Preoperative Assessment of Muscle Mass Using Computerized Tomography Scans to Predict Outcomes Following Orthotopic Liver Transplantation

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Background. Sarcopenia is an established risk factor predicting survival in chronically ill and trauma patients. We herein examine the assessment and clinical implication of sarcopenia in liver transplantation (LT). **Methods.** Computerized tomography scans from 172 patients waitlisted for LT were analyzed by applying 6 morphometric muscle scores, including 2 density indices (psoas density [PD] and skeletal muscle density [SMD]) and 4 scores based on muscle area (total psoas area, psoas muscle index, skeletal muscle area, and skeletal muscle index). **Results.** The prevalence of sarcopenia in our cohort ranged from 7.0% to 37.8%, depending on the score applied. Only sarcopenia as defined by the density indices PD and SMD (but not total psoas area, psoas muscle index, skeletal muscle area, or skeletal muscle index) revealed clinical relevance since it correlates significantly with postoperative complications (≥Grade III, Clavien-Dindo classification) and sepsis. Furthermore, sarcopenia predicted inferior patient and graft survival, with low muscle density (PD: <38.5 HU or SMD: <30 HU) representing an independent risk factor in a multivariate regression model ($P < 0.05$). Importantly, the widely used Eurotransplant donor risk index had a predictive value in nonsarcopenic patients but failed to predict graft survival in patients with sarcopenia. **Conclusions.** Sarcopenia revealed by low muscle density correlates with major complications following LT and acts as an independent predictor for patient and graft survival. Therefore, the application of a simple computerized tomography-morphologic index can refine an individual recipient's risk estimate in a personalized approach to transplantation.

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INTRODUCTION

In the light of donor organ shortage, a trend to accept more extended criteria donor organs has developed. Together with an increasing complexity and frailty in liver transplantation (LT) candidates, patient selection and donor-recipient matching have become increasingly complex.[1]

At present, the Model for End-Stage Liver Disease (MELD) score is a widely accepted tool for defining urgency in patients waitlisted for LT.[2-4] The MELD score, however, has little value in predicting postoperative patient or graft survival.[3,5-7] Several attempts have been made to develop more accurate predictive tools for posttransplant survival.[8] Among the most established of these scores, the "balance of risk score" combines 2 recipient factors (namely MELD score and recipient age) with selected donor factors to predict posttransplant survival.[9] The Survival Outcomes following Liver Transplantation score includes 13 recipient factors with the aim of achieving a better estimate of post-transplant survival.[10] Furthermore, Braat et al adjusted the donor risk index (DRI)[11] for the Eurotransplant (ET) region and created the ET-DRI, combining donor age, donor cause of death, donor gamma-glutamyltransferase (GGT), graft type, graft allocation, and graft procurement.[12]

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None of these scoring systems, however, have been uniformly applied to predict posttransplant patient and graft survival.[8,13]

Nutritional status is known to exert a significant impact on postoperative recovery and outcome.[14] Common means for estimating a patient's nutritional status are body weight and body mass index (BMI). However, as a result of fluid overload (like ascites and oedema), they are often inapplicable for patients with chronic liver disease. Therefore, conventional parameters poorly represent the nutritional status of chronic liver patients and fail to predict their outcome after LT.[7,14]

As muscle mass reflects the body's protein storage, it can be used as a parameter for the nutritional status.[14,15] In other chronic diseases, such as cancer or chronic renal failure, muscle mass analysis by computerized tomography (CT) scanning has been shown to accurately display the nutritional status, which correlates with patient mortality and morbidity.[14-16]

In the context of LT, Carey et al found preoperative sarcopenia defined by the skeletal muscle index (SMI) to correlate with wait-list mortality.[17] Furthermore, recent findings indicate that preoperative sarcopenia is associated with an increased rate of postoperative complications and lengthened hospital stay.[18,19] Some authors suggest a correlation between preoperative sarcopenia and posttransplant patient survival,[1,18,20,21] while others do not find a correlation,[19,22] and the influence on graft survival has not been explored.

The major obstacles are the various methods that have been proposed for the assessment of preoperative sarcopenia. Hence, the application of sarcopenia assessment in LT remains elusive in its potential clinical predictive value.[21,23,24]

The present study aims to evaluate whether the different methods of measuring muscle mass including determination of muscle density correlate with posttransplant complications and posttransplant patient and graft survival in our cohort. We attempt to identify the best tool for assessing preoperative muscle mass in LT candidates and establish a new definition of sarcopenia as relevant to the outcome of these patients.

MATERIALS AND METHODS

Study Design and Data Collection

Data from all patients undergoing LT at the Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck between January 1, 2011, and December 31, 2013, were analyzed retrospectively. Data collected from medical records included the following: recipient sex, age, preoperative MELD-score, indication for LT including staging of hepatocellular carcinoma (HCC), cold ischemia time (CIT), and type of graft. Donor data were obtained from the ET website using the donor data web application. Deceased donor LT and split LT were performed according to the previously described techniques.[25-29]

Image Evaluation

At our institution, LT candidates undergo an abdominal contrast-enhanced CT scan before waitlisting. CT cross-sectional images at the level of the third lumbar vertebra were used for quantitative muscle evaluation using the open source NIH ImageJ software package.

