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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



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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.

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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.

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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) (cm²) 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 m²) 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 cm²/m² (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 cm²/m², and for women, the cutoff is < 38.5 cm²/m² [37]. Thoracic cutoff values for sarcopenia at the T12 level were 42.6 cm²/m² for men and 30.6 cm²/m² for women, as proposed by *Nemec 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], *Nemec 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/m². 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

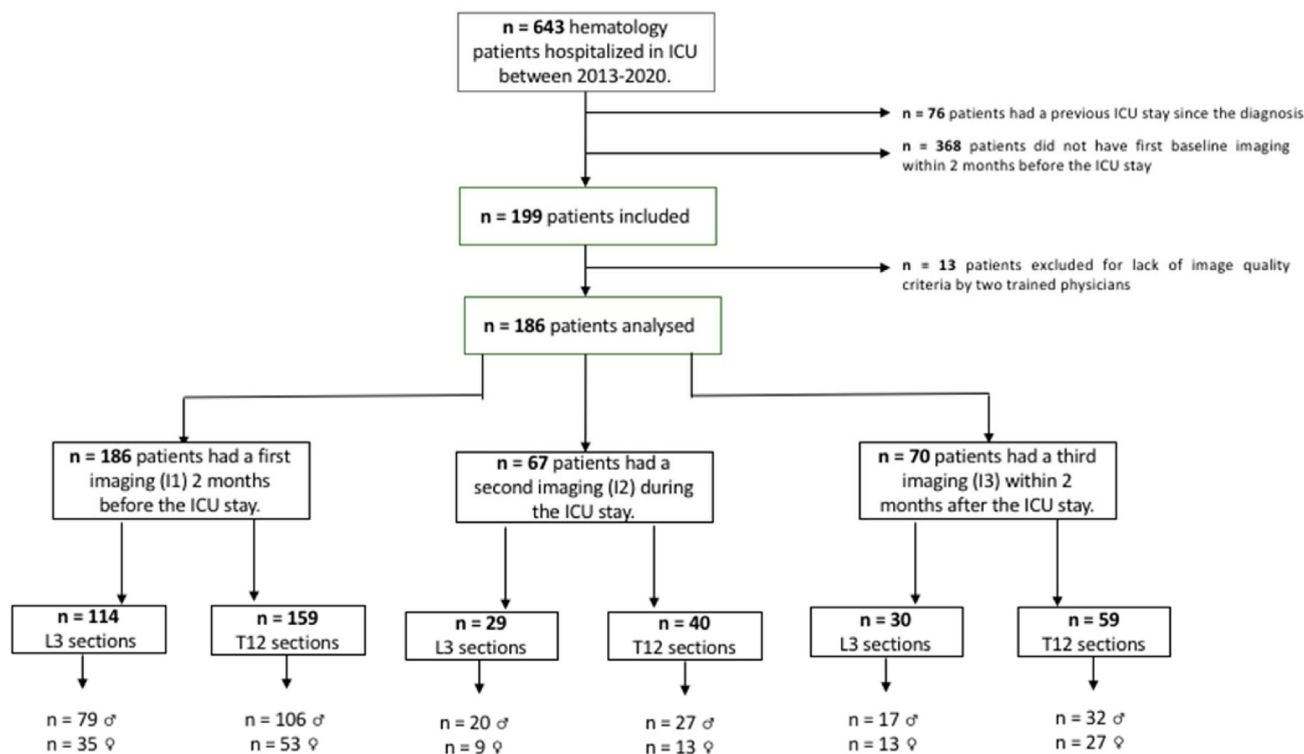


Fig. 1. Flow chart. ICU: intensive care unit; I1: first imaging of the study; I2: second imaging of the study; I3: third imaging of the study; ♂: men; ♀: women.

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 cm²/m²) (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/m² 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 cm²/m²) (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 ²)	24.4 [22; 29]
Weight at discharge (kg)	76.0 [65; 89]
BMI at discharge (kg/m ²)	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

