before ICU admission. Therefore, it is plausible that the impact of acute illness on muscle composition inducing a catabolic state might have already taken effect between the time of the CT imaging and admission to the ICU. Moreover, the cutoffs defining the thresholds of sarcopenia and adipopenia were based on data from the literature but not specifically on hematology patients and even less on intensive care patients. Tissue edema can lead to an overestimation of measurements of skeletal muscle CSA or subcutaneous fat [41]. Furthermore, the retrospective nature of this study is a limiting factor in the evaluation of the nutritional status of patients (only 42% of data for daily caloric intake, no measurement of the brachial circumference, the thickness of the skin folds, the MRC score (Medical Research Council score)). Third, survival analysis did not reach statistical significance due to lack of power with an insufficient number of patients analyzed and many confounding factors (severity of underlying hematologic malignancy, severity at admission in ICU, lack of data on nutritional support in ICU). Finally, we did not assess physical muscle strength/function, and we did not evaluate the impact of sarcopenia on the quality of life (through quality of life scores) of patients surviving the ICU stay, so we were unable to describe the functional status of our patients after ICU discharge. Similarly, the evaluation of sarcopenia at discharge from the ICU is limited by the small number of imaging studies performed (36.0% during the ICU stay and 37.6% after the stay).

Further research is warranted to assess the benefit of early detection and treatment of sarcopenia in hematology patients. In the ICU, strategies to reduce sarcopenia onset were less effective than in the non-ICU setting because skeletal muscle wasting in the ICU is rapid [59]. Hematologists and intensivists need to develop strategies to combat modifications in the body composition of their patients [60].

## 5. Conclusion

Pre-existing sarcopenia was highly prevalent in critically ill patients with hematologic malignancies admitted for sepsis or septic shock. Body composition assessment at the T12 level using CT scan was well correlated with the current L3 gold standard method. T12 level-determined, pre-existing sarcopenia unfavorably affected patient outcomes.

The role of body composition measurements as surrogate markers of frailty and a potential prognostic tool in patients with hematologic malignancies warrants further research. Future studies should consider, whenever possible, a more comprehensive assessment of body composition and long-term functional status outcomes such as long-term post-ICU disability.

## Grants and funding

None.

## Financial disclosure statement

Nothing to disclose.

## Ethics approval

This retrospective study was approved by the Centre Henri Becquerel internal review board (N°2006B) and by the Commission for the Qualification of Research Projects of Rouen University Hospital (N°595).

## Consent to participate

Patients' non opposition statement was obtained for all live participants.

## Consent for publication

The authors give the publisher their permission to publish the work.

## Availability of data and material

All data are available for review.

## Code availability (software application or custom code)

Not applicable.

## Authors' contributions

AH collected the data and wrote the manuscript.  
 VC designed the study, coordinated the work and edited the manuscript.  
 FT coordinated the work and edited the manuscript.  
 JL realized the database.  
 EL performed statistical analysis.  
 AH, PD and SDC analyzed the scanned slices.  
 PD wrote the segmentation macro for ImageJ.  
 All authors were involved in the care of the patients.  
 All authors read and approved the manuscript.

## Declaration of competing interest

No conflicts of interest.

## Acknowledgments

We would like to thank Ms. Doriane RICHARD, who provided administrative support. We would also like to thank the Centre de Traitement des Données du Cancéropôle Nord-Ouest (CTD-CNO) for data management support.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnesp.2023.04.007>.