Four established muscle area parameters were evaluated, that is total psoas area (TPA),[21] psoas muscle index (PMI),[23] skeletal muscle area (SMA), and SMI.[17] Additionally, 2 density parameters (psoas density [PD][30] and skeletal muscle density [SMD][31]) were assessed.[24]

First, psoas muscles were manually outlined, and TPA was automatically calculated from the cross-sectional area of both muscles in mm^2. PD (in Hounsfield unit [HU]) was semiautomatically obtained using threshold-based software to exclude excessive densities such as contrasted vessels.[32] PD was then computed from the weighted median of the 2 individual muscle densities.

Correspondingly, SMA was assessed by outlining the contours of anterior and lateral abdominal wall muscles, dorsal muscle group, and psoas muscles on cross-sectional images, with calculation of area as described earlier. SMD was computed from the weighted median of the muscle densities as outlined for measurement of SMA.[31]

Indices (PMI and SMI) were then calculated by dividing the TPA/SMA in cm^2 by the squared body height in meters.

Assessment of Sarcopenia and Outcome Parameters

Sarcopenia has been defined as decreased muscle mass in combination with low muscle strength or low muscle performance. In consideration of the objective to develop an easily available tool to evaluate sarcopenia, in the present study, we focused on the CT morphologic assessment of muscle indices as an objective measure.[30] The prevalence of sarcopenia was assessed using various definitions: TPA $<1561\,mm^2$ in men and $<1464\,mm^2$ in women[21]; PD of <38.5 HU in both women and men[30]; PMI $<6.36\,cm^2/m^2$ for men and $<3.92\,cm^2/m^2$ for women[23]; and SMI $<50\,cm^2/m^2$ for men and $<39\,cm^2/m^2$ for women.[17] Postoperative morbidity was assessed using the Clavien-Dindo classification. Patients' records were used to determine the timing and severity of complications Grade III to V.[33] Assessment of complications Grade I and II was dispensed in consideration of the complex surgical procedure and a very high prevalence.

Statistical Analysis

A descriptive analysis was performed for all study variables: absolute and relative frequencies were reported for categorical data; mean, SD, and range were reported for numerical data. For comparative analysis of categorical or ordinal variables (eg, assessment of sarcopenia and complications[33]), Fisher's exact test was used. Normal distribution of numerical data was assessed with the Shapiro-Wilk test. Differences in age and labMELD between sarcopenic and nonsarcopenic patients were determined by Mann-Whitney *U*-test. Strength and direction of relationships among ET-DRI, BMI, postoperative morbidity, and muscle mass assessments were examined by employing the Spearman's correlation analysis. The Kaplan-Meier method was used for survival analysis. Log-rank test was conducted to measure the differences in survival between sarcopenic and nonsarcopenic patients. Several binomial logistic regression models were constructed to explore

the effect of preoperative sarcopenia, preoperative BMI and labMELD on patient mortality, and the relevance of ET-DRI, donor age, and CIT on graft loss. Odds ratio (OR) and 95% confidence interval (CI) were reported for the executed binominal logistic regression models. We compared mortality in sarcopenic patients relative to the control group (1-y mortality in sarcopenic patients divided by 1-y mortality in nonsarcopenic patients) for various muscle mass assessments, using different percentiles as cutoff values defining sarcopenia. $P < 0.05$ was considered statistically significant. For statistical analysis, SPSS software was used.

Ethical Considerations

The study was approved by the ethics committee of the Medical University of Innsbruck (vote number: 1244/2017).

RESULTS

Patient Characteristics

The patient collective consisted of 43 females (23.1%) and 143 males (76.9%). Mean age at transplantation was 54.6 years, mean labMELD was 15.7, and mean BMI was 25.8. The 3 most frequent indications for LT were alcoholic liver disease (N = 67; 36.0%), viral hepatitis (N = 51; 27.4%), and nonalcoholic steatohepatitis (N = 32; 17.2%). A total of 59 (31.7%) patients had been diagnosed with HCC. Donors were male in 107 cases (57.5%) and female in 79 cases (42.5%). Mean donor age was 50.1 years, mean CIT 9.3 hours, and mean donor GGT was 103.1 U/L. A donation after circulatory death graft was transplanted in 2 cases (1.1%) and a split graft in 6 cases (3.2%). Donor procurement (as defined for the calculation of the ET-DRI) was "local" in 72 cases (38.7%), "regional" in 74 cases (39.8%) and "extra-regional" in 40 cases (21.5%). Cause of death was trauma in 48 cases (25.8%), anoxia in 16 cases (8.6%), cerebrovascular accident (CVA) in 117 cases (62.9%), and other in 5 cases (2.7%). Mean ET-DRI was 1.72.