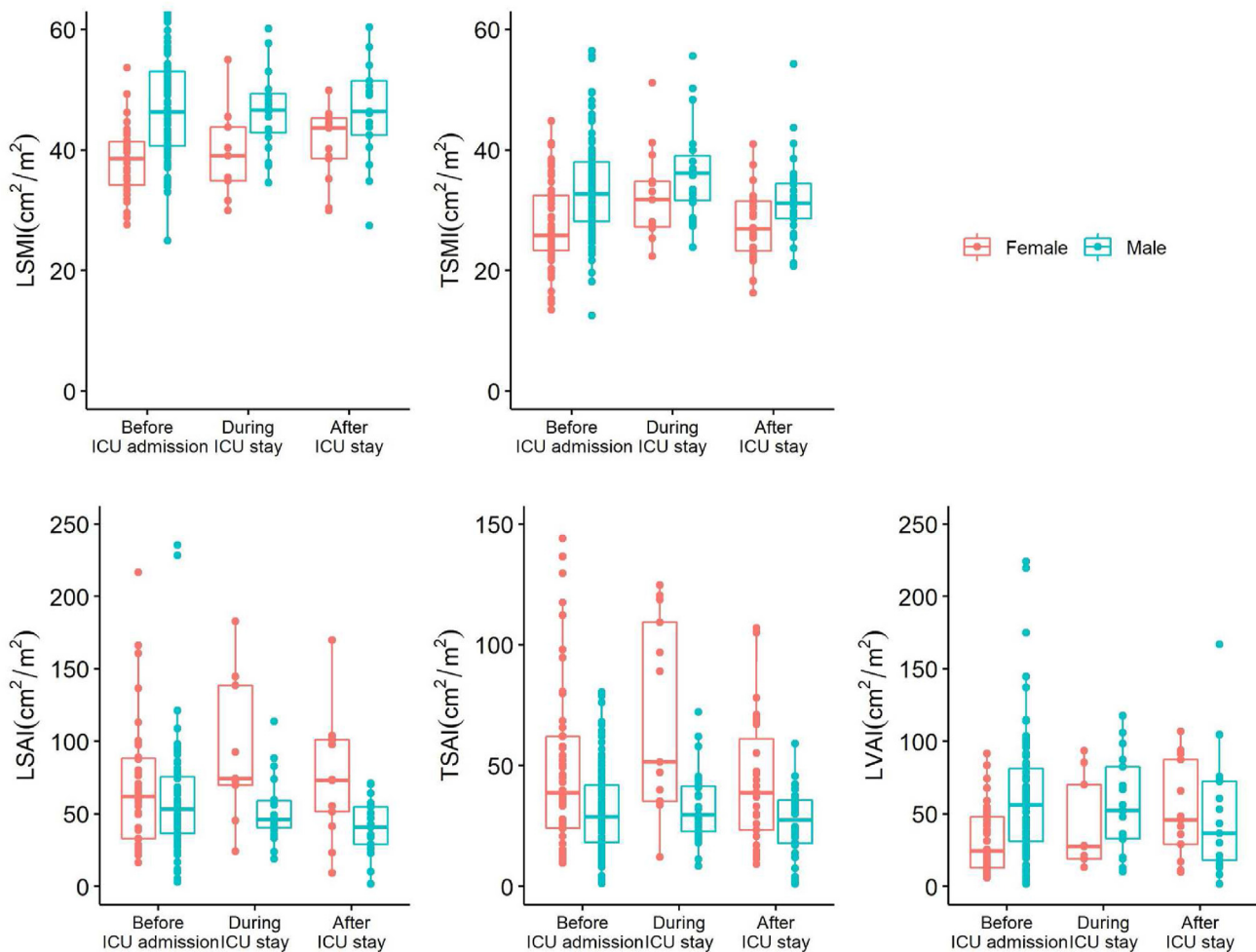


Fig. 2. Boxplots showing LSMI (A), LSAI (B), TSMI (C), TSAI (D), and LVAI (E) repartition at baseline (before ICU admission), during the ICU stay and after the end of the ICU stay, when available. LSMI: L3 skeletal muscle index; LSAI: L3 subcutaneous adipose tissue index; TSMI: T12 skeletal muscle index; 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) NA = 29 74 (64.9)	57 (72.2) NA = 43	4 (44.4) NA = 15 20 (68.9)	16 (80.0) NA = 23	3 (23.1) NA = 17 16 (53.3)	13 (76.5) NA = 23
Sarcopenia (T12)	37 (69.8) NA = 11 132 (83.0)	95 (89.6) NA = 16	6 (46.2) NA = 11 30 (75.0)	24 (88.9) NA = 16	19 (70.4) NA = 3 49 (83.0)	30 (93.8) NA = 8
Subcutaneous adipopenia (L3)	17 (48.6) NA = 29 56 (49.1)	39 (49.4) NA = 43	2 (22.2) NA = 15 14 (48.2)	12 (60.0) NA = 23	6 (46.2) NA = 17 18 (60.0)	12 (70.6) NA = 23
Subcutaneous adipopenia (T12)	27 (50.9) NA = 11 80 (50.3)	53 (50.0) NA = 16	4 (30.8) NA = 11 17 (42.5)	13 (48.1) NA = 16	14 (51.9) NA = 3 30 (50.8)	16 (50.0) NA = 8
Visceral adipopenia (L3)	18 (51.4) NA = 23 57 (52.3)	39 (49.4) NA = 43	4 (44.4) NA = 15 15 (53.5)	11 (55) NA = 23	3 (23.1) NA = 17 14 (46.6)	11 (64.7) 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
Univariate analysis		
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]	0.005
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]	0.001
SOFA score ≥9	3.47 [1.82, 6.6]	<0.001
Vasopressive drugs	5.21 [2.65, 10.23]	<0.001
Lactates > normal	2.81 [1.46, 5.39]	0.002
Mechanical ventilation	9.22 [4.22, 20.12]	<0.001
Acute kidney injury (KDIGO 3)	2.64 [1.19, 5.83]	0.017
Renal replacement therapy	3.27 [1.43, 7.47]	0.005
LSMI sarcopenia	1.33 [0.61, 2.89]	0.472
TSMI sarcopenia	2.13 [0.89, 5.1]	0.089
Multivariate analysis		
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]	0.039
Mechanical ventilation	15.57 [4.18, 58.02]	<0.001
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.