## References

- [1] Sant M, Minicozzi P, Mounier M, Anderson LA, Brenner H, Holleczeck B, et al. Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EURO-CARE-5, a population-based study. *Lancet Oncol* 2014 Aug;15(9):931–42.
- [2] Peigne V, Rusinová K, Karlin L, Darmon M, Femand JP, Schlemmer B, et al. Continued survival gains in recent years among critically ill myeloma patients. *Intensive Care Med* 2009 Mar;35(3):512–8.
- [3] Guidelines for intensive care unit admission, discharge, and triage. Task force of the American college of critical care medicine, society of critical care medicine. *Crit Care Med* 1999 Mar;27(3):633–8.
- [4] Azoulay E, Mokart D, Pène F, Lambert J, Kouatchet A, Mayaux J, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium—a groupe de recherche respiratoire en réanimation onco-hématologique study. *J Clin Oncol* 2013 Aug 1;31(22):2810–8.
- [5] Seo DW, Kim KW, Sohn CH, Ryoo SM, Kim YJ, Shin A, et al. Progressive loss of muscle mass could be an adverse prognostic factor of 28-day mortality in septic shock patients. *Sci Rep* 2019 Nov 11;9(1):16471.
- [6] Stevens RD, Marshall SA, Cornblath DR, Hoke A, Needham DM, de Jonghe B, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med* 2009 Oct;37(10 Suppl):S299–308.
- [7] Klaude M, Mori M, Tjäder I, Gustafsson T, Wernerman J, Rooyackers O. Protein metabolism and gene expression in skeletal muscle of critically ill patients with sepsis. *Clin Sci* 2012 Feb;122(3):133–42.
- [8] Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian working group for sarcopenia: 2019 consensus update on 9sarcopenia diagnosis and treatment. *J Am Med Dir Assoc* 2020 Mar;21(3):300–7. e2.
- [9] Yilmaz M, Atilla FD, Sahin F, Saydam G. The effect of malnutrition on mortality in hospitalized patients with hematologic malignancy. *Support Care Cancer* 2020 Mar;28(3):1441–8.
- [10] Surov A, Wienke A. Sarcopenia predicts overall survival in patients with malignant hematological diseases: a meta-analysis. *Clin Nutr* 2021 Mar;40(3):1155–60.
- [11] Price S, Kim Y. Body composition impacts hematopoietic stem cell transplant outcomes in both autologous and allogeneic transplants: a systematic review. *Nutr Cancer* 2021 Dec 28;1–12.
- [12] Ando T, Fujisawa S, Teshigawara H, Matsumura A, Sakuma T, Suzuki T, et al. Computed tomography-defined sarcopenia: prognostic predictor of non-relapse mortality after allogeneic hematopoietic stem cell transplantation: a multicenter retrospective study. *Int J Hematol* 2020 Jul;112(1):46–56.
- [13] Loosen SH, Schulze-Hagen M, Püngel T, Bündgens L, Wirtz T, Kather JN, et al. Skeletal muscle composition predicts outcome in critically ill patients. *Crit Care Explor* 2020 Aug;2(8):e0171.
- [14] Mourtzakis M, Prado CMM, Liefers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metabol* 2008 Oct;33(5):997–1006.
- [15] Prado CMM, Birdsell LA, Baracos VE. The emerging role of computerized tomography in assessing cancer cachexia. *Curr Opin Support Palliat Care* 2009 Dec;3(4):269–75.
- [16] Yanagi N, Kamiya K, Hamazaki N, Matsuzawa R, Nozaki K, Ichikawa T, et al. Post-intensive care syndrome as a predictor of mortality in patients with critical illness: a cohort study. *PLoS One* 2021;16(3):e0244564.
- [17] Schefold JC, Bierbrauer J, Weber-Carstens S. Intensive care unit-acquired weakness (ICUAW) and muscle wasting in critically ill patients with severe sepsis and septic shock. *J Cachexia Sarcopenia Muscle* 2010 Dec;1(2):147–57.
- [18] Oh HJ, Kim JH, Kim HR, Ahn JY, Jeong SJ, Ku NS, et al. The impact of sarcopenia on short-term and long-term mortality in patients with septic shock. *J Cachexia Sarcopenia Muscle* 2022 Aug;13(4):2054–63. <https://doi.org/10.1002/jcsm.12995>. Epub 2022 Apr 27.
- [19] Zduniak A, Mihailescu SD, Lequesne J, Lenain P, Contentin N, Pepin LF, et al. Outcomes after intensive care unit admission in newly diagnosed diffuse large B-cell lymphoma patients: a real-life study. *Eur J Haematol* 2021 Jun;106(6):788–99.
- [20] Cox MC, Booth M, Ghita G, Wang Z, Gardner A, Hawkins RB, et al. The impact of sarcopenia and acute muscle mass loss on long-term outcomes in critically ill patients with intra-abdominal sepsis. *J Cachexia Sarcopenia Muscle* 2021 Oct;12(5):1203–13.
- [21] Kochanek M, Schalk E, von Bergwelt-Baildon M, Beutel G, Buchheidt D, Hentrich M, et al. Management of sepsis in neutropenic cancer patients: 2018 guidelines from the infectious diseases working party (AGIHO) and intensive care working party (iCHOP) of the German society of hematology and medical oncology (DGHO). *Ann Hematol* 2019 May;98(5):1051–69.
- [22] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016 Feb 23;315(8):801–10.
- [23] Probst L, Schalk E, Liebrechts T, Zeremski V, Tzalavras A, von Bergwelt-Baildon M, et al. Prognostic accuracy of SOFA, qSOFA and SIRS criteria in hematological cancer patients: a retrospective multicenter study. *J Intensive Care* 2019;7:41.