Of all 186 patients, 178 (95.7%) were transplanted using a cava-replacing technique and 8 (4.3%) using piggy-back technique. High-urgency LT was performed in 16 (8.6%) cases and retransplantation in 20 (10.8%) cases (Table S1, SDC, http://links.lww.com/TP/B736).

Muscle Mass Assessment and Prevalence of Sarcopenia

As the prevalence of preoperative sarcopenia in patients waitlisted for LT remains unknown, we aimed to define this prevalence in our patient cohort. Mean time between CT scan and transplantation was 12.6 weeks (median: 10.0 wk). In 172 cases, a CT scan appropriate for the requirement was available.

Sarcopenia was present in 37 (21.5%) patients when using the definition established by Golse et al, in 57 (33.1%) patients when using Hamaguchi's definition, in 12 (7.0%) patients using Yoo's definition, and in 71 (37.8%) patients applying Carey's definition (Table 1).

Preoperative BMI correlated with 4 established muscle area indices, namely TPA ($P < 0.01$), PMI ($P < 0.01$), SMA ($P < 0.01$), and SMI ($P < 0.01$) but not with the 2 muscle density indices (PD [$P = 0.39$] and SMD [$P = 0.08$]).

Postoperative Morbidity

To investigate whether preoperative sarcopenia correlates with postoperative morbidity, we evaluated patient medical records for occurrence of sepsis and Clavien-Dindo complications grade III to V.

Twelve (6.5%) patients suffered from postoperative sepsis during their hospital stay. Importantly, patients with sepsis had lower SMD on preoperative CT scans than

TABLE 1.

Prevalence of sarcopenia differed from 7.0% to 37.8% depending on which definition of sarcopenia was applied

Definition of sarcopenia/muscle mass assessment	N (%)/mean	SD	Range	Association with occurrence of complications[a]	P	Correlation with severity of complications[a]	P
Golse (22) ♂: TPA <1561 mm^2 ♀: TPA <1464 mm^2	37 (21.5%)			No	–		
Hamaguchi (33) ♂: PMI <6.36 cm^2/m^2 ♀: PMI <3.92 cm^2/m^2	57 (33.1%)			No	–		
Yoo (32) PD < 38.5 HU	12 (7.0%)			Yes	0.02		
Carey (17) ♂: SMI <50 cm^2/m^2 ♀: SMI <39 cm^2/m^2	71 (37.8%)			No			
TPA, mm^2	1960.1	630.0	3263.0			No	0.99
PMI, cm^2/m^2	6.5	1.8	9.3			No	0.67
PD, HU	51.2	9.1	51.8			Yes	<0.01
SMA, mm^2	14752.7	3563.2	21308.0			No	0.50
SMI, cm^2/m^2	49.2	9.2	48.2			No	0.28
SMD, HU	41.9	8.7	49.1			Yes	<0.01

Muscle densities correlate with occurrence and severity of complications grade III to V.
[a]Complications defined as Clavien-Dindo grade III to V.
HU, hounsfield unit; PD, psoas density; PMI, psoas muscle index; SMA, skeletal muscle area; SMD, skeletal muscle density; SMI, skeletal muscle index; TPA, total psoas area.

patients without sepsis ($P = 0.03$). Clavien-Dindo complications Grade III to V occurred in 131 (70.5%) patients. One hundred and three (55.4%) patients required postoperative dialysis due to kidney failure. A complication Grade IIIb occurred in 27 patients (14.5%), IVa in 90 patients (48.4%), and IVb in 10 (5.4%) patients. Four patients died during the immediate postoperative course (Clavien-Dindo V in 2.2%). A negative correlation between the severity of complications and PD ($P < 0.01$) as well as SMD ($P < 0.01$) was detected. Muscle area indices (TPA [$P = 0.99$], PMI [$P = 0.67$], SMA [$P = 0.50$], and SMI [$P = 0.28$]) did not correlate with postoperative complications (Table 1).

When using Yoo's definition, a significant association was seen between sarcopenia and occurrence of postoperative complications ($P = 0.02$). All 12 sarcopenic patients (100.0%) had a complication of ≥Grade III, whereas in nonsarcopenic patients this was the case in 107 of 160 (66.9%).

Such patients with the lowest 10% of SMD also showed a clear correlation between sarcopenia and complications ≥Grade III ($P = 0.02$). Although a ≥Grade III complication applied for 16 out of 17 sarcopenic patients (94.1%), in nonsarcopenic patients this was the case in 66.5% (103 out of 155 cases) only (Table 1).

Patient Survival in Sarcopenic Versus Nonsarcopenic Patients

Overall 1- and 3-year patient survival were 86.9% and 83.1%, respectively. When using Yoo's definition as a cutoff value to characterize sarcopenia, log-rank test revealed a significantly lower patient survival in sarcopenic patients ($P = 0.02$). The estimated survival for nonsarcopenic patients was 65.1 versus 42.5 months for sarcopenic patients. Comparing sarcopenic and nonsarcopenic patients, we found no differences with respect to gender ($P = 0.72$), recipient age ($P = 0.68$), or indication for LT or preoperative HCC ($P = 0.06$). Sarcopenic patients had a higher labMELD than nonsarcopenic patients (labMELD 20.1 versus 15.0; $P = 0.01$).