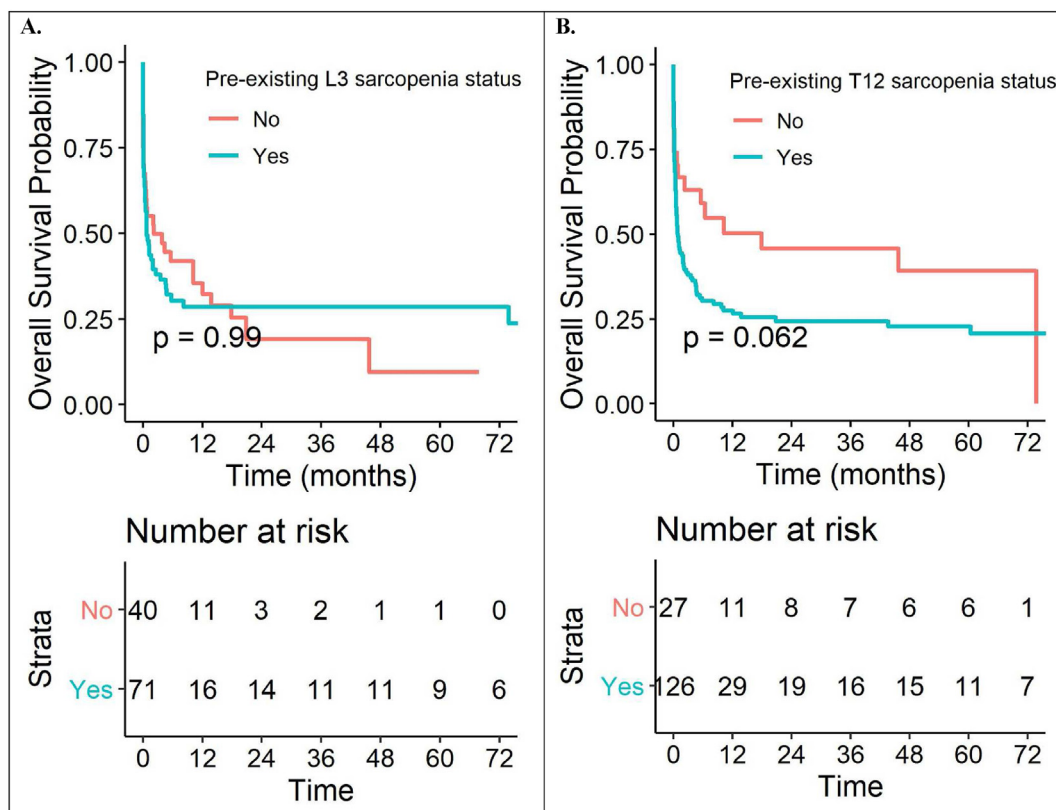


Fig. 3. Kaplan–Meier curve estimates of overall survival according to pre-existing L3 sarcopenia (A); overall survival according to pre-existing T12 sarcopenia (B).

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) N (%) Median [IQR]	Sarcopenic patients (n = 74) N (%) Median [IQR]	p value
Basic characteristics			
Age, years	58.0 [51, 67]	58.0 [42, 68]	0.465
Male gender	22 (55.0)	57 (77.0)	0.015
Performance status 2-4	11 (27.5)	30 (40.5)	0.66
Hematological malignancies			
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
Severity of illness score at ICU admission			
SOFA day 1	7 [5, 11]	9 [5, 12]	0.766
Characteristics of ICU stay			
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
Biological parameters at diagnosis			
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.

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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.

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Appendix A. Supplementary data

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