- [24] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021 Nov;47(11):1181–247.
- [25] Lamia B, Hellot MF, Girault C, Tamion F, Dachraoui F, Lenain P, et al. Changes in severity and organ failure scores as prognostic factors in onco-hematological malignancy patients admitted to the ICU. *Intensive Care Med* 2006 Oct;32(10):1560–8.
- [26] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994 Nov;47(11):1245–51.
- [27] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine. *Intensive Care Med* 1996 Jul;22(7):707–10.
- [28] Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993 Dec 22;270(24):2957–63.
- [29] Ross R. Advances in the application of imaging methods in applied and clinical physiology. *Acta Diabetol* 2003 Oct;40(Suppl 1):S45–50.
- [30] Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019 Jan 1;48(1):16–31.
- [31] Nemeč U, Heidinger B, Sokas C, Chu L, Eisenberg RL. Diagnosing sarcopenia on thoracic computed tomography: quantitative assessment of skeletal muscle mass in patients undergoing transcatheter aortic valve replacement. *Acad Radiol* 2017 Sep;24(9):1154–61.
- [32] Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods* 2012 Jul;9(7):671–5.
- [33] Gomez-Perez S, McKeever L, Sheehan P. Tutorial: A step-by-step guide (version 2.0) for measuring abdominal circumference and skeletal muscle from a single cross-sectional computed-tomography image using the national institutes of health ImageJ. *JPEN - J Parenter Enter Nutr* 2020 Mar;44(3):419–24.
- [34] Decazes P. Free macro for ImageJ to segment manually muscles, subcutaneous adipose tissue and visceral adipose tissue at level L3 on computed tomography. 2019.
- [35] Decazes P, Tonnelet D, Vera P, Gardin I. Anthropometer3D: automatic multi-slice segmentation software for the measurement of anthropometric parameters from CT of PET/CT. *J Digit Imag* 2019 Apr;32(2):241–50.
- [36] Tolonen A, Pakarinen T, Sassi A, Kyttä J, Cancino W, Rinta-Kiikka I, et al. Methodology, clinical applications, and future directions of body composition analysis using computed tomography (CT) images: a review. *Eur J Radiol* 2021 Dec;145:109943.
- [37] Prado CMM, Liefers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008 Jul;9(7):629–35.
- [38] Liu W, Hu C, Zhao S. Sarcopenia and mortality risk of patients with sepsis: a meta-analysis. *Int J Clin Pract* 2022;2022:4974410.
- [39] Nathan N, Sculier JP, Ameye L, Paesmans M, Bogdan-Drăgoc G, Meert AP. Sepsis and septic shock definitions in patients with cancer admitted in ICU. *J Intensive Care Med* 2021 Mar;36(3):255–61.
- [40] Moon SW, Kim SY, Choi JS, Leem AY, Lee SH, Park MS, et al. Thoracic skeletal muscle quantification using computed tomography and prognosis of elderly ICU patients. *Sci Rep* 2021 Dec 6;11(1):23461.
- [41] Campbell IT, Watt T, Withers D, England R, Sukumar S, Keegan MA, et al. Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema. *Am J Clin Nutr* 1995 Sep;62(3):533–9.
- [42] Mundi MS, Patel JJ, Martindale R. Body composition technology: implications for the ICU. *Nutr Clin Pract* 2019 Feb;34(1):48–58.
- [43] Meyer HJ, Wienke A, Surov A. Computed tomography-defined low skeletal muscle mass as a prognostic marker for short-term mortality in critically ill patients: a systematic review and meta-analysis. *Nutrition* 2021 Dec;91–92:111417.
- [44] Zhang XM, Chen D, Xie XH, Zhang JE, Zeng Y, Cheng AS. Sarcopenia as a predictor of mortality among the critically ill in an intensive care unit: a systematic review and meta-analysis. *BMC Geriatr* 2021 Jun 2;21(1):339.
- [45] Toptas M, Yalcin M, Akkoc İ, Demir E, Metin C, Savas Y, et al. The relation between sarcopenia and mortality in patients at intensive care unit. *BioMed Res Int* 2018;2018:5263208.
- [46] Joyce PR, O'Dempsey R, Kirby G, Anstey C. A retrospective observational study of sarcopenia and outcomes in critically ill patients. *Anaesth Intensive Care* 2020 May;48(3):229–35.
- [47] Jiang T, Lin T, Shu X, Song Q, Dai M, Zhao Y, et al. Prevalence and prognostic value of preexisting sarcopenia in patients with mechanical ventilation: a systematic review and meta-analysis. *Crit Care* 2022 May 16;26(1):140.
- [48] Elfassy MD, Ferreyro BL, Rozenberg D, Sklar MC, Mathur S, Detsky ME, et al. Association of thoracic computed tomographic measurements and outcomes in patients with hematologic malignancies requiring mechanical ventilation. *Ann Am Thorac Soc* 2021 Jul;18(7):1219–26.
- [49] Meza-Valderrama D, Marco E, Dávalos-Yerovi V, Muns MD, Tejero-Sánchez M, Duarte E, et al. Adapting definitions and terminology of nutritional disorders in older people with cancer. *Nutrients* 2021 Feb 26;13(3):761.
- [50] Yang M, Shen Y, Tan L, Li W. Prognostic value of sarcopenia in lung cancer: a systematic review and meta-analysis. *Chest* 2019 Jul;156(1):101–11.