Golse's, Hamaguchi's, and Carey's definitions of sarcopenia revealed a numerical difference in the estimated survival rates, but the observed difference was not statistically significant ($P = 0.46$, $P = 0.98$, and $P = 0.58$) (Table S2, SDC, http://links.lww.com/TP/B736).

Furthermore, we analyzed patients in the lowest quartile (N = 43) and the lowest 10th percentile (N = 17) of all 6 muscle mass assessments (Table S2, SDC, http://links.lww.com/TP/B736). This approach revealed a significantly poorer survival for patients with the lowest 10.0% of SMD only (Figure 1). In summary, sarcopenia assessed by muscle density indices in LT recipients is related to increased mortality. In contrast, assessment of sarcopenia via muscle area indices does not aid in predicting mortality (Figure 2).

We then constructed a binomial logistic regression model to explore the effects of preoperative sarcopenia (Yoo's definition), preoperative BMI, and labMELD on patient mortality. In this assessment, solely preoperative sarcopenia had an impact on patient mortality (OR = 3.84; 95% CI = 1.09 to 13.59; $P = 0.04$). LabMELD ($P = 0.92$) and preoperative BMI ($P = 0.62$) did not influence survival (Table 2).

Graft Survival in Sarcopenic Versus Nonsarcopenic Patients

Overall 1- and 3-year graft survival were 82.6% and 78.2%, respectively. Graft survival was inferior in patients with sarcopenia when using Yoo's definition ($P < 0.01$). The estimated survival for nonsarcopenic patients was 61.6 months versus 31.4 months for sarcopenic patients (Figure 3). When other definitions for sarcopenia were applied, no difference was observed (Table S3, SDC, http://links.lww.com/TP/B736). Noteworthy, comparing donor characteristics, no differences were found regarding ET-DRI ($P = 0.44$), donor age ($P = 0.65$), CIT ($P = 0.70$), donor GGT ($P = 0.23$), split grafts ($P = 0.99$), rescue allocation ($P = 0.99$), procurement ($P = 0.43$), and donor cause of death ($P = 0.85$).

Analogous to patient survival, muscle densities, and in particular SMD, best displayed the higher graft loss in sarcopenic patients, while muscle area assessments (TPA, PMI, SMA, and SMI) did not correlate with graft mortality (Figures 3 and 4).

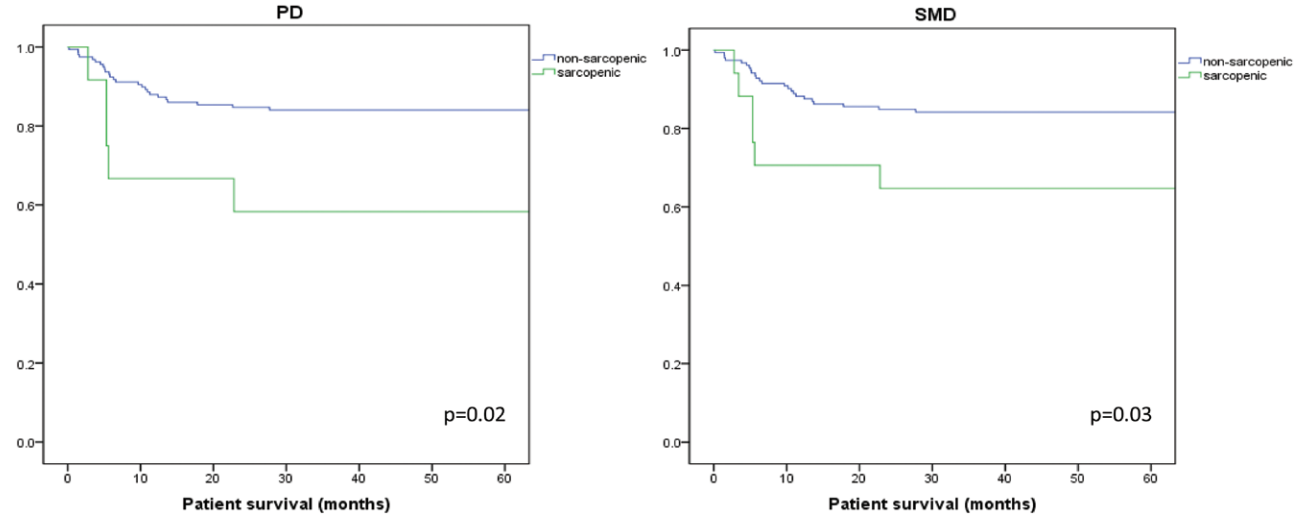
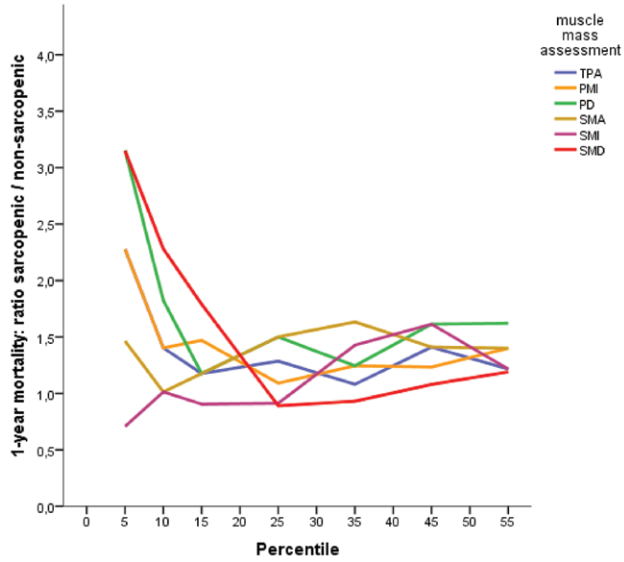


