Sex is a major effect modifier between body composition and mortality in patients with cirrhosis assessed for liver transplantation

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ABSTRACT

Background & aims

Body composition predicts mortality in patients with cirrhosis. The impact of sex on this association is unknown. We investigated the impact of sex on this association in patients with cirrhosis assessed for liver transplantation.

Methods

This single centre retrospective cohort study included adults assessed for liver transplantation. Nutritional status was assessed using the Royal Free Hospital-Global Assessment (RFH-GA). Body composition at third lumbar vertebrae was determined. Sarcopenia^{SMI} was defined as Skeletal Muscle Index <50cm^2/m^2 in males and <39cm^2/m^2 in females. Sarcopenia^{PMI} was defined as the sex-specific 25th percentile of Psoas Muscle Index. Patients were assessed for occurrence of liver transplantation and death. Analyses were stratified by sex.

Results

The cohort comprised 628 patients, including 199 females and 429 males. Both groups were similar in terms of baseline liver disease severity by Model for End-stage Liver Disease (MELD) (p=0.98), and nutritional status (p=0.24). Sarcopenia^{SMI} was present in 41% of males compared to 27% of females (p<0.001). In the male cohort, when adjusted for age and MELD, sarcopenia^{PMI} (aHR1.74, 95%CI 1.08-2.80) and RFH-GA (aHR1.40, 95%CI 1.03-1.90) remained independent predictors of mortality. Adipose tissue had no impact on outcomes in males. In female patients,

adipose tissue (TATI or VATI depending on the multivariable model) were independently associated with mortality whereas sarcopenia and malnutrition were not.

Conclusions

This study demonstrates that male patients were susceptible to low muscle mass, while female patients were not. Future research in this patient population should minimize sex-related bias, and present data for both groups separately.

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Lay summary

Sarcopenia and malnutrition are associated with mortality in patients with cirrhosis awaiting liver transplantation. The impact of sex on this association is poorly investigated and reported. Sarcopenia and malnutrition were predictors of mortality in male patients but not females. Future research should present data separately for males and females to minimize sex bias.

Keywords

Sarcopenia, Adipose tissue, Malnutrition, Sex, Cirrhosis, Liver transplantation

INTRODUCTION

Patients with decompensated cirrhosis are at high risk of dying with a median survival of 2 years (1, 2). The Model for End Stage of Liver Disease (MELD) score is used to prioritize liver organ allocation to those with the highest medical need (3, 4). Despite that, some patients on the waiting list become too sick or die before being transplanted. Although a plethora of factors can be invoked including regional variability in organ availability, the rate of death or removal from the waiting list due to worsening of liver disease approaches 10% at 90 days (5-7). It is therefore important to identify and prioritize patients at highest risk of waiting list mortality.

Malnutrition, which is not included in the MELD score, is a frequent complication of cirrhosis and is associated with increased hospitalisation, hepatic encephalopathy (HE) and mortality (8-10). Unfortunately, assessing a patient's nutritional status can be challenging. The Royal Free Hospital-Global Assessment (RFH-GA) which includes body mass index (BMI), mid-arm muscle circumference (MAMC), and the patient's dietary intake is a validated tool that classifies patients as adequately nourished, moderately malnourished or severely malnourished (11). RFH-GA has good interobserver agreement and is significantly associated with total body protein in patients with cirrhosis (11). It can also predict mortality in severely malnourished individuals (12). In the post-transplant setting, it is associated with higher rates of in-hospital infection, longer mechanical ventilation, and ICU stay (13).

Beyond nutritional tools such as the RFH-GA, the presence of sarcopenia shortens the survival of patients with cirrhosis (14, 15). Pre-transplant sarcopenia is associated with longer post-transplant hospital stay and increased 12-month mortality (13). Muscle mass can be determined objectively

through the use of cross-sectional imaging(16). Validated markers previously published in the literature include the psoas muscle index (PMI) and total skeletal muscle index at the third lumbar vertebrae (SMI) (13, 17). Sarcopenia has been defined using both PMI or SMI. Sarcopenia^{SMI} is defined as a SMI below 50cm^2/m^2 in males, and 39cm^2/m^2 in females (17). Sarcopenia^{PMI} is defined as a PMI below the sex-specific 25th percentile (13). Recent evidence suggests that low subcutaneous adipose tissue increases mortality in female patients with cirrhosis awaiting liver transplantation, while male appeared more vulnerable to low muscle mass (18). This study has not yet been replicated or validated.

A growing concern in the hepatology literature reminds us that important sex-based differences might exist in the clinical outcomes of patients with cirrhosis awaiting transplantation(19). For instance, the MELD score disadvantages female transplant candidates as it incorporates the creatinine level, which is not adjusted for sex within the score(20, 21). To date, only a few studies have assessed the impact of malnutrition, sarcopenia or adipopenia in males and females separately(14, 18). In addition, these studies often look at these markers individually, and therefore only provide a partial view of the patient's overall condition. This study aims overcome these limitations by including a comprehensive assessment of the ability of the RFH-GA, sarcopenia and adipose tissue measurements to predict mortality in females and males evaluated for liver transplantation due to cirrhosis, providing a more wholesome understanding of their nutritional status.

