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Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score

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Abstract

Background Although malnutrition and sarcopenia are prevalent in cirrhosis, their impact on outcomes following liver transplantation is not well documented.

Methods The associations of nutritional status and sarcopenia with post-transplant infections, requirement for mechanical ventilation, intensive care (ICU) and hospital stay, and 1 year mortality were assessed in 232 consecutive transplant recipients. Nutritional status and sarcopenia were assessed using the Royal Free Hospital-Global Assessment (RFH-GA) tool and the L3-psoas muscle index (L3-PMI) on CT, respectively.

Results A wide range of RFH-SGA and L3-PMI were observed within similar Model for End-stage Liver Disease (MELD) subcategories. Malnutrition and sarcopenia were independent predictors of all outcomes. Post-transplant infections were associated with MELD (OR = 1.055, 95%CI = 1.002–1.11) and severe malnutrition (OR = 6.55, 95%CI = 1.99–21.5); ventilation $>$ 24 h with MELD (OR = 1.1, 95%CI = 1.036–1.168), severe malnutrition (OR = 8.5, 95%CI = 1.48–48.87) and suboptimal donor liver (OR = 2.326, 95% CI = 1.056–5.12); ICU stay $>$ 5 days, with age (OR = 1.054, 95%CI = 1.004–1.106), MELD (OR = 1.137, 95%CI = 1.057–1.223) and severe malnutrition (OR = 7.46, 95%CI = 1.57–35.43); hospital stay $>$ 20 days with male sex (OR = 2.107, 95%CI = 1.004–4.419) and L3-PMI (OR = 0.996, 95%CI = 0.994–0.999); 1 year mortality with L3-PMI (OR = 0.996, 95%CI = 0.992–0.999). Patients at the lowest L3-PMI receiving suboptimal grafts had longer ICU/hospital stay and higher incidence of infections.

Conclusions Malnutrition and sarcopenia are associated with early post-liver transplant morbidity/mortality. Allocation indices do not include nutritional status and may jeopardize outcomes in nutritionally compromised individuals.

Keywords Cirrhosis; Prognosis; Nutritional assessment; Morbidity; Mortality

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Introduction

Malnutrition is a common complication of end-stage liver disease.[1] It adversely affects health-related quality of life, is associated with an increased risk for developing the complications of cirrhosis, including hepatic encephalopathy, and has detrimental effects on outcome following liver transplantation and survival.[2] The deterioration of nutritional status in end-stage liver disease is multifactorial and includes inadequate dietary intake because of nausea or vomiting, dietary restriction of salt and proteins, anorexia, presence of ascites and/or encephalopathy, malabsorption because of pancreatic

insufficiency, small bowel bacterial overgrowth or cholestasis, side-effects of drug therapy, or liver disease-related metabolic disturbances.[3] Sarcopenia is not synonymous with malnutrition although there is an important overlap among them.[4] In a cohort of 300 patients with cirrhosis, malnutrition was prevalent in 75% and increased from 46% to 84% and 95% across Child–Pugh A, B, and C stages.[5] Patients with malnutrition and/or sarcopenia have longer hospital stay, increased incidence of ascites and hepatorenal syndrome, and increased in-hospital mortality.[6,7]

Despite its high significance, assessment of nutritional status in cirrhosis is often neglected. In a nationwide study,[6] only 6% of patients with cirrhosis who were admitted to hospital were diagnosed with malnutrition compared with 2% of the general admissions, implying that nutritional assessment is often overlooked; thus, its prevalence could be even higher than reported. Various indexes and methods have been proposed to evaluate nutrition in end-stage liver disease with diverse results among them.[8,9] Usual markers of body composition, such as body mass index (BMI), skin fold thickness, or bioelectrical impendance, are limited by the lack of availability and/or reproducibility, inter-observer variability, or decreased accuracy because of fluid retention in cirrhosis.[9,10] The Royal Free Hospital-Global Assessment (RFH-GA) is a subjective index for nutritional assessment which combines BMI, triceps skin fold thickness, and mid-arm muscle circumference (MAMC) with dietary intake.[11] It therefore incorporates both malnutrition and sarcopenia in an easily reproducible score. In a cohort of 222 patients with cirrhosis, RFH-GA was independently associated with mortality with a relative hazard ratio of 5.26 for severely malnourished patients.[12] One-year mortality in well nourished, mildly/moderately malnourished, and severely malnourished patients was 5%, 20%, and 35%, respectively, in this cohort.[12]

CT scan and MRI are considered the gold standards to assess skeletal muscle mass and to detect sarcopenia.[13,14] Sarcopenia estimated by cross-sectional area of psoas or other muscles at the level of third or fourth lumbar vertebrae (L3 or L4) has been associated with overall mortality in patients with cirrhosis,[15,16] waiting-list mortality,[17] post-transplant severe infections or sepsis,[18] and longer post-operative hospital stay.[19] Considering that prolonged mechanical ventilation and intensive care unit (ICU) stay, bacterial infections, and prolonged hospital stay are well-validated negative predictors for post-liver transplant (LT) survival,[20] the impact of malnutrition and muscle depletion on these variables is pivotal.

