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ORIGINAL ARTICLE

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Myosteatosis to predict inferior perioperative outcome in patients undergoing orthotopic liver transplantation

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Muscle wasting and alterations of body composition are linked to clinical outcomes in numerous medical conditions. The role of myosteatosis in posttransplant outcomes remains to be determined. Here we investigated skeletal muscle mass and myosteatosis as prognostic factors in patients undergoing orthotopic liver transplantation (OLT). The data of 225 consecutive OLT recipients from a prospective database were retrospectively analyzed (May 2010-December 2017). Computed tomography–based skeletal-muscle-index (muscle mass), visceral-fat-area (visceral adiposity), and mean skeletal-muscle-radiation-attenuation (myosteatosis) were calculated using a segmentation tool. Cut-off values of myosteatosis resulted in a good stratification of patients into low- and high-risk groups in terms of morbidity (Clavien-Dindo ≥3b). Patients with myosteatosis had significantly higher complication rates (90-day Comprehensive Complication Index 68 ± 32 vs 44 ± 30, $P < .001$) and also displayed significantly longer intensive care (18 ± 25 vs 11 ± 21 days, $P < .001$) and hospital stay (56 ± 55 vs 33 ± 24 days, $P < .001$). Estimated costs were 44% higher compared to patients without myosteatosis. Multivariable analysis identified myosteatosis as an independent prognostic factor for major morbidity (odds ratio: 2.772, confidence interval: 1.516-5.066, $P = .001$). Adding myosteatosis to the well-established Balance-of-Risk-(BAR) score resulted in an increased prognostic value compared to the original BAR score. Myosteatosis may be a useful parameter to predict perioperative outcome in patients undergoing OLT, supporting the role of muscle quality (myosteatosis) over quantity (muscle mass) in this setting.

KEYWORDS
body composition, clinical decision-making, clinical research/practice, complication, liver transplantation/hepatology, myosteatosis, sarcopenia

Abbreviations: AASLDAmerican Association for the Study of Liver Diseases AUC area under the curve AUROC area under the receiver operating characteristics curve BAR balance of risk BC body composition BMIbody mass index CCI comprehensive complication index CDC lavien-Dindo classification CT computed tomography EAD early allograft dysfunction EASL European Association for the Study of the Liver ECD extended criteria donor FFP unitsfresh frozen plasma units HU Hounsfield unit ICH International Conference on Harmonisation ICU Intensive Care Unit KPS Karnofsky Performance Score MELD Model of End-stage Liver Disease OLT orthotopic liver transplantation RBC units red blood cell units ROC receiver operating characteristics SM-RA skeletal muscle radiation attenuation SMI skeletal muscle index SMM skeletal muscle mass SOFT survival outcomes following liver transplantation TEur Thousand Euros UH-RWTH University Hospital of the RWTH University VFA visceral fat area

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1 | INTRODUCTION

Body composition (BC) is defined as the relative proportion of protein, fat, water, and mineral components in the body. It varies among individuals as a result of differences in age, body density, and the degree of obesity.[1] Muscle depletion is frequently seen in critically ill patients and BC correlates with clinical outcomes in various medical conditions.[2,3] Besides the pure loss of muscle mass and function known as sarcopenia, qualitative structural changes, such as myosteatosis, characterized by the presence of inter- and intramyocellular fat deposition,[4] have been shown to be associated with reduced muscle strength and poor clinical outcomes in patients undergoing surgery for colorectal or pancreatic cancer.[5-7]

In the face of critical organ shortage with increased utilization of marginal allografts procured from extended criteria donors (ECD), one of the most challenging clinical decisions in the liver transplantation setting is the optimal risk-quantification and the identification of high-risk recipients and/or donor-recipient combinations.[8] In this regard, several clinical risk-assessment systems, using donor and recipient factors (eg, Balance-of-Risk or BAR score), have been developed over the past 10-15 years.[8-13] While some of these models are helpful in predicting posttransplant outcomes, none of these scores include information on the recipient's BC.[14] Cross-sectional computed tomography (CT) imaging studies are validated and widely available, and as such, BC could be easily integrated in the process of risk-stratification and routine clinical workup of transplant recipients.[2,15]

The importance of nutritional status and its assessment in patients with chronic liver disease are further highlighted by the recent European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines on nutrition in chronic liver disease.[16-18] Patients with terminal liver disease are frequently burdened by malnutrition and muscle wasting. While some studies have recently reported an association of sarcopenia with clinical outcome in cirrhosis and orthotopic liver transplantation (OLT),[15,19-23] the prognostic value of muscle quality (skeletal muscle density and myosteatosis) compared to muscle quantity (skeletal muscle mass-SMM, as the morphological aspect of sarcopenia) remains to be determined.[2,19-22]

The goal of the present study was to comprehensively assess the role of different CT-based recipient BC profiles and compare the value and limitations of reduced muscle mass and myosteatosis in predicting perioperative outcomes in adult patients undergoing deceased donor OLT.

2 | PATIENTS AND METHODS

2.1 | Patients and ethics

Between May 2010 and December 2017, all consecutive patients undergoing OLT at the University Hospital RWTH Aachen (UH-RWTH), Aachen, Germany, were considered for inclusion. Although during the study period all patients have received a pretransplant CT imaging, patients with CT scans older than 6 months and/or those not including the L3 level were excluded. Patients receiving living related or split liver transplantation were also excluded. Patients undergoing re-OLT have been assessed related to the primary transplantation, and consecutive transplantations were included in the follow-up. The study was conducted at the UH-RWTH in accordance with the current version of the Declaration of Helsinki as well as the Declaration of Istanbul, and the good clinical practice (International Conference on Harmonisation-Good Clinical Practice) guidelines. The study was approved by the responsible Institutional Review Board of the RWTH-Aachen University (EK 047/18). Informed consent was waived due to the retrospective study design and collection of readily available clinical data.

2.2 | CT imaging and segmentation

All CTs were performed by using a Dual-Source-CT-scanner (Siemens Somatom Force, Siemens AG, München, Germany). The technical parameters for CT imaging were as follows: tube voltage, 120 kVp; 0.5 s/rotation, and 5-mm reconstruction thickness.