METHODS

We conducted a retrospective cohort study including all adult patients who were evaluated for liver transplantation at the Royal Free Hospital, London, United Kingdom between February 2006 and February 2017. Patients were identified through review of a prospectively maintained database of all patients assessed for liver transplantation. To be included, patients had to be above 18 years of age, be assessed for liver transplantation due to cirrhosis, and have available cross-sectional imaging within six months of the date of liver transplant assessment. Patients were excluded if abdominal imaging was not available or if they were being transplanted for other reasons than cirrhosis.

Definition of study groups

We divided our population into a male and female cohort. Nutritional status was assessed by a dedicated liver dietitian and was categorised based on the RFH-GA at first assessment as: well nourished, moderately malnourished and severely malnourished(11). Body compartments were assessed using cross-sectional imaging within 6 months of the assessment date. Transverse sections of cross-sectional imaging at the third lumbar vertebrae were analyzed. Images showing both transverse processes were used. All slices measured were downloaded in DICOM format and processed using Image J (version 1.52, Wayne Rasband, National Institutes of Health). Skeletal muscle was identified by using a Hundsfield Unit (HU) threshold of -29 to +150 HU(22). The delineated pixels were translated into a muscle area. The total muscle area was used by combining the specific right and left muscles. The total area was then divided by the height squared to obtain the muscle index. The following muscle indexes were calculated: total skeletal muscle index (SMI) and total psoas muscle index (PMI). Using previously validated definitions, sarcopenia was

defined for SMI and PMI separately. Sarcopenia^{PMI} was present if the PMI was in the lowest quartile as stratified by sex. Women and men with SMI under 39cm^2/m^2 and 50cm^2/m^2, respectively, were categorized as having Sarcopenia^{SMI}. The main measure of sarcopenia used in this publication was Sarcopenia^{PMI}. Adipose tissue was identified using a HU threshold of -190 to -30 HU. Once total adipose tissue index (TATI) was obtained, visceral adipose tissue index (VATI) was subtracted to obtain subcutaneous adipose tissue index (SATI).

Outcome measures

Clinical parameters were collected from electronic medical records including demographic, anthropometric, and laboratory data. Recorded BMI was based on dry weight estimate. Triceps skin fold (TSF), MAMC, and handgrip strength (HGS) were recorded at assessment. The Child Pugh score, and MELD were calculated at assessment date (23). Patients were followed by the liver transplant team as appropriate, and were offered listing if criteria were met. Whether patients were listed for liver transplantation, or delisted for being too unwell was recorded. Key events of interest included mortality and liver transplantation. Follow-up ended at the time of liver transplantation, death, last clinic appointment or administrative censoring on May 3, 2018. Time to event was defined as the time from assessment date to the event of interest.

Statistical analysis

Categorical variables are presented as numbers (percentages), continuous variables with a non-normal distribution as median (interquartile range, IQR), and continuous variables with a normal distribution as mean (standard deviation, SD). Normal distribution was assessed using the Kolmogorov-Smirnov test. Fisher's exact test was used for dichotomous variables, chi-squared

test for categorical variables, Wilcoxon Rank sum for continuous variables with a non-normal distribution, and student T-test for continuous variables with normal distribution. Univariate Cox regression analysis reporting hazard ratio (HR) with 95% confidence interval (95%CI) was performed to identify predictors of mortality in the entire cohort and both sub-cohorts, where patients who underwent liver transplantation were censored as alive. Variables with p-value < 0.1 in the univariate analysis were then assessed by multivariate analysis. Kaplan-Meier plots show overall survival with between group comparison using the log-rank test. A competing risk analysis was also performed for the survival analysis considering liver transplantation as a competing event reporting sub-distribution hazard ratio (SHR) with 95% CI using the Fine and Gray method. This was performed for the entire cohort and for both male and female sub-cohorts. Kaplan Meier curve was constructed to show survival stratified by MELD and Sarcopenia^{PMI} status with log-rank statistics. Statistical analysis was carried using SPSS (version 27.0, IBM, New York, NY, USA) and STATA (version 16, STATA Corp LLC, College Station, TX, USA).