The aim of the study was to assess the prevalence and determine the predictors of sarcopenia and malnutrition in a consecutive cohort of transplanted patients and to further evaluate their effect on relevant post-LT outcomes including occurrence of infections, duration of mechanical ventilation, length of ICU and hospital stay, and 1 year mortality.

Patients and methods

Study population

The study comprised of 232 consecutive patients with cirrhosis who were transplanted at the Royal Free Hospital between January 2008 and December 2012 and fulfilled the inclusion criteria. These patients were selected from a cohort of 329 liver transplant recipients between 2008 and 2012. Patients with CT scan date >12 weeks pre-LT or >1 week post-LT ($n = 39$), unavailable CT scan at the third lumbar (L3) section ($n = 12$), acute liver failure ($n = 44$), or previous LT ($n = 2$), were excluded from the analysis. In the UK, initial transplant eligibility is based on a minimum UKELD score, which is different than the Model for End-stage Liver Disease (MELD) score in the sense that it also incorporates sodium and is calibrated to predict 12 month rather than 3 month survival.[21] Moreover, the allocation system is centre based rather than patient based, i.e. the graft goes to a specific transplant centre that then decides on allocation rather than to a specific patient based on a prioritization score.

Clinical and laboratory data

All data were recovered retrospectively from the institutions electronic database, medical files (hard copies) and clinical correspondence. ICU data and outcomes were collected for every patient. The data collected included recipient age and gender, donor age and gender, cold ischemia time (CIT), donor liver appearance (steatotic or non-steatotic), type of donor graft [donation before or after cardiac death (DCD)], ethnicity, indication for LT, nutritional assessment and anthropometric characteristics, laboratory investigations, presence of ascites or encephalopathy, and dates of LT and CT scan. Marginal liver grafts were defined as grafts with steatotic appearance and a CIT > 12 h. The primary outcomes were the duration of mechanical ventilation, the length of ICU and hospital stay, the development of in-hospital infections, and the 12 month mortality following LT. The diagnosis of presence and type of infection was based on internationally accepted Center for Disease Control (CDC) criteria.[22] The severity of liver disease was assessed by the Child–Pugh score and the MELD within 1 week from the CT scan used to determine psoas muscle measurements.

Nutritional assessment

A detailed nutritional assessment was performed by a specialist liver transplant dietitian (SA) as part of the routine patients' pre-LT assessment.[11] The assessment was conducted using the Royal Free Hospital Global Assessment (RFH-GA)

which comprises of a mixture of subjective and objective, anthropometric variables. It has been validated for use against the four-component mode.[11]

The RFH-GA provides a validated assessment of nutritional status and is accepted as the gold standard for nutritional assessment of liver disease patients in the UK. All eight liver transplant units in the UK and Southern Ireland use this tool for the assessment of patient being considered for a liver transplant. In-depth questioning was undertaken to obtain the information needed for completion of the subjective component of the RFH-GA. Full details about the RFH-GA tool are provided in the Web Appendix.

The anthropometric measurements were undertaken using a standard protocol and collection instruments as outlined below. Measurements were undertaken on the non-dominant arm using the writing hand to define dominance unless anatomical abnormalities or the siting of intravenous infusions precluded access.

Mid arm circumference was measured using a tape measure (Holtain Ltd, Crymych, Dyfed, UK) between the acromial process of the scapular and the olecranon process of the elbow using the Parenteral and Enteral Group of the British dietetic association (PENG) method. The triceps skinfold thickness (TSF) was measured to 0.2 mm using Holtain/Tanner-Whitehouse skinfold calipers measured in triplicate at the site of the MAC measurement and the mean calculated. Measures of MAC and TSF below the 5th percentile are indicative of malnutrition. These two measurements are used to calculate MAMC:

$$\mathrm{MAMC(cm)} = \mathrm{MAC(cm)} - [3.14 \times \mathrm{TSF(cm)}].$$

Data compared with published standards and expressed in relation to percentiles for the appropriate age and gender categories. Hand grip strength was measured in kilogramme on the non-dominant hand using Takei A5401 digital hand grip dynamometer and compared with the references ranges set by Goode et al and Klidjian et al by age and gender. Height was measured to the nearest centimetre using a wall mounted or frees standing measure (Seca, Hamberg, Germany). Current weight was recorded to the nearest 0.1 kg using a weighing (Seca) or seat balance scale (Marsden W/M Group, London, UK). Dry body weight was estimated using published suggested adjustment for the degree of fluid retention, if appropriate, together with dietetic clinical judgement and a dry BMI estimated.[23] The overall adequacy of the diet in relation to estimated requirements assessed using Schofield's modification of the Harris–Benedict equations was estimated and categorized as adequate, if it met estimated requirements, inadequate, if it failed to meet estimated requirements but exceeded 500 kcal/day, or negligible if it provided less than 500 kcal daily.

The collected data on BMI, MAMC, and dietary intake were then utilized to categorize nutritional status as per the construct algorithm (Appendix). In a minority of cases, a subjective override was applied as previously described to allow the assessor to change the nutritional category by a single grading if warranted on clinical grounds.[11] This override could be used, for example, to reclassify an individual who reported profound recent weight loss yet still maintained a BMI above 20 kg/m2 from adequately nourished to moderately malnourished. Patients' nutritional status was finally categorized as adequate/unimpaired, moderately malnourished or at risk of malnutrition, or severely malnourished.[11]

Sarcopenia assessment by CT scanning

CT scans were performed as part of the LT assessment or dictated from acute medical conditions. Scans were acceptable if performed up to 12 weeks prior to LT or within a week post LT and if sections included the L3 vertebrae. A word document was kept that recorded all issues towards technique's standardization. Transverse CT sections were analysed at the third lumbar level (L3). Total psoas muscle area (TPA) was measured as previously described.[24] The psoas muscle was selected from other skeletal muscles of the region because it is located centrally, is easily identified and is not directly affected by abdominal distension in the presence of ascites.[25,26] All CT images were analysed by a dedicated radiologist.[27] Cross-sectional psoas muscle area was normalized for stature and the L3-psoas muscle index (L3-PMI) was defined as psoas muscle area/height^2 (mm/m^2). Patients were grouped into sex-stratified L3-PMI quartiles to avoid the well-documented sex influence on muscle mass. Patients in the lowest sex-stratified L3-PMI quartiles were deemed as sarcopenic.

Statistical analysis

Numerical data were expressed as mean ± standard deviation if the distribution was normal or median with interquartile range if not, and categorical data as frequencies. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. In univariate analysis, categorical variables were tested using the chi-square and Fisher's exact test. Continuous variables with and without normal distribution were compared using Student's *t*-test or the Mann–Whitney U test, respectively. Correlations between continuous variables were tested using the Spearman correlation coefficient (*r*) analysis. Variables significant at the 0.1 level were included in the multivariate analysis. Multivariate ordinal regression analysis was used to define predictors of malnutrition based on RFH-GA. Multivariate binary logistic regression analysis was used to determine independent predictors for the lowest quartile of L3-PMI and to define the predictive factors for post-LT infections, mechanical ventilation $>$ 24 h, ICU stay $>$ 5 days, and hospital stay $>$ 20 days. Collinearity between RFH-GA and

L3-PMI was tested using the tolerance and VIF measure in the multivariate models; no collinearity was observed. The following variables were considered for possible inclusion in the multivariate regression model and were tested using univariate analysis: height, dry weight, BMI, MAC, MAMC, TSF, HGS, dietary intake, RFH-GA, recipient age and gender, donor age and gender, smoking, CIT, donor liver appearance, type of donor graft, ethnicity, indication for LT, hepatocellular carcinoma, presence of ascites and encephalopathy, MELD score, and L3-PMI. Univariate and multivariate Cox regression analysis was used to define independent predictor for 12 month mortality post liver transplantation. All statistical tests were two sided. The SPSS statistical package (version 22.0, IBM, New York, NY, USA) was used.