Data of the most recent preoperative CT imaging were retrieved from digital storage in the Picture Archiving and Communication System. Briefly, a single cross-sectional CT image at the level of the third lumbar vertebra (L3) was used and the segmentation of skeletal muscle and adipose tissue was performed using the 3D Slicer software platform version 4.1 and BC module (https://www.slicer.org/, [24]) in a semiautomatic fashion. Skeletal muscle area, including psoas major, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis were identified and quantified by using attenuation values of −29 to 150 Hounsfield units (HU). Skeletal muscle index (SMI) has been calculated by normalizing the measured muscle area to the square height of the patient (cm^2/m^2). Skeletal muscle radiation attenuation (SM-RA) as an indicator of muscle density and myosteatosis has also been recorded in HUs. Visceral fat area (VFA) was quantified by using the attenuation values −150 to −50 HU. To identify subcutaneous adipose tissue, the attenuation values of −190 to −30 were used (Figure 1). All measurements were performed by the same researcher, experienced in complex image analysis and segmentation techniques.

Based on the SMI and SM-RA, reduced skeletal muscle mass and myosteatosis were defined using cut-off values determined specifically for patients on the OLT waiting list (SMI: female 39 cm^2/m^2, male 50 cm^2/m^2; SM-RA <41 HU for patients with a body mass index [BMI] up to 24.9 kg/m^2 and <33 HU for patients with a BMI ≥25 kg/m^2).[15,25] Established cut-off value of ≥100 cm^2 has been used for VFA to identify patients with visceral obesity.[15] Sarcopenic obesity was defined as the combination of reduced SMI and high VFA. Based on previous literature findings from patient cohorts with terminal liver disease, no differentiation was made based on sex in terms of SM-RA and VFA.[15]

2.3 | Data collection and follow-up

Clinical data were obtained from a prospective institutional database and analyzed retrospectively. Various OLT risk-scores (Table 1)

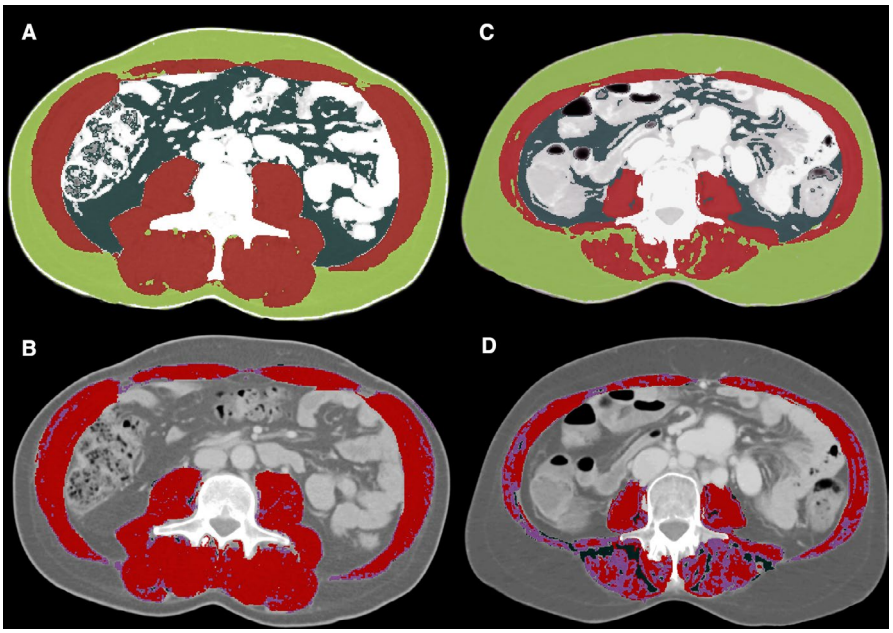


FIGURE 1 Cross-sectional computed tomography images of 2 OLT recipients after segmentation at the level of the third lumbar vertebra. (A and C) Skeletal muscle area (red) was identified by using computed tomography attenuation values of −29 to 150 HU. Subcutaneous fat area (light green) was depicted by using attenuation values of −190 to −30 Hounsfield units (HU). For visceral fat area (dark green) −150 to −50 HU attenuation values were used. Panels B and D depict structural alterations of the skeletal muscle on representative images from 2 OLT recipients. For this, intramuscular adipose tissue has been shown in dark green (−190 to −50 HU), and normal attenuation muscle has been marked red (+30 to 150 HU). Myosteatotic, low attenuation muscle was delineated in violet (−29 to 29 HU). Patient 1 (panels A and B) had a normal skeletal muscle index (SMI) of 83 cm^2/m^2 and normal muscle structure with low amount of intramuscular adipose tissue and insignificant amount of low attenuation (myosteatotic) muscle (skeletal muscle radiation attenuation [SM-RA]: 46 HU). Meanwhile, patient 2 (panels C and D) presented with quantitatively slightly reduced but still normal muscle mass, characterized by an SMI of 62 cm^2/m^2. However, note the severe qualitative alterations observed in patient 2, with increased amount of intramuscular fat (dark green on panel D) and significant myosteatosis (SM-RA: 32 HU), visualized by the strong presence of low attenuation muscle (violet in panel D)

have been calculated as described before.[10,13,26] Extended criteria donor allografts (ECD) were defined according to the definition of the German Medical Chamber (donor age >65 years, intensive care unit [ICU] with mechanical ventilation >7 days, BMI > 30, histologically confirmed graft steatosis >40%, serum sodium >165 mmol/L, serum alanine and/or aspartate aminotransferase >3× higher than the reference level, and serum total bilirubin >2 mg/dL).[27] To assess posttransplant early allograft dysfunction (EAD), the Olthoff criteria were adopted.[28] Postoperative morbidity was evaluated for all surgical complications observed during the first 90 days following OLT according to the Clavien-Dindo classification (CD) and quantified using the Comprehensive Complication Index (CCI©).[29,30] Cost estimation was performed based on recipient age and 90-day CCI score, according to Staigner et al, using a validated online cost-assessment tool for OLT (URL: https://www.assessurgery.com/cost-prediction/).[31] Recipient pre-OLT performance status has been assessed using the Karnofsky performance score (KPS).[32]

Postoperative transfusions were defined as any blood products given within the first 7 days following OLT. Blood products administered later in the postoperative period were categorized as postoperative complications according to the recommendations of the CD classification.[30] Length of ICU stay represents the initial stay after the OLT procedure until the transfer of the patient to our standard care transplantation unit. Hospital stay was defined by the date of admission for OLT and the day of discharge from the UH-RWTH. Readmission to the ICU was included within the total hospital stay. Our transplantation outpatient clinic as well as the responsible general practitioner and/or hepatologist provided all follow-up data used in this study.