RESULTS

Description of main cohort

Overall, 882 patients were potentially eligible for inclusion. Of these, 254 did not meet eligibility criteria as they were either missing cross-sectional imaging or the available imaging was outside the 6-month window (Figure 1). A final cohort of 628 patients was therefore available for analysis with a median follow-up of 6.3 (IQR 11.6) months. This cohort comprised 199 (31.7%) females and 429 (68.3%) males. Key differences existed between sub-cohorts. Specifically, the distribution of etiology of liver disease was different (p<0.001), with females having less alcohol related liver disease (18.6% vs 34.7%), more autoimmune or cholestatic liver diseases (41.2% vs 16.1%), and

less hepatocellular carcinoma (18.6% vs 32.4%, p<0.001) compared to males. Biochemically, females had a higher bilirubin than males (p=0.018). Otherwise, duration of follow-up, age, MELD score, Child Pugh score, and the presence ascites or hepatic encephalopathy were similar between both groups. Rest of baseline characteristics are presented in Table 1.

Nutritional and body composition assessment

Important differences in the body composition of males and females were identified (Table1). Males had higher BMI, handgrip strength, and MAMC, while females had higher TSF. Regarding muscle mass, males had higher SMI and PMI when compared to females (p<0.001 for all). Although males had higher muscle mass, Sarcopenia^{SMI} was more frequent in this group when compared to females (41.3% vs 26.6%, p<0.001). Since Sarcopenia^{PMI} is defined as a sex-specific percentile, there was no difference in terms of prevalence of Sarcopenia^{PMI} in either groups (p=0.69). In terms of adipose tissue, although males had numerically higher TATI compared to females, this was not statistically significant (97.1 [IQR 79.7] cm^2/m^2 vs 85.0 [IQR 64.5] cm^2/m^2, p=0.51). Females had significantly higher SATI (53.8 [IQR 44.3] cm^2/m^2 vs 46.8 [IQR 43.3] cm^2/m^2, p=0.002) and lower VATI (29.8 [IQR 25.9] cm^2/m^2 vs 46.0 [IQR 40.8] cm^2/m^2, p<0.0001) compared to males. Finally, the distribution of nutritional status as assessed by the RFH-GA was similar between both sexes. This is presented in more detail in Table1.

Liver Events

Liver events, including transplantation, delisting, and death were similar between both groups. In the total cohort, 476 (75.8%) patients were listed, of whom 355 (74.6%) were transplanted. The median time to transplantation was 5.1 (IQR 6.6) months. In the male cohort, 328 (76.5%) patients

were listed, of whom 246 (75.0%) were transplanted, and 44 (13.4%) died while waiting. In the 101 patients that were not listed, 38 (37.6%) patients died. In the female sub-cohort, 148 (74.4%) were listed, of whom, 109 (73.6%) underwent liver transplantation and 21 (14.2%) died while waiting. Of the 51 patients that were not listed, 23 (45.1%) died. The median time from assessment to liver transplantation was 5.1 (IQR 5.9) months in males and 5.3 (IQR 7.2) months in females (p=0.29).

Total Cohort

Body comportments and Nutritional status as predictors of mortality

On univariate cox regression analysis, PMI and Sarcopenia^{PMI} were the only muscle-related variables associated with worse prognosis in the total cohort, while SMI or Sarcopenia^{SMI} were not (Table 2). Being severely malnourished as per RFH-GA was associated with worse survival. The other predictors included increasing age, MELD, and Child-Pugh score. Adipose tissue compartments, etiology of liver disease, and presence of HCC were not associated with mortality (Table 2). On multivariate analysis, when adjusted for age and MELD, severe malnutrition as per RFH-GA (aHR1.97, 95% CI 1.21-3.21) and Sarcopenia^{PMI} (aHR1.52, 95%CI 1.02-2.26) remained predictive of mortality (Table S1). On multivariate competing risk analysis using liver transplantation as the competing event, when adjusted for age and MELD, Sarcopenia^{PMI} was very close to being a significant predictor of mortality (aSHR 1.48, 95%CI 0.99-2.22), while severe malnutrition by RFH-GA remained significant (aSHR1.29, 95%CI 1.00-1.67) (Table S1).

Impact of Sarcopenia when stratified by MELD 15

When patients were classified by Sarcopenia^{PMI} status and MELD above or below 15, those with best prognosis were not sarcopenic and had a MELD < 15, while those with the worst prognosis had both MELD $\geq$ 15 and were sarcopenic (p<0.001). Patients with Sarcopenia^{PMI} and MELD < 15 had a similar prognosis to without sarcopenia but MELD $\geq$ 15 (p = 0.38).