Results

Baseline clinical and biochemical characteristics

Baseline characteristics of the included patients are shown in *Table* 1. Mean age was 53 (22–70) years and 162 (69.8%) were males. The main indication for liver transplantation was chronic hepatitis C ($n = 68$, 29.3%) followed by alcoholic liver disease ($n = 55$, 23.7%), primary sclerosing cholangitis ($n = 29$, 12.5%) and primary biliary cirrhosis ($n = 17$, 7.3%). All CT scans were performed at a median of 10.6 (−12 to 1) weeks before LT. The lowest L3-PMI quartile cut-off was 340 mm^2/m^2 for men ($n = 40$, 24.7%) and 264 mm^2/m^2 ($n = 17$, 24.3%) for women. Approximately 38% of the donors were older than 50 years. Sex mismatch between liver recipients and donors was present in 120 cases (51.7%). Among the 64 suboptimal donor livers, 90.6% ($n = 58$) had steatosis on visual inspection (48.4% mild, 40.6% moderate, 1.6% severe), 3.1% ($n = 2$) were liver size-mismatched, and 6.3% ($n = 4$) had liver trauma. At 1 year post-LT, 216 (93%) of patients were alive. All alive patients were back to a normal nutritional status within 6–9 months after their transplant. In contrast, in 35 patients on the transplant waiting list that were seen at least twice by a dedicated dietitian within 6 months, the nutritional status did not change despite targeted interventions.

Correlation of L3-psoas muscle index (L3-PMI) with baseline characteristics

Males had significantly higher L3-PMI compared with female patients ($P < 0.001$). L3-PMI was positively correlated with dry weight ($r = 0.403$, $P < 0.001$), BMI ($r = 0.34$, $P < 0.001$), MAC ($r = 0.396$, $P < 0.001$), MAMC ($r = 0.385$, $P < 0.001$), triceps skin fold thickness ($r = 0.164$, $P = 0.03$), handgrip strength ($r = 0.382$, $P < 0.001$), RFH-GA ($P < 0.001$), and MELD ($r = -0.18$, $P = 0.007$). *Figure* 1 shows a wide range of L3-PMI across the different sub-categories of RFH-GA. There was also a wide variation and overlap of L3-PMI across similar MELD scores (*Figure* 2). In the multivariate binary logistic regression analysis, independent predictors for sarcopenia, defined as the lowest quartile of L3-PMI, were severe malnutrition [odds ratio (OR): 6.56, 95%CI 1.76–24.4] and handgrip strength (OR: 1.067, 95%CI 1.02–1.117). The baseline characteristics and outcomes of patients are shown in *Table* 1.

Correlation of Royal Free Hospital-Global Assessment with baseline characteristics

Moderate/severe malnutrition as indicated by a RFH-GA score of 2 or 3 was independently associated with male sex (OR = 3.76, 95% CI: 1.787–7.913), younger age (OR = 0.953, 95% CI: 0.924–0.983) and lower L3-PMI (OR = 0.993, 95% CI: 0.991–0.996). Severe malnutrition was independently associated with age (OR: 0.914, 95% CI: 0.87–0.96) and L3-PMI (OR: 0.989–0.999), but not with male sex. RFH-GA was not associated with the MELD score. *Figure* 3 demonstrates the distribution rates of the well-nourished, mild/moderately malnourished and severely malnourished patients (assessed with RFH-SGA) in different sub-categories of the MELD score.

Predictors of post-LT outcomes

(i) In-hospital infections: Post-LT infections were documented in 76 (32.8%) patients. The rates of fungal infections, bacteremia, chest, urinary tract, and abdominal infections during hospitalization were 5.2% ($n = 12$), 15.1% ($n = 35$), 13.8% ($n = 32$), 15.9% ($n = 37$), and 16.4% ($n = 38$), respectively. There was no association of L3-PMI with the type of infection. However, a significant positive correlation was observed between overall post-LT infections and RFH-GA as well as with the MELD score. In multivariate binary regression analysis, severe malnutrition (RFH-GA score 3: OR = 6.55, 95%CI = 1.99–21.5) and MELD (OR = 1.055, 95%CI = 1.002–1.11) were independent predictors of post-LT infections.

(ii) Mechanical ventilation duration >24 h: The median duration of mechanical ventilation post-LT was 21 (1–1920) h. Eighty four patients (36.2%) required mechanical ventilation for more than 24 h. In multivariate analysis, MV for >24 h was independently associated with MELD (OR = 1.1, 95%CI = 1.036–1.168), severe malnutrition (RFH-GA score 3: OR = 8.5, 95%CI = 1.48–48.87) and suboptimal donor liver (OR = 2.326, 95%CI = 1.056–5.12).