2.4 | Surgical- and perioperative approach

All OLT waiting list indications were discussed and decided within a multidisciplinary liver transplantation board in accordance with the German national and Eurotransplant guidelines. Organ allocation followed national and Eurotransplant regulations. The liver transplantation procedure was performed using a standardized approach of total cava replacement as previously described.[33,34] The standard perioperative care and immunosuppression regimen consisted of basiliximab, tacrolimus, mycophenolate mofetil, and corticosteroids.[33,34]

2.5 | Study endpoints and statistical analysis

Ninety-day major morbidity (Clavien-Dindo-CD ≥3b) following OLT was chosen as the primary endpoint for the binary logistic regression analyses

TABLE 1 Donor and recipient characteristics

Characteristics	n = 225
Donor characteristics	
Donor age (y)	55 ± 16
Donor BMI	30 ± 8
Donor sex ratio (F:M)	108 (48%): 117 (52%)
DRI[a]	1.77 ± 0.35
Donor cause of death	CVA 138 (61%)
	Anoxia 51 (23%)
	Trauma 25 (11%)
	Other 11 (5%)
ECD[b]	154 (68%)
Recipient characteristics	
Recipient age (y)	54 ± 12
Recipient BMI	27 ± 5
Recipient sex ratio (F:M)	75 (33%) : 150 (67%)
Cause of liver disease	ALF 31 (14%)
	HCC 63 (28%)
	Alcoholic cirrhosis 45 (20%)
	Viral 15 (7%)
	PSC/PBC 21 (9%)
	Graft failure 4 (2%)
	Other 46 (20%)
Pretransplant Child-Pugh Score	7 ± 2
Pretransplant labMELD	20 ± 11
BAR Score[c]	9 ± 6
SOFT Score[d]	15 ± 10
Recipient pretransplant ICU	56 (25%)
Recipient pretransplant abdominal surgery	82 (36%)
Recipient pretransplant encephalopathy	90 (40%)
Karnofsky Performance Score[e]	60 ± 25
SMI (cm^2/m^2) Male:Female	57 ± 39 : 47 ± 11
SM-RA (HU) Male:Female	35 ± 11 : 32 ± 11
VFA (cm^2) Male:Female	130 ± 92 : 94 ± 156
Cold ischemic time (min)	516 ± 139
Warm ischemic time (min)	46 ± 7
Intraoperative platelet transfusions (units)	1 ± 2
Intraoperative red blood cell transfusions (units)	9 ± 8
Intraoperative fresh frozen plasma transfusions (units)	18 ± 10
Postoperative platelet transfusions (units)[f]	1 ± 2
Postoperative red blood cell transfusions (units)[f]	4 ± 6
Postoperative fresh frozen plasma transfusions (units)[f]	6 ± 11

Values are given as mean ± standard deviation or numbers and (percent).
ALF, acute liver failure; BAR, balance of risk; BMI, body mass index; CVA, cerebrovascular accident; DRI, donor risk index; ECD, extended criteria donor allografts; HCC, hepatocellular carcinoma; HU, Hounsfield units; ICU, intensive care unit; MELD, model for end-stage liver disease; PBC, primary biliary cirrhosis; POD, postoperative day; PSC, primary sclerosing cholangitis; SMI, lumbar 3 skeletal muscle index; SM-RA, lumbar 3 skeletal muscle radiation attenuation; SOFT, survival outcomes following liver transplantation; VFA, lumbar 3 visceral fat area.
[a]Refers to Feng et al.[9]
[b]Refers to German Medical Chamber Guidelines.[27]
[c]Refers to Schlegel et al.[13]
[d]Refers to Rana et al.[12]
[e]Refers to Kelly et al.[32]
[f]Refers to blood products given during the first 7 d following orthotopic liver transplantation.

to demonstrate the association of certain factors with early morbidity.[30] Perioperative outcome, length of ICU- and hospital stay, mortality, EAD, and procedural costs comprised the secondary endpoints.

For analysis of categorical data, the X^2 test and the Fisher exact test were used. For comparison of continuous variables, the Mann-Whitney *U* test was applied. In case of continuous data stratified into more than 2 groups, the 1-way analysis of variance with Bonferroni post hoc test was used. To determine the ability of BC to predict perioperative outcome, uni- and multivariable logistic regression analysis was performed. The Spearman correlation coefficient was used to study the association between BC and various clinical parameters. The prognostic value of the BAR score and the new proposed "BAR-Myosteatosis" score (including myosteatosis) for 90-day outcome was assessed using the receiver operating characteristic curve analysis calculating the area under the receiver operating characteristic curve (AUROC). This new score was calculated by adding points for myosteatosis to the standard BAR score.[8] The Hosmer-Lemeshow X^2 goodness-of-fit test was applied to test model suitability. All *P* values < .05 were considered statistically significant. Statistical analysis has been performed using SPSS Statistics v24 (IBM Corp., Armonk, NY).

3 | RESULTS

3.1 | Recipient and donor characteristics

Out of all 357 consecutive OLTs performed within the given time frame, 225 patients met the predefined inclusion and exclusion criteria. Among 132 excluded patients were recipients of living related (n = 5) or split liver allografts (n = 4), and cases without sufficient preoperative CT imaging, including the L3 level within the last 6 months (n = 123).