Male cohort

Body comportments and Nutritional status as predictors of mortality

On univariate cox regression analysis, PMI, Sarcopenia^{PMI}, SMI, Sarcopenia^{SMI}, and severe malnutrition by RFH-GA were predictive of mortality (Table 2). None of the adipose tissue compartments, including TATI, SATI and VATI, or HGS, TSF, and MAMC were associated with mortality. Etiology of liver disease and presence of HCC were not predictive of mortality in univariate analysis either (Table 2). On multivariate analysis, when adjusted for age and MELD, Sarcopenia^{PMI} (aHR 1.76, 95%CI 1.09-2.84) and severe malnutrition by RFH-GA (aHR1.94, 95%CI 1.06-3.56) remained independent predictors of mortality (Table 3). Although etiology was not predictive of mortality in univariate analysis, it was also included in a supplemental multivariate analysis and it was not predictive of mortality either (Table S2). In the competing risk analysis where liver transplantation was considered a competing event, when adjusted for age and MELD, Sarcopenia^{PMI} (aSHR 1.80, 95%CI 1.10-2.92) was predictive of mortality while RFH-GA was not (aSHR1.61, 95%CI 0.88-2-94) (Table 3).

Impact of Sarcopenia when stratified by MELD 15

When patients were classified by Sarcopenia^{PMI} status and MELD above or below 15, those with best prognosis were not sarcopenic and had a MELD < 15, while those with the worst prognosis had both MELD $\geq$ 15 and Sarcopenia^{PMI} ($p < 0.001$) (Figure 2). Patients with Sarcopenia^{PMI} and MELD < 15 had a similar prognosis than those without sarcopenia but MELD $\geq$ 15 ($p = 0.53$). In patients with a MELD < 15, when adjusted for age, Sarcopenia^{PMI} was independently associated with mortality (aHR2.05, 95%CI 1.05-3.99, p=0.04). In patients with a MELD $\geq$ 15, when adjusted for age, Sarcopenia^{PMI} tended to be associated with mortality (aHR 1.80, 95%CI 0.94-3.46, p=0.08).

Female cohort

Body comportments and Nutritional status as predictors of mortality

On univariate cox regression analysis, increasing adipose tissue (TATI and VATI) and TSF were predictive of mortality (Table 2). Increasing SATI tended toward significance (p=0.08). In terms of muscle compartments, PMI or Sarcopenia^{PMI} were not associated with mortality (Table 2). On the other hand, SMI as a continuous variable was associated with mortality in the female cohort, but not Sarcopenia^{SMI} using the cut-offs that have been recommended (Table 2). Although nutritional status by RFH-GA was not statistically associated with increasing mortality, female patients with severe malnutrition had a higher risk of death compared to those with normal nutritional status (HR 1.55, 95%CI 0.68-3.57). Etiology of liver disease and the presence of HCC were not predictive of mortality in the univariate analysis (Table 2). On multivariate analysis, when adjusted for age and MELD, Sarcopenia^{PMI} (aHR 1.08, 95%CI 0.47-2.46) and severe malnutrition (aHR 1.83, 95%CI 0.73-4.53) were not associated with mortality while VATI was (aHR1.02,

95%CI 1.01-1.03) (Table 4). When PMI was replaced by SMI in the multivariate analysis, SMI as a continuous variable was not associated with mortality after adjusting for confounders (Table S3). Although etiology was not predictive of mortality in univariate analysis, it was also included in a supplemental multivariate analysis and it was not predictive of mortality either (Table S4). In the competing risk analysis where liver transplantation was considered a competing event, when adjusted for age and MELD, severe malnutrition (aSHR2.32, 95%CI 0.94-5.72) tended towards statistical significance, while VATI was significant (aSHR 1.01, 95%CI 1.00-1.03), and Sarcopenia^{PMI} was not (aSHR 0.85, 95%CI 0.38-1.91).

Impact of Sarcopenia when stratified by MELD 15

Prognosis of female patients was not influenced by classifying them by Sarcopenia^{PMI} and MELD strata (p=0.67) (Figure 3).

DISCUSSION

A growing body of evidence suggests that body composition plays a major role in the clinical course of patients with cirrhosis awaiting liver transplantation. Initial studies focussing on muscle mass identified sarcopenia as being a significant predictor of mortality. More recent data caution that female sarcopenia might not be associated with a worse prognosis as it appears to be in males (14). Our study is the first of its kind to assess the impact of an objective assessment of nutritional status (RFH-GA) and body compartments, including both muscle and adipose tissue, to predict mortality in patients with cirrhosis awaiting liver transplantation. We therefore provide a comprehensive assessment of a patient's nutritional condition as opposed to previous studies that

only focussed on one of these aspects. In addition, our study focussed on male and female patients separately due to important sex-based differences.

In our study, although male patients had more muscle mass than females, they were more often sarcopenic by SMI definition. In addition, male Sarcopenia^{PMI} is independently associated with worse survival, but this is not the case for female patients. In terms of adipose tissue distribution, male and female patients have similar total adipose tissue, but females have less visceral and more subcutaneous fat compared to males. Regarding adipose tissue, increase in TATI and VATI seemed to have an independent effect on mortality in females, but not in males. Severe malnutrition as assessed by the RFH-GA is a useful predictor of mortality independently of Sarcopenia^{PMI} in the total cohort and the male sub-cohort. Although not statistically significant in females, the point estimate suggests it is a useful predictor. These differences are seen while both cohorts had similar age, MELD score, Child Pugh score, ascites, and hepatic encephalopathy.