(iii) ICU stay >5 days: The median duration of ICU stay was 3 (0–88) days. Forty-eight patients (20.7%) required an ICU stay of >5 days. In multivariate binary logistic regression analysis, MELD score (OR: 1.137, 95%CI: 1.057–1.223), age (OR = 1.054, 95%CI = 1.004–1.106) and severe

Table 1 Characteristics of liver transplant recipients at the time of waiting list registration, statistics for selected donor and transplant parameters and for outcomes of interest in the total study population

Recipient factors		Total population
Age (years), median (range)		54 (22–70)
Sex (M/F), *n* (%)		162/70 (69.8/30.2)
Ethnicity, *n* (%)(Caucasian/African/Asian/Other)		177/13/39/3 (76.3/5.6/16.8/1.3)
Height (cm), median (range)		172 (150–200)
Dry weight (kg), median (range)		74 (44–150)
BMI (kg/m^2), median (range)		25 (16–41.7)
MAC (cm), median (range)		28.5 (18–46)
MAMC (cm), median (range)		26 (16–50.6)
TSF (mm), median (range)		14 (2–72)
HGS (kg), median (range)		25.6 (1–79)
RFH-GA, *n* (%)	Well-nourished	94 (53.4)
	Mild/Moderately malnourished	67 (38.1)
	Severely malnourished	15 (8.5)
Cause of liver disease, *n* (%)(autoimmune[a]/viral/alcohol/other)		47/81/55/49 (20.3/34.9/23.7/21.1)
Hepatocellular carcinoma, *n* (%)		58 (25)
MELD score, median (range)		14 (6–42)
CP score, median (range)		8 (5–15)
CP class (A/B/C), *n* (%)		59/111/62 (25.4/47.8/26.7)
Ascites, *n* (%)		115 (49.6)
L3 PMI (mm^2/m^2), median (range)	Total	406.3 (78.9–983)
	Males	428.8 (162.5–983)
	Females	352.4 (78.9–763.8)
Lowest L3-PMI, *n* (%)		57 (24.6%)
Donor factors		
Age (years), median (range)		47.5 (13–80)
Sex (M/F), *n* (%)		113/119 (48.7/51.3)
DCD, *n* (%)		35 (15)
Transplant factors		
Suboptimal liver appearance, *n* (%)		64 (27.6)
CID (min), median (range)		473.5 (42–1057)
Outcomes		
In-hospital infections, *n* (%)		76 (32.8)
MV duration (h), median (range)		21 (0–1920)
MV duration >24 h, *n* (%)		84 (36.2)
ICU stay (days), median (range)		3 (0–88)
ICU stay >5 days, *n* (%)		48 (20.7)
Hospital stay (days), median (range)		22 (11–389)
Hospital stay >20 days, *n* (%)		132 (56.9)
12 month mortality, *n* (%)		16 (6.9%)

BMI, body mass index; CID, cold ischemia time; CP, Child–Pugh; DCD, donation after cardiac death; HCC, hepatocellular carcinoma; HGS, hand grip strength; ICU, intensive care unit; MAC, mid arm circumference; MAMC, mid arm muscle circumference; MELD, Model for End-stage Liver Disease; M/F, males/females; MV, mechanical ventilation; PMI, psoas muscle index; RFH-GA, Royal Free Hospital Global Assessment; TSF, triceps skin fold.
[a]Including primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis.

malnutrition (RFH-GA score 3: OR = 7.46, 95%CI = 1.57–35.43) were independently associated with ICU stay of more than 5 days.

(iv) Hospital stay >20 days: The median hospital stay was 22 (11–389) days. One-hundred thirty-two patients (56.9%) required a hospital stay of >20 days. In multivariate binary regression analysis, male sex (OR = 2.107, 95%CI = 1.004–4.419) and L3-PMI (OR = 0.996, 95% CI = 0.994–0.999) were independent predictors for a hospital stay >20 days.

(v) 12 month mortality: Sixteen (6.9%) patients died within 12 months post-transplant. In multivariate Cox regression analysis including age, sex, L3-PMI and RFH-GA as co-factors, only low L3-PMI was significantly associated with higher 12 month mortality risk (OR = 0.996, 95% CI = 0.992–0.999). The median L3-PMI between survivors and non-survivors was 410.1 vs. 337.2 mm^2/m^2, respectively. Malnourishment, assessed with RFH-GA score, and MELD score were not found significant.

The univariate and multivariate analyses of the post-LT outcomes of interest are shown in Supplementary *Table* 1 and *Table* 2, respectively.

Sarcopenia and malnutrition in patients receiving marginal grafts

In the subgroup analysis of patients that received a marginal graft (*n* = 10), the median MV duration was 28.5 (4–1920) h

Figure 1 Box plots of L3-psoas muscle index (L3-PMI) for male and female patients stratified according to Royal Free Hospital-Global Assessment (RFH-GA). Males well-nourished: median PMI = 492.7 (range 224.2–856.1), mild/moderately malnourished: median PMI = 399.05.4 (187.3–648.7), severely malnourished: median PMI = 313.5 (195.8–454.9). Females well-nourished: median PMI = 388.8 (range 210.4–763.8), mild/moderately malnourished: median PMI = 309.4 (78.9–589.9), severely malnourished: median PMI = 317.65 (215.8–508.1).