FIGURE 1. Preoperative sarcopenia assessed by low muscle density scores is associated with inferior patient survival following LT. (PD is presented as defined by Yoo et al[30] [<38.5 HU]; SMD is defined as lowest 10th percentile [<30.0 HU]). HU, Hounsfield unit; LT, liver transplantation; PD, psoas density; SMD, skeletal muscle density.



Percentile	Psoas area (mm^2)	Psoas index (cm^2/m^2)	Psoas density (HU)	Skeletal muscle area (mm^2)	Skeletal muscle index (cm^2/m^2)	Skeletal muscle density (HU)
5	928.9	3.678	36.43	9086.1	34.785	27.46
10	1156.4	4.247	40.52	10361.5	36.121	29.91
15	1325.7	4.587	42.99	10842.1	40.124	32.89
25	1561.8	5.277	45.05	12383.5	43.186	36.70
35	1693.6	5.701	46.91	13813.9	44.785	38.86
45	1853.1	6.258	49.99	14621.2	47.558	41.59
55	2004.6	6.796	52.22	15230.1	50.507	43.70

FIGURE 2. The increased mortality of sarcopenic patients is only revealed by muscle mass assessment using the muscle density indices PD (green) and SMD (red) but no other commonly applied indices (TPA, PMI, SMA, SMI). (The y-axis indicates the ratio of 1-year mortality in sarcopenic patients divided by the 1-year mortality of nonsarcopenic patients. The percentiles of the muscle mass used as cutoff value to define sarcopenia are displayed on the x-axis). HU, Hounsfield unit; PD, psoas density; PMI, psoas muscle index; SMA, skeletal muscle area; SMD, skeletal muscle density; SMI, skeletal muscle index; TPA, total psoas area.

Next, we applied a binomial logistic regression model to characterize the influence of preoperative sarcopenia (lowest 10th percentile of SMD as cutoff value), ET-DRI, and donor age on graft mortality. Preoperative sarcopenia was identified as an independent risk factor for graft loss (OR = 5.40; 95% CI = 1.85 to 15.77; $P < 0.01$). Although CIT was a risk factor, OR and 95% CI show that the effect on graft survival was minimal (OR = 1.00; 95% CI = 1.00 to 1.01; $P = 0.03$) (Table 2).

When deceased patients were excluded to correct for death with functioning graft, a significantly higher graft loss in sarcopenic patients was revealed (27.3% versus 6.1%; $P = 0.04$). Sarcopenic patients (SMD <30 HU) displayed an inferior graft survival when compared with nonsarcopenic patients ($P < 0.01$).

The binominal logistic regression model (including CIT and preoperative sarcopenia) showed preoperative sarcopenia to be the sole independent risk factor for graft loss (OR = 7.38; 95% CI = 1.51 to 35.97; $P = 0.01$) (Table 2).

TABLE 2.

Preoperative sarcopenia is an independent risk factor for patient and graft loss (binominal logistic regression model)

Patient loss	*P*	OR
Independent variables		
Preoperative sarcopenia (PD <38.5 HU)	0.04	3.84
labMELD	0.92	
BMI	0.62	
Graft loss		
Independent variables		
Preoperative sarcopenia (SMD < 30 HU)	<0.01	5.40
ET-DRI	0.97	
Donor age	0.11	
Cold ischemia period	0.03	1.00
Graft loss (corrected for death with functioning graft)		
Independent variables		
Preoperative sarcopenia (SMD < 30 HU)	0.01	7.38
Cold ischemia period	0.06	

BMI, body mass index; ET-DRI, Eurotransplant donor risk index; HU, hounsfield unit; OR, odds ratio; PD, psoas density; SMD, skeletal muscle index.