The mean donor- and recipient ages were 55 ± 16 and 54 ± 12 years, respectively. Sixty-seven percent of the recipients

were male and the most common reasons for OLT were hepatocellular carcinoma (28%) and alcoholic liver cirrhosis (20%) followed by acute liver failure (14%). The mean pre-OLT laboratory Model of End-stage Liver Disease (MELD) score was 20 ± 11, whereas the mean BAR and survival outcomes following liver transplantation (SOFT) scores were 9 ± 6 and 15 ± 10, respectively. The mean recipient BMI was 27 ± 5. Further patients' characteristics are shown in Table 1.

3.2 | BC analysis

The median time between the CT imaging used for segmentation and OLT was 5 weeks (range 0-24). The mean SMI was 57 ± 39 cm^2/m^2 for male and 47 ± 11 cm^2/m^2 for female patients. The mean SM-RA were 35 ± 11 HU for male and 32 ± 11 HU for female patients, while VFA were 130 ± 92 cm^2 for male and 94 ± 156 cm^2 for female patients, respectively. The main BC profiles calculated from the CT analysis and the stratification of the patient cohort based on the specific cut-off values are summarized in Table 2. Males had slightly but significantly higher SMI, SM-RA, and VFA than females ($P < .05$). Briefly, based on the aforementioned cut-offs, 84 patients showed reduced muscle mass and 98 had myosteatosis, indicating a higher incidence of myosteatosis than reduced SMM only. One hundred three patients have been found to have visceral obesity and 34 were sarcopenically obese (Table 2). The BC parameters used have shown weak-to-moderate strong correlations with various recipient characteristics, including recipient age, BMI, labMELD, and Child-Pugh scores, pretransplant albumin levels, and platelet counts (Supplementary Table S1A). SMI only showed significant moderate correlation with recipient BMI ($r = 0.466$, $P < .001$). Negative associations were found between SM-RA and recipient pretransplant labMELD and Child-Pugh scores (labMELD: $r = -0.403$, $P < .001$; Child-Pugh: $r = -0.338$, $P < .001$; Supplementary Table S1A). Recipient pre-OLT functional status (KPS) has shown a moderate strong association with the SM-RA values ($r = 0.438$, $P < .001$, Supplementary Table S1A). Accordingly, KPS was significantly lower in patients with myosteatosis compared to the rest of the cohort (50 ± 20 vs 70 ± 20, $P < .001$).

TABLE 2 Stratification of the cohort based on body composition features

Categories		No. of patients (n = 225)	%
Skeletal muscle mass (SMI)	No	141	63
	Yes	84	37
Myosteatosis (SM-RA)	No	127	56
	Yes	98	44
Visceral obesity (VFA)	No	122	54
	Yes	103	46
Sarcopenic obesity	No	191	85
	Yes	34	15

SMI, lumbar 3 skeletal muscle index; SM-RA, lumbar 3 skeletal muscle radiation attenuation; VFA, lumbar 3 visceral fat area.

3.3 | Perioperative outcome and morbidity

One hundred fourteen patients (51%) developed major complications (CD ≥ 3b) within 90 days after OLT (Table 3). The mean CCI score was 54 ± 33 (Table 3). Among all BC parameters tested, only SM-RA showed statistically significant and clinically meaningful AUROC values (AUROC ≈0.7) for major morbidity (CD ≥ 3b; SM-RA male, AUROC 0.678; SM-RA female, AUROC 0.700, $P < .001$, Supplementary Table S1B). Significantly more patients in the myosteatosis group had major complications compared to the recipients with normal muscle density (67% vs 38%, $P < .001$) accompanied by a higher 90-day mortality rate in these patients (15% vs 3%, $P = .001$, Table 3).

Accordingly, patients with myosteatosis also had markedly higher CCI scores (68 ± 32 vs 44 ± 30; $P < .001$) (Table 3). The incidence of EAD was significantly higher (36% vs 20%, $P = .006$, Table 3). Myosteatotic patients received significantly more transfusions of RBC and FFP units intraoperatively (RBC: 12 ± 10 vs 7 ± 6 units, $P < .001$; FFP 20 ± 12 vs 16 ± 7 units, $P < .001$, respectively; Table 3). Similar to myosteatosis, sarcopenic obesity was also associated with an increased need for intraoperative transfusions (Table 3).

The mean number of days that patients spent on the ICU and in the hospital were 14 ± 23 days and 43 ± 42 days, respectively (Table 3). Patients with myosteatosis stayed significantly longer on ICU (18 ± 25 vs 11 ± 21 days, $P < .001$) and had a significantly longer total hospital stay (56 ± 55 vs 33 ± 24 days, $P < .001$) compared to patients over the defined SM-RA cut-offs (Table 3). Accordingly, the mean procedural costs were considerably higher in cases with preoperative myosteatosis (72 ± 29 vs 50 ± 22 thousand euros [TEuro], $P < .001$, respectively; Table 3). With regard to hospital stay, a substantial but statistically nonsignificant difference was noted between sarcopenic obese patients and the rest of the cohort (64 ± 81 vs 39 ± 29 days, $P = .344$; Table 3). Interestingly, neither the presence of reduced skeletal muscle mass alone nor visceral obesity affected significantly any of the above-described outcome parameters (Table 3).

In line with the findings above, a significant association was observed between the SM-RA values and the days spent on ICU and in the hospital, as well as with CCI score and estimated costs (ICU stay: $r = -0.392$, $P < .001$; hospital stay: $r = -0.333$, $P < .001$; CCI score: $r = -0.373$, $P < .001$; costs: $r = -0.400$, $P < .001$; Table 4). Neither SMI nor VFA showed a significant correlation with any of these parameters (Table 4).