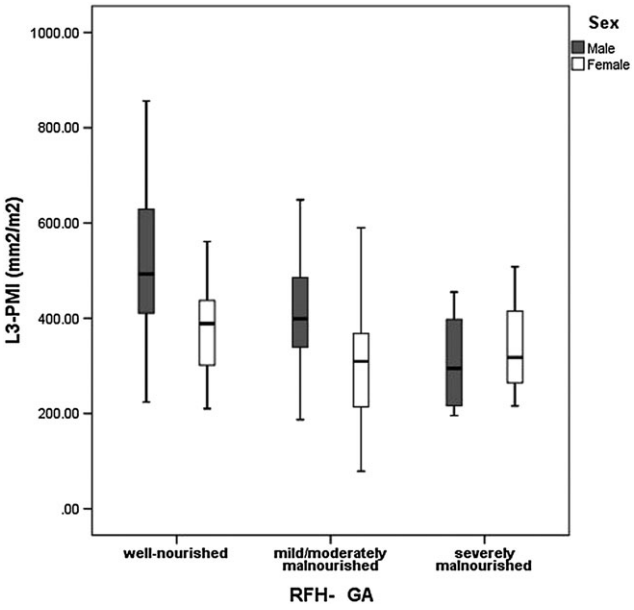
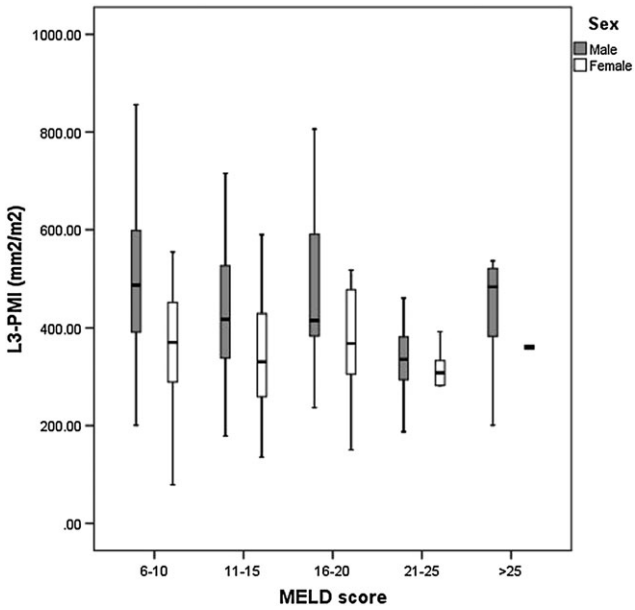
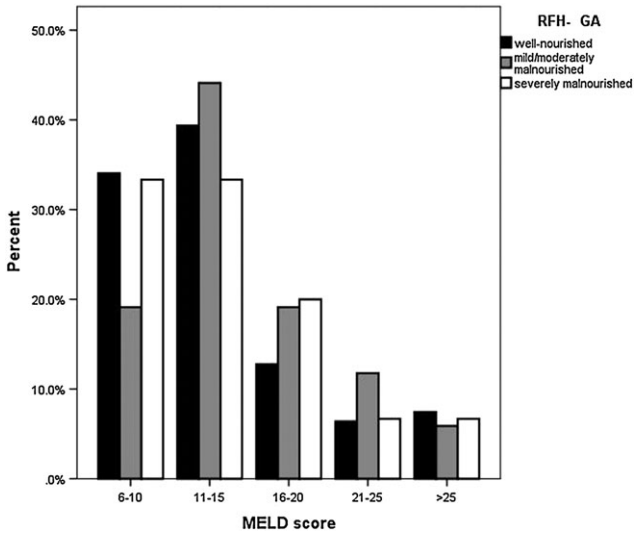


Figure 2 Box-plots of L3-psoas muscle index (L3-PMI) for male and female patients stratified according to Model for End-stage Liver Disease (MELD). Males: median L3-PMI levels were 486.6 (range 200.8–856.1), 417.6 (178.9–817.3), 415.15 (236.7–806.2), 335.6 (187.3–536.2), and 483.2 (162.5–983) mm^2/m^2 for MELD score ≤10, 11–15, 16–20, 21–25, and >25, respectively. Females: median L3-PMI levels were 370.5 (range 78.9–554.6), 330.75 (135.4–589.9), 368.3 (150.5–763.8), 308 (205.4–392.3), and 359.9 (215.8–394.9) mm^2/m^2 for MELD score ≤10, 11–15, 16–20, 21–25, and >25, respectively.