- [51] Camus V, Lanic H, Kraut J, Modzelewski R, Clatot F, Picquenot JM, et al. Prognostic impact of fat tissue loss and cachexia assessed by computed tomography scan in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Eur J Haematol* 2014 Jul;93(1):9–18.
- [52] Lanic H, Kraut-Tauzia J, Modzelewski R, Clatot F, Mareschal S, Picquenot JM, et al. Sarcopenia is an independent prognostic factor in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Leuk Lymphoma* 2014 Apr;55(4):817–23.
- [53] Sarkozy C, Camus V, Tilly H, Salles G, Jardin F. Body mass index and other anthropometric parameters in patients with diffuse large B-cell lymphoma: physiopathological significance and predictive value in the immunochemotherapy era. *Leuk Lymphoma* 2015 Jul;56(7):1959–68.
- [54] Agustsson T, Rydén M, Hoffstedt J, van Harmelen V, Dicker A, Laurencikiene J, et al. Mechanism of increased lipolysis in cancer cachexia. *Cancer Res* 2007 Jun 1;67(11):5531–7.
- [55] Rydén M, Arner P. Fat loss in cachexia—is there a role for adipocyte lipolysis? *Clin Nutr* 2007 Feb;26(1):1–6.
- [56] Murphy RA, Wilke MS, Perrine M, Pawlowicz M, Mourtzakis M, Lieffers JR, et al. Loss of adipose tissue and plasma phospholipids: relationship to survival in advanced cancer patients. *Clin Nutr* 2010 Aug;29(4):482–7.
- [57] Berentzen T, Sørensen TIA. Effects of intended weight loss on morbidity and mortality: possible explanations of controversial results. *Nutr Rev* 2006 Nov;64(11):502–7.
- [58] McKendry J, Thomas ACQ, Phillips SM. Muscle mass loss in the older critically ill population: potential therapeutic strategies. *Nutr Clin Pract* 2020 Aug;35(4):607–16.
- [59] Parry SM, El-Ansary D, Cartwright MS, Sarwal A, Berney S, Koopman R, et al. Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function. *J Crit Care* 2015 Oct;30(5):1151.e9. 14.
- [60] Akan B. Influence of sarcopenia focused on critically ill patients. *Acute Crit Care* 2021 Feb;36(1):15–21.