To further analyze the effects of myosteatosis on perioperative outcomes, patients have been divided into quartiles based in the SM-RA values. This led to a gradual reduction of ICU- and hospital stay, CCI scores, mean procedural costs, and the need for intraoperative transfusions between the subgroups of patients belonging to the various quartiles. There was a significant difference between the group of patients in the first and last quartiles in each examined parameter (quartile 1 vs 4; ICU stay, 7 ± 12 vs 22 ± 28 days, $P = .004$; hospital stay, 27 ± 15 vs 54 ± 36 days, $P = .001$; 90-day CCI score, 39 ± 27 vs 72 ± 25, $P < .001$; estimated procedural costs, 45 ± 17 vs 75 ± 27 TEur, $P < .001$; intraoperative transfusion of RBC units, 6 ± 6 vs 13 ± 9 units, $P < .001$; intraoperative transfusion of FFP units, 15 ± 7 vs 21 ± 12 units, $P = .026$; Figure 2).

TABLE 3 Perioperative outcome stratified by body composition

Outcome	All patients	No	Yes	*P* value
Reduced skeletal muscle mass	n = 225	n = 141	n = 84	
90-d ≥CD3b complications[a] n (%)	114 (51)	70 (50)	44 (52)	.890
90-d mortality n (%)	19 (8)	12 (9)	7 (8)	.959
Early allograft dysfunction[b] n (%)	60 (27)	38 (27)	22 (26)	.877
ICU stay (d)	14 ± 23	13 ± 20	16 ± 27	.101
Hospital stay (d)	43 ± 42	39 ± 29	50 ± 58	.815
Intraoperative RBC transfusion (units)	9 ± 8	9 ± 7	10 ± 10	.386
Intraoperative FFP transfusion (units)	18 ± 10	17 ± 8	18 ± 13	.690
90-d CCI[c]	54 ± 33	53 ± 32	56 ± 34	.663
Cost estimation (TEuro)[d]	60 ± 27	59 ± 27	60 ± 27	.721
Myosteatosis	n = 225	n = 127	n = 98	
90-d ≥CD3b complications n (%)	114 (51)	48 (38)	66 (67)	.000
90-d mortality n (%)	19 (8)	4 (3)	15 (15)	.001
Early allograft dysfunction n (%)	60 (27)	25 (20)	35 (36)	.006
ICU stay (d)	14 ± 23	11 ± 21	18 ± 25	.000
Hospital stay (d)	43 ± 42	33 ± 24	56 ± 55	.000
Intraoperative RBC transfusion (units)	9 ± 8	7 ± 6	12 ± 10	.000
Intraoperative FFP transfusion (units)	18 ± 10	16 ± 7	20 ± 12	.000
90-d CCI	54 ± 33	44 ± 30	68 ± 32	.000
Cost estimation (TEuro)	60 ± 27	50 ± 22	72 ± 29	.000
Visceral obesity	n = 225	n = 122	n = 103	
90-d ≥CD3b complications n (%)	114 (51)	57 (47)	57 (55)	.271
90-d mortality n (%)	19 (8)	11 (9)	8 (8)	.812
Early allograft dysfunction n (%)	60 (27)	30 (25)	30 (29)	.469
ICU stay (d)	14 ± 23	14 ± 20	14 ± 25	.671
Hospital stay (d)	43 ± 42	42 ± 31	45 ± 53	.541
Intraoperative RBC transfusion (units)	9 ± 8	9 ± 7	10 ± 9	.534
Intraoperative FFP transfusion (units)	18 ± 10	17 ± 9	18 ± 11	.241
90-d CCI	54 ± 33	54 ± 34	55 ± 32	.846
Cost estimation (TEuro)	60 ± 27	59 ± 28	60 ± 26	.681
Sarcopenic obesity	n = 225	n = 191	n = 34	
90-d ≥CD3b complications n (%)	114 (51)	94 (49)	20 (59)	.227
90-d mortality n (%)	19 (8)	16 (8)	3 (9)	.743
Early allograft dysfunction n (%)	60 (27)	49 (26)	11 (32)	.377
ICU stay (d)	14 ± 23	14 ± 21	16 ± 30	.952
Hospital stay (d)	43 ± 42	39 ± 29	64 ± 81	.344
Intraoperative RBC transfusion (units)	9 ± 8	9 ± 7	13 ± 12	.015
Intraoperative FFP transfusion (units)	18 ± 10	17 ± 8	22 ± 15	.031
90-d CCI	54 ± 33	53 ± 33	62 ± 33	.163
Cost estimation (TEuro)	60 ± 27	59 ± 27	65 ± 27	.142

CD, Clavien-Dindo classification; CCI, Comprehensive Complication Index; FFP, fresh frozen plasma units; ICU, intensive care unit; RBC, red blood cell units; TEuro, thousand Euros.

[a]Refers to Clavien et al.[30]

[b]Refers to Olthoff et al.[28]

[c]Refers to Slankamenac et al.[29]

[d]Refers to Staiger et al.[31]

TABLE 4 Correlation of outcome with body composition parameters

	ICU stay		Hospital stay		CCI		Costs	
Body composition	***r***	***P***	***r***	***P***	***r***	***P***	***R***	***P***
SMI (cm^2/m^2)	.037	.584	−.011	.871	−.011	.868	−.013	.847
SM-RA (HU)	−.392	.000	−.333	.000	−.373	.000	−.400	.000
VFA (cm^2)	−.025	.708	−.074	.267	−.002	.982	.024	.721

CCI, Comprehensive Complication Index; HU, Hounsfield units; ICU, intensive care unit; SMI, lumbar 3 skeletal muscle index; SM-RA, lumbar 3 skeletal muscle radiation attenuation; VFA, lumbar 3 visceral fat area.

3.4 | Predictors of 90-day morbidity

Univariable logistic regression analysis showed that pretransplant Child-Pugh Score, labMELD, pretransplant ICU stay, KPS, and myosteatosis were significantly associated with major postoperative morbidity (Clavien-Dindo ≥3b) (Table 5).

In the multivariable analysis, myosteatosis (odds ratio 2.772, 95% confidence interval 1.516-5.066, $P = .001$) remained significant and have been identified as an independent predictor of major morbidity following OLT (Table 5).