and the median ICU and hospital stay were 2.5 (1–88) and 23.5 (11–174) days, respectively. ICU and hospital stay was longer for patients at the lowest L3-PMI [$n = 2$, median ICU stay: 55.5 (23–88) days; median hospital stay: 151 (128–174) days] compared with the other L3-PMI quartiles [median ICU stay: 2 (1–5) days, $P = 0.034$; median hospital stay: 22.5 (1–34) days, $P = 0.036$], while the incidence of infections was also higher (100% vs. 12.5%, $P = 0.016$). The MELD score of the patients at the lowest L3-PMI did not significantly differ from that of patients from the other L3-PMI quartiles (15 vs. 18). Six of 7 (85.7%) patients with available RFH-GA were moderately/severely malnourished therefore no meaningful comparisons could be performed.

Figure 3 Nutritional status of the transplant recipients assessed by Royal Free Hospital-Global Assessment (RFH-GA) stratified according to Model for End-stage Liver Disease (MELD) score.



Discussion

The identification of patients listed for LT that are susceptible to increased post-operative morbidity and mortality is pivotal in order to optimize candidate selection, organ allocation and optimal graft-to-recipient matching. Malnutrition and sarcopenia are well-recognized predictors of pre-LT morbidity and mortality;[12,16] indeed, nutritional status was one of the components of the original Child–Pugh score,[28] implicating that its impact on patients with end-stage liver disease is well recognized for a long time. In this study, we have shown that both are independent predictors of longer mechanical

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Table 2 Multivariate analysis of factors associated with post-transplant outcomes

Factors	OR (95% CI)	*P* value
	Multivariate analysis for in-hospital infections	
MELD score, median (range)	1.055 (1.002–1.11)	0.041
RFH-GA category 3, *n* (%)[a]	6.55 (1.99–21.5)	0.011
	MV duration >24 h	
MELD score, median (range)	1.1 (1.036–1.168)	0.002
RFH-GA category 3, *n* (%)[a]	8.5 (1.48–48.87)	0.016
Suboptimal donor liver, *n* (%)	2.326 (1.056–5.12)	0.036
	ICU stay >5 days	
Age (years), median (range)	1.054 (1.004–1.106)	0.033
MELD score, median (range)	1.137 (1.057–1.223)	0.001
RFH-GA category 3, *n* (%)[a]	7.46 (1.57–35.43)	0.004
	Hospital stay >20 days	
Male sex, *n* (%)	2.107 (1.004–4.419)	0.049
L3-PMI (mm^2/m^2), median (range)	0.996 (0.994–0.999)	0.006
	12 month mortality	
L3-PMI (mm^2/m^2), median (range)	0.996 (0.992–0.999)	0.05

CI, confidence interval; L3-PMI, psoas muscle index; MV, mechanical ventilation; OR, odds ratio; MELD, model for end-stage liver disease; RFH-GA, Royal Free Hospital global assessment.
[a]Reference category: RFH-SGA category 1 (well nourished).

ventilation, longer ICU and hospital stay, increased incidence of infections, and of 12 month mortality post-LT.

We analysed separately malnutrition and sarcopenia, in order to ascertain their relative influence in such outcomes. When analysing sarcopenia, we have chosen the cross-sectional area of the psoas muscle because it is easy to measure, more generalizable, with no need for computation and, thus, simpler to use in clinical practice compared with the skeletal muscle cross-sectional area, which includes all surrounding muscles in the L3 region. Psoas muscle is not easily affected by abdominal distention in cases of ascites and has been shown to be predictive of mortality in cirrhosis both before and after transplantation.[16,24] Furthermore, we used RFH-GA, which is a composite score that takes into account both nutritional status and sarcopenia and links nutrition with functional muscle mass in a given individual.

Few studies have looked at the effect of sarcopenia in post-LT outcomes, and all had important limiting factors in the analysis, while no study has analysed the nutritional status of the patients. Compared with these studies,[18,19] we evaluated donor and graft characteristics such as suboptimal graft appearance, CIT and type of grafts, which are known predictors of poor early post-LT outcome[29,30] and we included a wide range of clinically relevant outcomes including post-transplant mortality. In a retrospective cohort of 245 patients,[19] the effect of sarcopenia on the length of hospital stay was not tested in a multivariate analysis with other known predictive factors such as liver disease severity, whereas the cut-offs used for the definition of sarcopenia have not been validated in patients with cirrhosis.[13] In another study, only post-transplant infections were analysed as an endpoint.[18]

The results of our study have important implications for graft-recipient matching but also for optimizing patients' nutrition while on the transplant waiting list. First, we showed that patients with muscle depletion or malnutrition who received a steatotic liver graft with prolonged CIT (>12 h) had a significantly longer ICU and hospital stay and a higher rate of infections despite similar MELD scores, implying the need for allocation of more optimal grafts in malnourished patients with sarcopenia.