Correlation ET-DRI and Graft Survival

In the overall collective, the ET-DRI did not significantly correlate with graft survival. Importantly, subgroup analysis revealed that this effect was solely due to the sarcopenic fraction of patients. After the exclusion of sarcopenic patients, ET-DRI significantly correlated with graft survival ($P = 0.02$). We constructed a graph to illustrate differences in 1-year graft survival between sarcopenic and nonsarcopenic patients in reference to the different ET-DRI categories (SMD as cutoff value to define sarcopenia) (Figure 5).

Effect on the Length of Stay

The average stay was 29.2 days (median: 22 days). SMD ($P = 0.04$) and PD ($P = 0.02$) showed a weak negative correlation with the length of stay. On the contrary, the muscle area indices TPA, PMI, SMA, and SMI showed no significant correlation.

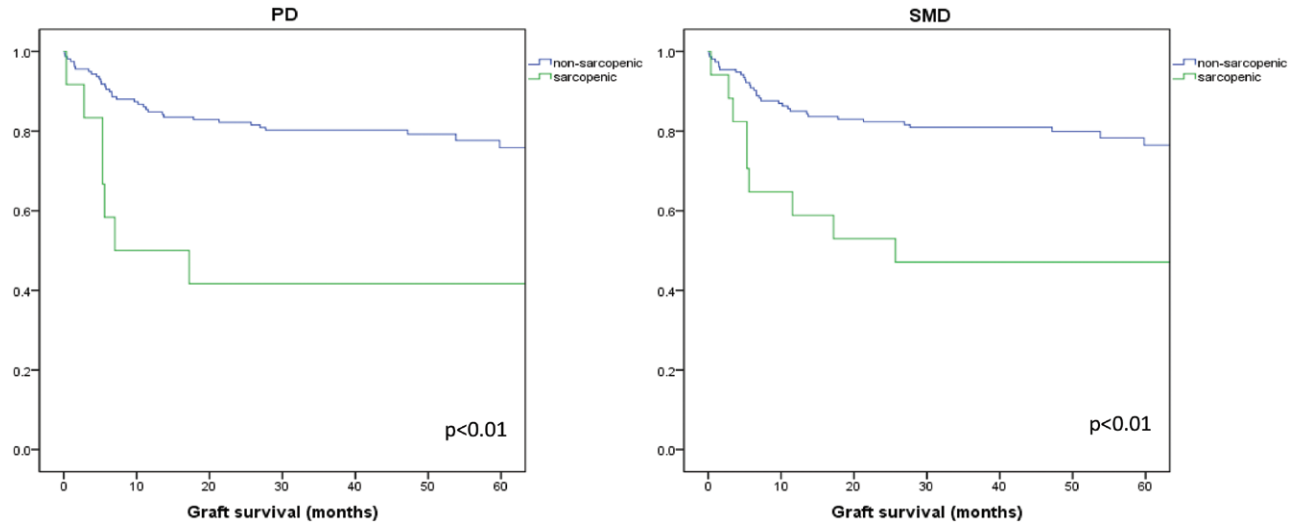
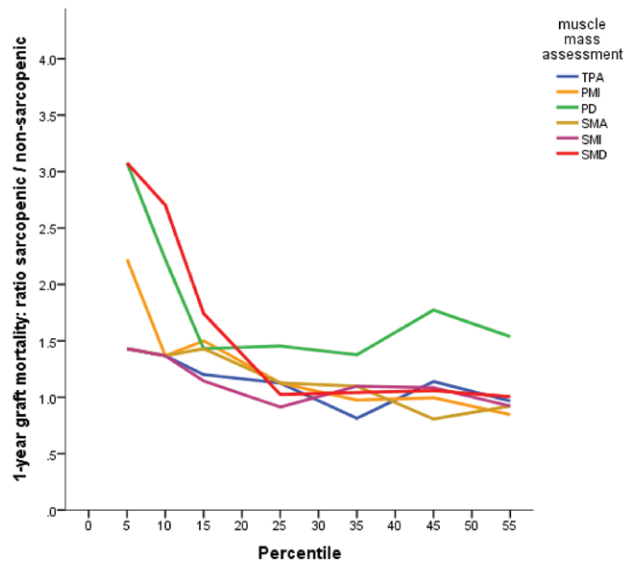


FIGURE 3. Preoperative sarcopenia assessed by low muscle density scores is associated with inferior graft survival following LT. (PD is presented as defined by Yoo et al.[30] [<38.5 HU]; SMD: defined as lowest 10th percentile [<30.0 HU]). HU, Hounsfield unit; LT, liver transplantation; PD, psoas density; SMD, skeletal muscle density.

DISCUSSION

Muscle mass is assumed to be a valuable indicator for the prediction of patient mortality and morbidity in chronically ill patients.[14,15] This study aimed to investigate whether this approach could be applicable for patients undergoing LT.