3.5 | Combining myosteatosis with a validated prediction model: "the BAR-Myosteatosis" score

The prognostic value of the original BAR score and the newly proposed BAR-Myosteatosis score have been compared based on the AUROC values calculated for 90-day major morbidity and mortality. Accordingly, the AUROC increased gradually from 0.677 and 0.821 (original BAR score) to 0.710 and 0.853 by adding points to the BAR score for patients with preoperative myosteatosis, confirming a potential added value of myosteatosis as a predictor of early outcomes (Table 6).

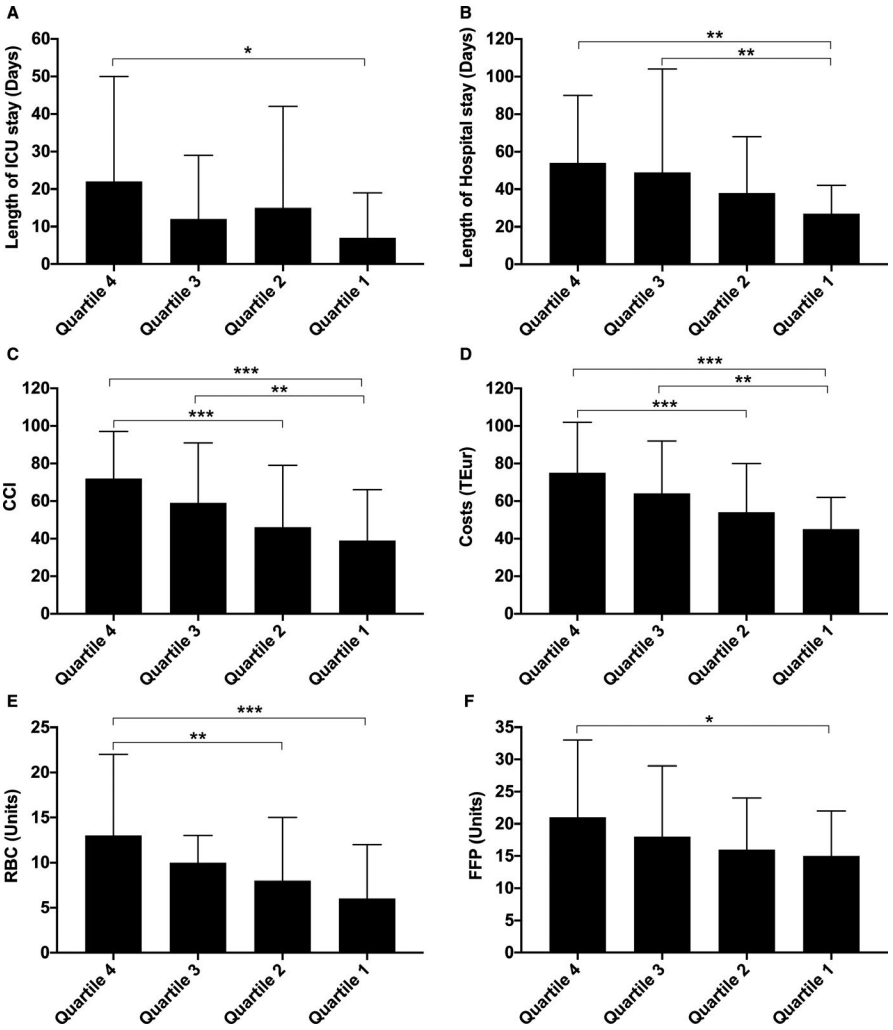


FIGURE 2 Perioperative outcome and procedural costs stratified by the quartiles of skeletal muscle radiation attenuation (SM-RA). Length of intensive care unit (ICU) stay (A), length of hospital stay (B), Comprehensive Complication Index (CCI) (C), procedural costs (D), intraoperative transfusion of red blood cell units (RBC) (E), and intraoperative transfusion of fresh frozen plasma units (FFP) (F) grouped according to the quartiles of skeletal muscle radiation attenuation values (SM-RA) (mean ± standard deviation, $^*P < .05$, $^{**}P < .01$, $^{***}P < .001$, one-way ANOVA and Bonferroni post hoc test, n = 54, 58, 57, 56, respectively). TEur, thousand euros

TABLE 5 Uni- and multivariable logistic regression analysis for 90-d major morbidity (Clavien-Dindo ≥3b)

	Major complications (CD ≥ 3b)[a] n = 114	No- /minor complications (CD1-3a)[a] n = 111	Univariable analysis		Multivariable analysis	
			Odds ratio (95% CI)	*P* value[c]	Odds ratio (95% CI)	*P* value
Donor age ≥60 y	49 (43)	43 (39)	1.175 (0.688-2.006)	.554		
Donor BMI ≥ 25	91 (80)	85 (77)	1.168 (0.610-2.236)	.640		
Donor sex male	63 (55)	54 (49)	1.331 (0.785-2.258)	.288		
Pretransplant Child-Pugh Score ≥7	80 (70)	60 (54)	1.889 (1.091-3.269)	.023	0.942 (0.464-1.912)	.868
ECD[b] Yes	80 (70)	74 (67)	1.099 (0.625-1.932)	.743		
Recipient age ≥60 y	44 (39)	42 (38)	1.017 (0.593-1.746)	.951		
Recipient BMI ≥25	84 (74)	68 (61)	1.746 (0.985-3.098)	.057		
Recipient sex Male	77 (68)	73 (66)	1.056 (0.604-1.845)	.849		
Cause of liver disease				.314		
ALF	13 (11)	18 (16)	0.628 (0.247-1.594)			
HCC	28 (25)	35 (31)	0.671 (0.307-1.466)			
Alcoholic cirrhosis	30 (26)	15 (14)	1.863 (0.779-4.459)			
Viral	6 (5)	9 (8)	0.580 (0.176-1.914)			
PSC/PBC	10 (9)	11 (10)	0.791 (0.278-2.248)			
Graft failure	2 (2)	2 (2)	0.870 (0.112-6.751)			
Other	25 (22)	21 (19)	1			
Pretransplant labMELD ≥25	53 (46)	21 (19)	3.447 (1.886-6.301)	.000	2.340 (0.803-6.820)	.119
Recipient pretransplant ICU Yes	40 (35)	16 (14)	3.434 (1.761-6.694)	.000	1.867 (0.699-4.985)	.213
Recipient pretransplant abdominal surgery Yes	43 (38)	39 (35)	1.105 (0.639-1.913)	.721		
Recipient pretransplant encephalopathy Yes	50 (44)	40 (36)	1.425 (0.830-2.444)	.199		
Karnofsky Performance Score <60	58 (51)	30 (27)	2.975 (1.687-5.247)	.000	0.794 (0.242-2.609)	.704
Cold ischemic time ≥480 (min)	65 (57)	58 (52)	1.245 (0.728-2.129)	.423		
Warm ischemic time ≥45 min	53 (46)	60 (54)	0.728 (0.427-1.243)	.245		
Reduced skeletal muscle mass (SMI) Yes	43 (38)	41 (37)	1.060 (0.615-1.826)	.835		
Myosteatosis (SM-RA) Yes	66 (58)	32 (29)	3.407 (1.949-5.958)	.000	2.772 (1.516-5.066)	.001
Visceral obesity (VFA) Yes	56 (49)	47 (42)	1.346 (0.792-2.285)	.272		
Sarcopenic obesity Yes	20 (18)	14 (13)	1.588 (0.747-3.376)	.229		