Our study confirms the importance of identifying sarcopenia, whether with PMI or SMI, in male patients awaiting liver transplantation as they have a worse prognosis. Both methods have their advantages and disadvantages. While the SMI cut-off provides a specific numerical threshold, it necessitates the use of a proprietary software which might not be available outside of a research setting. The advantage of using psoas muscle is that it can be easily measured using standard radiology software. If assessment of sarcopenia is not feasible, liver transplant centers can rely on the RFH-GA as male patients noted to have severe malnutrition also died earlier. Whether it is through the use of objective sarcopenia measurements or nutritional assessment, these could provide tangible targets used to monitor treatments aimed at reversing sarcopenia or malnutrition.

In female patients, increases in adipose tissue, more specifically TATI and VATI were predictive of increased mortality. This was replicated with a simple marker of adipose tissue, the TSF. Indeed, an increase in TSF is also associated with mortality. Visceral adipose tissue is a more metabolically active organ which secretes pro-inflammatory cytokines including tumor necrosis factor-alpha and interleukin-6 when compared to subcutaneous adipose tissue (24). This pro-inflammatory milieu has been associated with advanced hepatic inflammation and fibrosis (25). Increases in visceral adipose tissue has also been associated with an increase in all-cause mortality in women (26). Other studies have linked it with cardiovascular mortality and an unfavorable metabolic profile (27). Visceral fat has also been implicated in oncological disorders including higher HCC prevalence and recurrence in men and breast cancer in women (26) (28).

Although severe malnutrition by RFH-GA was not statistically associated with our outcome in female patients, worsening nutritional status numerically increased the probability of death. It is therefore possible that this was not statistically significant due to our sample size, despite having a large cohort of female patients. Our findings diverge from a previous study by Ebadi et al. where a low SATI was associated with mortality in female patients with cirrhosis awaiting transplantation (18). It must be noted that our cohort is very different as our female patients had a lower BMI (24 kg/m^2 vs 27 kg/m^2), less HCC (19% vs 29%), less NAFLD (6% vs 30%), a lower SATI and a lower VATI compared to theirs. In addition, our follow-up was shorter as a higher percentage of our patients were transplanted (75% vs 54%) and this within a median of 6 months. Another difference is that they found that increasing age was protective against mortality which might highlight the presence of an uncounted selection bias. It is important to remember that while their

findings might be internally valid, it might not be extrapolated to other populations where the distribution of significant patient characteristics and transplant wait-time dynamics are different.

Our study has many strengths. We are the first to present a large cohort of patients with an objective marker of nutritional assessment, such as the RFH-GA, multiple non-invasive scales for muscle strength and adipose tissue, including HGS and TSF, and more importantly radiological assessment of muscle and adipose tissue. Second, given the important impact of sex as an effect modifier on the outcome, the data is stratified and presented separately for both sex. Our study also has limitations which stem from its retrospective design. As liver transplantation is a major competing event in the survival of patients with cirrhosis, we have performed a competing risk analyses which has mostly confirmed the findings on cox regression analysis. Our findings are also influenced by our transplant waitlist duration. Regarding the female cohort, although we included 199 female patients, a larger female cohort would improve the power to identify subtle changes in outcome with alterations in body composition, and larger studies would be required. Finally, although we assessed muscle mass by using two different measurements, specifically PMI and SMI, transversal psoas muscle thickness (TPMT) can also serve as a marker of sarcopenia. Indeed, it has recently been shown to have prognostic value in patients with cirrhosis (29). TPMT and the new sex-specific cut-offs that have been suggested should be further validated (30).

In conclusion, our study demonstrates that sex is a major effect modifier on the relationship between body composition and mortality in patients with cirrhosis. This justifies a sex-specific approach. Prospective studies that integrate sex-based considerations in the collection, analysis, and interpretation of data are urgently needed. We recommend that this should be done separately for males and females in order to orient sex-specific interventions.

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Table 1. Baseline characteristics of patients divided by sex.