Data pointing toward a superiority of 1 of the numerous methods of muscle mass assessment as the "gold standard" for defining sarcopenia in the context of LT are lacking.[34] Recent studies use mostly PMI, TPA, or SMI for the assessment of sarcopenia.[1,21,35,36] By contrast, muscle densities are not commonly used. In various studies, however, low muscle density was clearly associated with poor outcome in entities such as trauma and malignancies.[30,37-39] Importantly, a recent study showed that low muscle density affects mortality following hepatopancreaticobiliary



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55	2004.6	6.796	52.22	15230.1	50.507	43.70

FIGURE 4. Sarcopenic patients display an increased graft mortality. This risk factor can be visualised using the muscle density indices PD (green) and SMD (red) but no other commonly applied indices (TPA, PMI, SMA, or SMI). (The ratio of 1-y graft-mortality in sarcopenic patients divided by the 1-y graft-mortality of nonsarcopenic patients is shown on the y-axis. The percentiles of the muscle mass used as cutoff value to define sarcopenia are displayed on the x-axis.) HU, Hounsfield unit; PD, psoas density; PMI, psoas muscle index; SMA, skeletal muscle area; SMD, skeletal muscle density; SMI, skeletal muscle index; TPA, total psoas area.

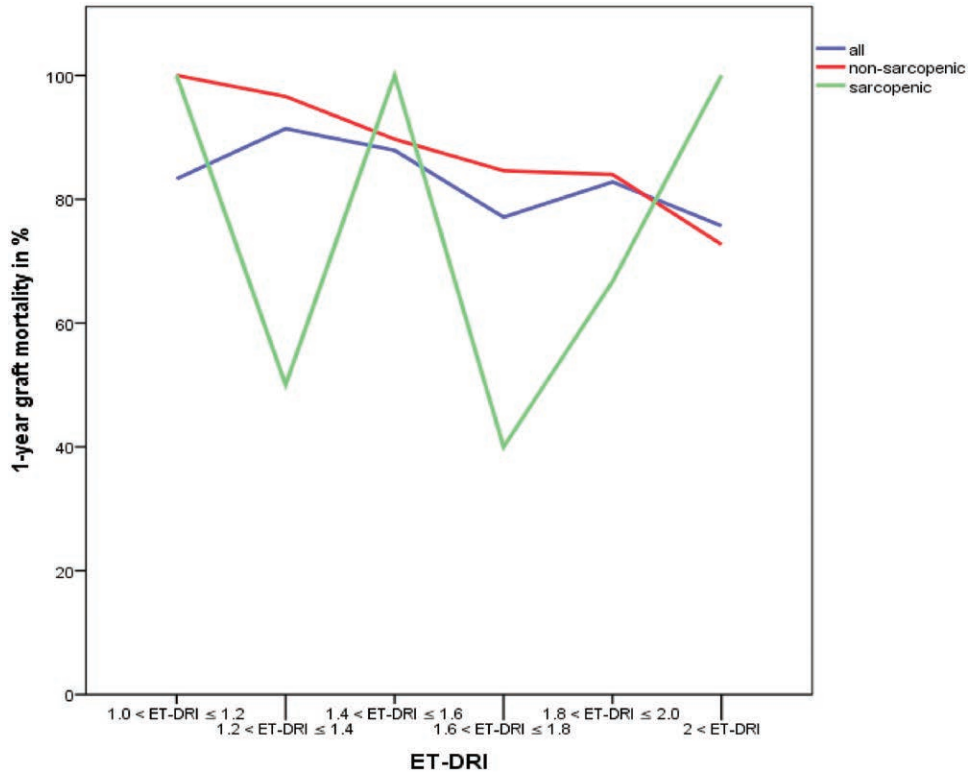

FIGURE 5. The ET-DRI displays a predictive value for graft survival in nonsarcopenic patients (red), whereas this is not the case when sarcopenia is present (green). The figure illustrates the correlation between ET-DRI categories[12] and the specific 1-year graft survival in either nonsarcopenic (green) or sarcopenic (red) patients. ET-DRI, Eurotransplant donor risk index.

surgery in the elderly.[40] In the present study, muscle mass was assessed by 4 commonly utilized muscle area indices and 2 muscle density indices in the setting of LT. CT scans from 172 LT patients transplanted at a single center were analyzed using these 6 muscle mass assessments (TPA, PMI, PD, SMA, SMI, and SMD) to define the prevalence of sarcopenia and identify a potential correlation with clinical outcomes.

The prevalence of preoperative sarcopenia in patients on the LT waiting list remains unknown. Recent studies addressing the rate of sarcopenia revealed highly varying results and estimates ranged from 22.2% to 70.0%. According to van Vugt and Kallwitz, these vast discrepancies result from a lack of standardization of methods in the assessment and an inconsistent definition of sarcopenia.[24,34] Accordingly, the prevalence of sarcopenia in our patient cohort ranged from 7.0% to 37.8%, depending on the definition of sarcopenia applied. As anticipated by van Vugt and Kallwitz, our findings emphasize the necessity to standardize muscle mass assessment in LT candidates.