Values are given as mean ± standard deviation or numbers and (percent). Results of the logistic regression were given as odds ratios with 95% confidence interval.

ALF, acute liver failure; BMI, body mass index; CD, Clavien-Dindo classification; CI, confidence interval; ECD, extended criteria donor allografts; HCC, hepatocellular carcinoma; ICU, intensive care unit; PBC, primary biliary cirrhosis; MELD, model for end-stage liver disease; PSC, primary sclerosing cholangitis; SM-RA, lumbar 3 skeletal muscle radiation attenuation; SMI, lumbar 3 skeletal muscle index; VFA, lumbar 3 visceral fat area.

[a]Refers to Clavien et al.[30]

[b]Refers to German Medical Chamber Guidelines.[27]

[c]Factors showing significant results in the univariable analysis were included in the multivariable logistic regression model. Only significant results are shown. To avoid a multicollinearity effect, certain variables were not included in the logistic regression analysis.

4 | DISCUSSION

The present study indicates that BC alterations are highly prevalent in patients with terminal liver disease. While >40% of our recipients presented with myosteatosis before OLT, we show here for the first time the superior prognostic value of myosteatosis (muscle quality) over reduced skeletal muscle mass only (morphological manifestation of sarcopenia) in predicting perioperative outcomes in deceased donor OLT. Myosteatosis was significantly associated with poor perioperative outcome, including transfusion of blood and blood products, morbidity, mortality, EAD, ICU- and hospital stay. The estimated procedural costs over the first 90 days when transplanting patients with myosteatosis were significantly higher and myosteatosis was identified as an independent predictor of major surgical complications.

BC can be assessed using different methods, including bioelectrical impedance analysis, air displacement plethysmography, and

TABLE 6 The "BAR-Myosteatosis" score

Variable	AUC	SE	95% CI	*P* value	χ^{2a}	*P* value#
90-d major morbidity (≥CD3b)						
BAR	0.677	0.036	0.606-0.748	.000	5.011	.659
BAR-Myosteatosis (2 pts)	0.695	0.035	0.625-0.764	.000	6.276	.616
BAR-Myosteatosis (4 pts)	0.704	0.035	0.635-0.772	.000	9.812	.279
BAR-Myosteatosis (6 pts)	0.706	0.035	0.638-0.775	.000	9.908	.194
BAR-Myosteatosis (8 pts)	0.710	0.035	0.642-0.778	.000	7.245	.510
90-d mortality						
BAR	0.821	0.060	0.702-0.939	.000	3.363	.850
BAR-Myosteatosis (2 pts)	0.838	0.052	0.736-0.941	.000	6.645	.575
BAR-Myosteatosis (4 pts)	0.848	0.046	0.757-0.939	.000	5.300	.725
BAR-Myosteatosis (6 pts)	0.855	0.041	0.774-0.935	.000	3.231	.863
BAR-Myosteatosis (8 pts)	0.853	0.039	0.777-0.929	.000	6.714	.568

AUC, area under the curve; BAR, Balance of Risk; CD, Clavien-Dindo classification; CI, confidence interval; SE, standard error.
[a]Hosmer-Lemeshow χ^2; # in case of a *P* value of <.05, the test rejects the null hypothesis of an adequate fit.

dual-energy x-ray absorptiometry.[2,15] The sensitivity of these techniques to differentiate between muscle quantity and quality, however, is limited and often biased by the significant amount of fluid overload in patients with terminal liver disease.[2] In these patients, the clinical estimation of BC and the assessment of their physical strength using conventional parameters (body weight, waist circumference, BMI, ability to walk or physical activity, and handgrip) are usually difficult and often compromised by the presence of ascites and/or encephalopathy. Therefore, CT imaging is currently the gold standard for the quantification of muscle mass and muscle quality in patients with terminal liver disease.[2,16,20]

While some studies have suggested a potential role of myosteatosis in OLT, all of these reports were focusing predominantly on sarcopenia and/or living donor liver transplantation.[2,15,22,35,36] The specific effect of myosteatosis on the perioperative outcomes of deceased donor OLT remains to be determined. In our cohort, patients with myosteatosis had significantly more major complications over the first 3 months and low muscle density was additionally associated with increased rates of EAD, higher CCI scores, and an increased need for intraoperative blood transfusions. In this regard, it should be noted that a significantly prolonged ICU- and hospital stay may also reflect an increased surgical morbidity and an overall delayed functional recovery in these patients. The estimated mean procedural costs were more than 20 TEur higher in patients with myosteatosis compared to the rest of our cohort. In myosteatosis, an increasing intramuscular fat accumulation (Figure 1) is associated with a pro-inflammatory microenvironment that potentially impairs immune function via proinflammatory cytokines and adipocytokines.[35,36] These humoral factors and muscle-to-liver cross-talk, together with the limited functional reserves in myosteatotic patients (eg, reduced KPS score, greater need for intraoperative transfusions) may contribute to an increased oxidative stress and graft injury with a higher incidence of EAD during the perioperative phase.[19,37,38]

The association of myosteatosis with the abovementioned parameters of perioperative outcome is further supported by the correlation and quartile analyses, demonstrating that gradually decreasing muscle density leads to more perioperative complications, longer in-hospital stay, and higher estimated costs. Of note, reduced SMM, visceral obesity, and sarcopenic obesity were not associated with increased morbidity in our cohort.