	All patients (n=628)	Male (n=429)	Female (n=199)	p-value
Age, years, IQR	54.5 (14)	55.0 (14.0)	53.0 (16.0)	0.136
Follow-up, days, IQR	192 (352)	186 (301)	219 (394)	0.226
Etiology, n(%)				<0.001
Viral	187 (29.8)	141 (32.9)	46 (23.1)	
ArLD	186 (29.6)	149 (34.7)	39 (19.6)	
NAFLD	48 (7.6)	37 (8.6)	7 (3.5)	
Cholestatic	119 (18.6)	59 (13.8)	82 (41.2)	
Other	88 (14.0)	43 (10.0)	11 (5.5)	
Child Pugh Score, IQR	9 (3)	9 (4)	9(3)	0.575
A, n(%)	41(6.5)	25 (5.8)	16 (8.0)	
B, n(%)	300 (47.8)	209 (48.7)	91 (45.7)	
C, n(%)	286 (45.5)	194 (45.2)	92 (46.2)	
Hepatocellular carcinoma, n(%)	176 (28)	139 (32.4)	37 (18.6)	<0.001
Hepatic Encephalopathy, n (%)	518 (82.5)	356 (83.2)	162 (81.4)	0.297
Ascites, n (%)	561 (89.3)	382 (89.3)	179 (89.9)	0.404
MAMC, in cm, IQR	24.5 (5.2)	25.4 (4.9)	22.4 (4.6)	<0.001
Triceps skin fold, in mm, IQR	12.0 (8.8)	11.0 (7.3)	14.2 (10.7)	<0.001
Handgrip strength, in kg, IQR	24.4 (13.6)	26.5 (13.0)	19.7 (11.7)	<0.001
RFH-GA, n (%)				0.238
Adequately nourished	230 (36.6)	155 (36.1)	75 (37.7)	
Moderately malnourished	259 (41.2)	171 (39.9)	88 (44.2)	
Severely malnourished	139 (22.1)	103 (24.0)	36 (18.1)	
BMI, kg/m^2 , IQR	24.6 (7.0)	25.2 (6.9)	23.6 (6.4)	0.001
Platelets, $x10^9/L$, IQR	97 (86)	96 (79)	107 (104)	0.256
Serum bilirubin, µmol/L, IQR	36 (50)	34 (41)	40 (60)	0.018
Serum albumin, g/L, IQR	34 (9)	34 (10)	33 (9)	0.548
MELD, IQR	13.5 (7)	13.5 (7.2)	13.5 (6.6)	0.928
SMI, cm^2/m^2, IQR	49.3 (12.9)	52.1 (11.3)	43.5 (10.3)	<0.001
$Sarcopenia^{SMI}$, n(%)	230 (36.6)	177 (41.3)	53 (26.6)	<0.001
PMI, mm^2/m^2, IQR	509.1 (225.2)	558.1 (229.4)	420.5 (171.2)	<0.001
$Sarcopenia^{PMI}$, n(%)	158 (25.2)	106 (24.7)	52 (26.1)	0.702
TATI, cm^2/m^2, IQR	94.0 (75.3)	97.1 (79.7)	85.0 (64.7)	0.508
SATI, cm^2/m^2, IQR	48.4 (43.2)	46.8 (43.2)	53.8 (44.4)	0.002
VATI, cm^2/m^2, IQR	39.5 (37.4)	46.0 (40.8)	29.7 (26.3)	<0.001

Legend: Categorical variables are expressed as numbers (%), continuous variables with a non-normal distribution are expressed as median (IQR), unless otherwise specified. ArLD, alcohol-related liver disease; BMI, body mass index; IQR, interquartile range; INR, international normalized ratio; MAMC, mid-arm muscle circumference; MELD, model for end stage liver disease; NAFLD, non-alcoholic fatty liver disease; PMI, total psoas muscle area indexed for height at the third lumbar vertebrae; RFH-GA, Royal Free Hospital Subjective Global Assessment; SATI, total subcutaneous tissue indexed at the third lumbar vertebrae; SMI, skeletal muscle area indexed for height at the third lumbar vertebrae; TATI, total adipose tissue indexed at the third lumbar vertebrae; VATI; total visceral adipose tissue indexed at the third lumbar vertebrae.

Table 2. Univariate Cox regression analysis in the whole cohort, male cohort and female cohort for mortality.