Second, we showed that sarcopenia and malnutrition are not reflected in the MELD score, as they showed a wide overlap of values across different MELD scores. Although MELD consists of objective variables, it has certain limitations that could lead to misclassification of some patients.[31] Considering that malnutrition is a common feature in advanced cirrhosis, as reflected in our study and others,[2] an objective, cost-effective, easy to administer, and well-validated marker of nutritional status is needed to enhance the c-statistic of MELD score. RFH-GA has the advantages of lower cost, and higher availability and reproducibility compared with CT muscle measurements,[11] whereas the latter provides an objective and quantitative muscle mass assessment.[14] Therefore, the potential effect of both scores on enhancing the discrimination and calibration ability of MELD should be further investigated.

Third, we showed for the first time the importance of RFH-GA in determining post-LT outcomes. RFH-GA is considered a 'nutritional review' and provides a valid assessment of nutritional status in patients with cirrhosis.[11] In such patients, poor nutritional status as assessed by RFH-GA, is associated with worse survival independently of the severity of liver disease as assessed by prognostic scores,[11] and adds significantly to the predictive accuracy of both Child–Pugh and MELD score.[12] In the present study, pre-transplant malnutrition predicted post-LT outcomes independently of the severity of liver disease and other established predictive factors. Despite the

strong correlation between them, RFH-GA was better than psoas muscle mass measurement in predicting post-LT in-hospital infections and ICU stay. Therefore these emphasize the critical need for pre-operative assessment of nutritional status in all LT candidates and also for the potential development and validation of a tool to predict post-transplant outcomes. The current results could be regarded as a proof of concept that malnutrition/sarcopenia should be part of this tool.

Pre-LT malnutrition/sarcopenia, although not easily, could be potentially modifiable. The effect of pre-LT nutritional supplementation on modifying the nutritional status of these patients and, subsequently, improving post-LT outcomes and resource utilization should be elucidated, preferably in randomized controlled studies. Moreover, it seems that the combination of simple anthropometric measures (BMI and MAMC) together with the evaluation of dietary intake (all used in the RFH-GA assessment) can efficiently predict significant post-LT outcomes and might have higher predictive discrimination than CT muscle mass measurements. On the other hand, despite the observed strong association between RFH-GA and TPA, we found that malnourished patients demonstrate a wide range of PMI values, implying that not all patients classified as malnourished with RFH-GA have sarcopenia.

We evaluated the potential impact of gender on outcomes considering, first, the gender differences in body composition parameters and, second, reports[32] on the higher cumulative survival rates of women with cirrhosis compared with male patients. Our findings suggest that male gender is a confounding factor for both psoas muscle cross-sectional area and RFH-GA, and that it was independently associated with prolonged hospital stay and time on mechanical ventilation. A potential explanation is that malnutrition in male patients with cirrhosis is characterized mainly by muscle mass loss, whereas in women by fat loss.[11,33] It is therefore presumed that males might have worse post-LT outcomes compared with females because of less muscle mass in cases of malnutrition; however, this needs to be further elucidated.

This study must be considered within the context of its limitations as it reports on a relative small sample size of a single-centre experience and it has a retrospective design. However, it is unlikely that our findings are because of type I error. Furthermore, the sample size of patients receiving marginal grafts is very small, and the results should be interpreted with caution until confirmed in larger series. Finally, the majority of our patient population had relatively low MELD scores ($<$20), which is because of the centre-based allocation and also to a different allocation score that is used in the UK. However, we believe that these findings will be even more pronounced in patients with worse liver dysfunction.

In conclusion, nutritional indices and sarcopenia are significantly associated with post-LT outcomes; therefore, malnourished and/or sarcopenic patients need to be identified pre-operatively for targeted nutritional interventions in order to optimize liver transplantation outcomes and reduce associated costs.[34] CT psoas muscle mass measurement is a reliable and objective marker of nutritional status and fairly simple to compute. RFH-GA, although subjective, is a simple bedside test and is a better predictor of post-LT outcomes. A major implication of the present study is the need to avoid marginal grafts in patients with sarcopenia irrespective of their MELD score.

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Online supplementary material

Supporting Information is available at Journal of Cachexia, Sarcopenia and Muscle online.

Table S1. Univariate and multivariate analysis of factors associated with post-transplant outcomes.

Conflict of interest

All authors declare that they have no conflict of interest.

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