The most interesting observation of the present study is the superiority of myosteatosis (muscle quality) over skeletal muscle mass alone (muscle quantity as a morphological aspect of sarcopenia) in predicting perioperative outcomes following OLT. Although earlier studies investigated changes in skeletal muscle mass to define sarcopenia, recent evidence suggests that fat accumulation within the muscle might be responsible for functional impairment and negative pathophysiological responses even in patients with quantitatively normal or nearly normal muscle mass.[15] In a recent report by Hamaguchi et al, the authors demonstrated the association of psoas muscle mass index and intramuscular adipose tissue content index with posttransplant survival in a single-center Japanese cohort of 200 recipients of living donor liver transplantation.[35] Furthermore, Bhanji et al have reported their observation in 675 cirrhotic patients and reported a significant association of myosteatosis with hepatic encephalopathy and mortality on the OLT waiting list.[21] Although myosteatosis has been linked to inferior survival in cirrhotic patients, the prognostic role of myosteatosis in post-OLT outcomes in deceased donor OLT remains to be determined.[2,21,22,39] In our study, myosteatosis was identified as the only and most important predictor of post-OLT morbidity. Although other relevant factors showed significant results in our univariable analysis (eg, labMELD, Child-Pugh Score, and pre-OLT ICU stay), they have lost their significant effect as independent predictors in the multivariable analysis. A possible explanation is the inherent complexity and heterogeneity of OLT cohorts in general, with a high number of factors potentially affecting

clinical outcomes (especially in terms of perioperative outcome). Given that high-MELD patients (>30) usually present with worse clinical outcome and higher complications rates, a relatively low MELD-score within our cohort (mean labMELD score 20 ± 11) may be the reason why MELD has lost its significance in multivariable analysis.

Myosteatosis is believed to occur when lipids intake exceeds the disposal capacity of the adipose tissue and muscle, functioning as a form of ectopic fat storage in overweight subjects.[19,40] While myosteatosis is also seen in normal weight or underweight patients,[41] it is reasonable to assume that the skeletal muscle does not only act as a plain ectopic storage of energy surplus, and as such mechanisms other than excessive fat intake may play an important role in the development of pathological muscle fat deposition.[19] In our study, myosteatosis was moderately but significantly associated with the severity of the underlying liver disease (labMELD, Child-Pugh Score, albumin, and platelet count), highlighting the importance of a complex and poorly understood liver-to-muscle cross-talk over a simple nutritional theory.[19]

Several clinical risk-assessment tools have been developed for assessing outcome following OLT.[13] Out of these, the BAR score, a promising tool developed by Dutkowski et al, includes easily available donor and recipient risk factors with the aim to clinically assess and predict the risk of poor post-OLT outcomes.[8,14] Based on an excellent stratification of patients at risk using myosteatosis, we propose a new "BAR-Myosteatosis" score adding myosteatosis as an adjunct parameter to the original BAR score. Interestingly, this novel score demonstrated superior AUROC values for perioperative morbidity and mortality compared to the original BAR score.

The findings of this study should be interpreted in the light of potential limitations. First, due to the inherent retrospective, single-center, and uncontrolled nature of our analysis, no or very limited preoperative functional assessment of patient fitness (except KPS) and nutritional status was possible. Second, we could not compare the performance of CT-based BC with other methods, and our evaluation did not include the routine assessment of muscle strength, such as handgrip, gait speed, or 6-minute walk tests.[22] While some centers may prefer the use of magnetic resonance imaging (MRI) over CT for cross-sectional imaging in OLT candidates, future studies should explore the possibilities of MRI-based assessment of BC and myosteatosis. Even though van Dijk et al recently confirmed that myosteatosis may be adequately assessed using either MRI or CT scans in a group of patients with periampullary cancer,[42] the prognostic value of MRI-based BC assessment for patients with end-stage liver disease remains to be determined. Based on current evidence, MRI-based BC assessment is therefore not yet implemented in current EASL and AASLD guidelines.[15,16,18]

Notwithstanding the aforementioned limitations, we have identified myosteatosis as an independent marker of prognosis in patients undergoing OLT. In addition, the superior prognostic value of muscle quality (myosteatosis as assessed by the SM-RA) over quantity (SMM as assessed by the SMI) in predicting perioperative outcomes does not only support the role of nutritional screening and therapeutic interventions in patients undergoing OLT, but also emphasizes the clinical relevance of myosteatosis in OLT risk assessment. Further research on the underlying molecular mechanisms of myosteatosis in OLT and external validation of our findings in prospective biomarker-embedded clinical trials are warranted. Future trials should also incorporate therapeutic interventions such as the monitoring of dietary intake, protein or branched-chain amino acid supplementation, prehabilitation, physical exercise, and/or pharmacotherapy.

AUTHOR CONTRIBUTIONS

The study was designed by the initiating study team (ZC, GL, UPN, WK, JB, and GvdK). Data collection and analysis were performed by ZC, WK, JB, GvdK, JoB, PS, MZ, GK, UPN, and GL. The manuscript was drafted by ZC, GL, PS, and GvdK. Further authors (WK, JB, JoB, GK, and UPN) have substantially contributed to the final version of the manuscript. All authors have read and approved the final version of the manuscript.

DISCLOSURE

The authors of this manuscript have no conflict of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

All relevant data were reported within the article. Further supporting data will be provided upon written request addressed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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