	Whole cohort			Male cohort			Female cohort		
	HR	95% C.I.	p-value	HR	95% C.I.	p-value	HR	95% C.I.	p-value
Clinical Variables									
Sex, ref male	1.04	0.71-1.52	0.83	--	--	--	--	--	--
Age, per year	**1.04**	**1.02-1.06**	**<0.001**	**1.04**	**1.01-1.06**	**0.003**	**1.05**	**1.02-1.09**	**0.001**
Presence HCC	0.78	0.52-1.19	0.26	0.67	0.41-1.10	0.11	1.27	0.58-2.78	0.54
Etiology, ref viral				--	--	--	--	--	--
ArLD	1.08	0.67-1.75	0.74	1.27	0.72-2.23	0.40	0.72	0.28-1.84	0.48
NAFLD	1.55	0.83-2.90	0.17	1.69	0.80-3.58	0.17	1.26	0.40-4.00	0.70
Cholestatic	1.34	0.80-2.26	0.26	1.61	0.82-3.15	0.16	0.94	0.41-2.18	0.89
Other	0.82	0.44-1.51	0.52	0.86	0.37-2.01	0.73	0.66	0.26-1.65	0.37
MAMC, per cm	0.98	0.92-1.02	0.28	0.95	0.89-1.02	0.19	0.99	0.91-1.08	0.80
Triceps skin fold, per mm	1.01	0.99-1.01	0.22	1.00	0.97-1.04	0.95	**1.03**	**1.00-1.06**	**0.03**
Handgrip strength, per kg	0.99	0.97-1.02	0.50	0.98	0.95-1.01	0.16	1.02	0.98-1.07	0.32
BMI, per kg/m^2	0.98	0.95-1.02	0.38	0.96	0.92-1.01	0.13	1.02	0.96-1.08	0.48
MELD, per point	**1.12**	**1.08-1.16**	**<0.001**	**1.12**	**1.07-1.16**	**<0.001**	**1.14**	**1.06-1.23**	**<0.001**
Child-Pugh Score, per point	**1.42**	**1.28-1.56**	**<0.001**	**1.45**	**1.29-1.63**	**<0.001**	**1.35**	**1.13-1.61**	**0.001**
Platelets	0.99	0.99-1.00	0.69	0.99	0.99-1.00	0.95	0.99	0.99-1.00	0.56
Muscle Mass									
PMI, per mm^2/m^2	**0.99**	**0.99-1.00**	**0.007**	**0.99**	**0.99-0.99**	**<0.001**	1.00	0.99 -1.00	0.31
Presence sarcopenia^{PMI}	**1.54**	**1.05-2.26**	**0.03**	**2.12**	**1.34-3.36**	**0.001**	0.81	0.40-1.66	0.57
SMI, per cm^2/m^2	0.99	0.97-1.01	0.20	**0.96**	**0.94-0.98**	**0.001**	**1.04**	**1.01-1.07**	**0.01**
Presence sarcopenia^{SMI}	1.34	0.93-1.93	0.11	**1.66**	**1.07-2.57**	**0.02**	0.83	0.38-1.81	0.65
Adipose Tissue Mass									
TATI, per cm^2/m^2	1.00	0.99-1.00	0.22	1.00	0.99-1.00	0.92	**1.00**	**1.00-1.01**	**0.02**
SATI, per cm^2/m^2	1.00	0.99-1.00	0.54	1.00	0.99-1.00	0.49	1.00	0.99-1.01	0.08
VATI, per cm^2/m^2	1.00	0.99-1.01	0.09	1.00	0.99-1.01	0.54	**1.02**	**1.00-1.03**	**0.005**
Nutritional Status									
RFH-GA									
Well nourished	1	--	--	1	--	--	1	--	--

Moderate malnutrition	1.33	0.87-2.04	0.19	1.49	0.87-2.55	0.15	1.12	0.56-2.25	0.75
Severe malnutrition	**1.86**	**1.17-2.95**	**0.01**	**2.06**	**1.17-3.61**	**0.01**	1.55	0.68-3.57	0.30

Abbreviations: ArLD: alcohol related liver disease; BMI, Body Mass Index; HR, Hazard Ratio; HCC, Hepatocellular carcinoma; MAMC, Mid-Arm muscle circumference; MELD, Model for end stage liver disease; NAFLD: non-alcoholic fatty liver disease; PMI, Total psoas muscle area indexed for height at third lumbar vertebrae; RFH-GA; Royal Free Hospital Global Assessment; SATI, Total subcutaneous tissue indexed at the third lumbar vertebrae; SMI, Skeletal muscle area indexed for height at the third lumbar vertebrae; TATI, Total adipose tissue indexed at the third lumbar vertebrae; VATI, Total visceral adipose tissue indexed at the third lumbar vertebrae.

Table 3. Multivariate Cox regression and competing risk analyses in the male cohort for mortality.

	Multivariate Cox Regression Analysis				Multivariate Competing Risk Analysis		
Parameters	HR	95% C.I.	p-value		SHR	95% C.I.	p-value
Model 1							
Age, per year	1.04	1.02-1.07	0.001		1.03	1.01-1.06	0.01
MELD score, per point	1.13	1.08-1.17	<0.001		1.06	1.02-1.11	0.004
Presence of Sarcopenia^{PMI}	1.99	1.26-3.16	0.003		1.99	1.24-3.20	0.004
Model 2							
Age, per year	1.05	1.02-1.07	<0.001		1.04	1.01-1.07	0.01
MELD score, per point	1.12	1.08-1.17	<0.001		1.06	1.02-1.11	0.005
Presence of Sarcopenia^{PMI}	1.76	1.09-2.84	0.02		1.80	1.10-2.92	0.02
RFH-GA, severe malnutrition	1.95	1.06-3.56	0.03		1.61	0.88-2.94	0.12

Abbreviations: C.I. confidence interval; HR, Hazard Ratio; MELD, Model for end stage liver disease; PMI, Total psoas muscle area indexed for height at third lumbar vertebrae; RFH-GA, Royal Free Hospital Global Assessment; SHR, Subdistribution hazard ratio.