Next, we evaluated the correlation between preoperative sarcopenia and postoperative morbidity following LT. Recently published studies suggested an association between preoperative muscle mass and the occurrence of postoperative sepsis[18,19,22,41] and ≥Grade III complications according to the Clavien-Dindo classification in LT recipients.[22] In our patient cohort, only muscle density indices were found to correlate with postoperative morbidity. Lower muscle density indices were associated with higher rates of postoperative sepsis and severe complications (Grades III to V). Muscle area measurements, which represent the sarcopenia parameter of choice in most studies, did not show a significant correlation with postoperative morbidity.

Interestingly, "extreme sarcopenia" was recently described to affect posttransplant mortality.[1,19,41] However, we found the assessment of sarcopenia to greatly vary between studies. Some authors defined "extreme sarcopenia" as the lowest tertile of TPA,[41] whereas others used the lowest quartile of TPA[1] or the lowest sixtile of SMI.[1,19,41] Thus, we investigated whether preoperative sarcopenia predicts posttransplant patient survival in our collective. Surprisingly, neither definitions of sarcopenia established for LT recipients using muscle area indices[21,23] nor application of lowest percentiles of the widely used muscle area indices proved to be predictive for patient survival in this cohort. In contrast, muscle density indices such as SMD and Yoo's definition developed for trauma patients[30] were identified as predictors of inferior patient survival.

Although a limited number of studies assess the influence of sarcopenia on patient survival, its effect on graft survival has not yet been investigated. Importantly, our data show that low muscle density is associated with elevated rates of early graft loss. This correlation stands also after correction for death with functioning graft with low muscle density indicating a higher rate of graft loss and shorter survival. In analogy to observations regarding patient survival, muscle area parameters had no predictive value for graft survival.

Even though some studies investigating BMI and graft survival point toward an association between preoperative sarcopenia and graft survival,[42] the present study is the first to identify sarcopenia as an independent risk factor for graft loss.

Recently, a similar phenomenon has been observed in pancreas transplantation.[43] The detailed mechanisms underlying this phenomenon remain elusive and are rather speculative at current. Likely, skeletal myocytes are crucially involved in the regulation of inflammatory cascades mediated by the immune systems in particular by the secretion of anti-inflammatory peptides, such as TGF-β.[44-46] Therefore, a decrease of muscle indices may result in a pronounced inflammatory response toward the graft.

Recapitulating all 6 muscle mass indices, muscle density indices but not the commonly utilized muscle area indices correlate with posttransplant patient and graft survival.

Importantly, we show that the ET-DRI[12] has a good predictive value in nonsarcopenic patients but fails to predict graft survival in sarcopenic patients. This finding underlines the importance of sarcopenia as an independent factor for the outcome following LT.

Both PD and SMD are easy evaluable CT-morphologic scores that can be assessed by radiologists within minutes (Figure S1, SDC, http://links.lww.com/TP/B736). Assessing sarcopenia in possible LT candidates can help to predict posttransplant outcomes. Therefore, the assessment of sarcopenia can be implemented in the process of recipient selection. At our own institution, extreme sarcopenia alone is not an absolute contraindication for waitlisting but a factor influencing the decision-making, for example, in case of utilization of marginal grafts. Extremely sarcopenic patients are also red-flagged to undergo close postoperative monitoring and surveillance. Furthermore, we consider the combination of immobilization and extreme sarcopenia as a contraindication for transplantation.

Concerning the amelioration of the nutritional status in chronic liver patients, a branched-chain amino acid–enriched diet should be considered, as this has been proven successful in previous trials.[47,48]

Because of the high donor rate and the national allocation policy, the time on the waiting list before LT is short in our region. Hence, not only the waiting-list mortality but also the average MELD-score at time of LT are low compared with other regions. While such an assessment may reveal a different outcome in other regions, it is reasonable to assume that a higher average MELD and longer waiting time may reveal an even higher impact of sarcopenia. Thus, the influence of pronounced sarcopenia on posttransplant mortality could be underrepresented in our analysis, partially explaining the lack of association between sarcopenia assessed by muscle area measurements and posttransplant survival as reported for aggregated data in the meta-analysis by vanVugt.[24] Particularly, the relevance of the progression of sarcopenia on the waiting list may play a major role in cases and regions with longer waiting times and be underrepresented in this study.

As our study consists of a retrospective analysis, results should be validated in a prospective setting and with a larger patient number.

CONCLUSION

Muscle density indices represent a novel, easily available tool to assess sarcopenia in LT recipients using a simple CT-morphologic index. Patients exhibiting pronounced sarcopenia assessed via PD or SMD have an increased risk for major postoperative complications, graft failure, and death. The variability between the muscle indices indicates the necessity to standardize muscle mass assessment in LT candidates. To define sarcopenia in LT recipients, we suggest a cutoff value of 38.5 HU for PD and a cutoff value of 30 HU for SMD. Application of these indices has the potential to refine an individual recipient's risk estimate in a personalized approach to transplantation.

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