Table 4. Multivariate Cox regression and competing risk analyses in the female cohort for mortality.

	Multivariate Cox Regression Analysis				Multivariate Competing Risk Analysis		
Parameters	HR	95% C.I.	p-value		SHR	95% C.I.	p-value
Model 1							
Age, per year	1.06	1.02-1.09	0.002		1.06	1.02-1.10	0.001
MELD score, per point	1.17	1.08-1.27	<0.001		1.05	0.98-1.12	0.13
Presence of sarcopenia^{PMI}	1.27	0.53-3.02	0.59		1.06	0.44-2.52	0.90
RFH-GA, severe malnourished	1.91	0.77-4.72	0.16		2.29	0.93-5.65	0.07
TATI, per cm^2/m^2	1.01	1.00-1.01	0.03		1.01	1.00-1.01	0.003
Model 2							
Age, per year	1.05	1.02-1.09	0.004		1.06	1.02-1.10	0.002
MELD score, per point	1.16	1.07-1.25	<0.001		1.04	0.97-1.12	0.25
Presence of sarcopenia^{PMI}	1.08	0.47-2.46	0.86		0.85	0.38-1.91	0.69
RFH-GA, severe malnutrition	1.83	0.73-4.54	0.20		2.32	0.94-5.72	0.07
VATI, per cm^2/m^2	1.02	1.01-1.03	0.04		1.01	1.00-1.03	0.03

Abbreviations: C.I. confidence interval; HR, Hazard Ratio; MELD, Model for end stage liver disease; PMI, Total psoas muscle area indexed for height at third lumbar vertebrae; RFH-GA, Royal Free Hospital Global Assessment; SHR, Subdistribution hazard ratio; TATI, Total adipose tissue indexed at the third lumbar vertebrae; VATI, total visceral adipose tissue indexed at the third lumbar vertebrae.

Figure 1. Patient flow chart.

Figure 2. Kaplan Meier curve of male patients stratified by Sarcopenia^{PMI} and MELD status.

Figure 3. Kaplan Meier curve of female patients stratified by Sarcopenia^{PMI} and MELD status.

Table S1. Multivariate Cox regression and competing risk analyses in the whole cohort for mortality.

	Multivariate Cox Regression Analysis				Multivariate Competing Risk Analysis		
Parameters	HR	95% C.I.	p-value		SHR	95% C.I.	p-value
Model 1							
Age, per year	1.05	1.03-1.07	<0.001		1.05	1.03-1.07	<0.001
MELD score, per point	1.14	1.10-1.18	<0.001		1.06	1.02-1.10	0.001
Presence sarcopenia^{PMI}	1.67	1.14-2.45	0.01		1.64	1.11-2.44	0.01
Model 2							
Age, per year	1.06	1.04-1.08	<0.001		1.05	1.03-1.07	<0.001
MELD score, per point	1.14	1.10-1.18	<0.001		1.06	1.02-1.10	0.001
Presence sarcopenia^{PMI}	1.52	1.02-2.26	0.04		1.49	0.99-2.24	0.05
RFH-GA, severe malnutrition	1.95	1.20-3.16	0.007		1.69	1.03-2.75	0.04

Abbreviations: C.I. confidence interval; HR, Hazard Ratio; MELD, Model for end stage liver disease; PMI, Total psoas muscle area indexed for height at third lumbar vertebrae; RFH-GA, Royal Free Hospital Global Assessment; SHR, Subdistribution hazard ratio.

Table S2. Multivariate Cox regression analysis in the male cohort for mortality, also adjusting for etiology

	Multivariate Cox Regression Analysis, Male Cohort		
Parameters	HR	95% C.I.	p-value
Model 1			
Age, per year	1.05	1.02-1.07	<0.001
MELD score, per point	1.14	1.09-1.20	<0.001
Presence of sarcopenia PMI	2.02	1.26-3.24	0.004
Etiology, ref viral	--	--	0.26
ArLD	0.81	0.44-1.49	0.49
NAFLD	1.02	0.46-2.24	0.96
Cholestatic	1.26	0.62-2.54	0.52
Other	0.44	0.17-1.10	0.08
Model 2			
Age, per year	1.05	1.02-1.08	<0.001
MELD score, per point	1.15	1.09-1.20	<0.001
Presence of sarcopenia PMI	1.77	1.09-2.88	0.02
RFH-GA, severe malnutrition	2.00	1.08-3.71	0.03
Etiology, ref viral	--	--	0.26
ArLD	0.77	0.42-1.42	0.41
NAFLD	1.03	0.47-2.28	0.94
Cholestatic	1.12	0.55-2.28	0.76
Other	0.40	0.15-1.04	0.06

Abbreviations: ArLD: alcohol related liver disease; C.I. confidence interval; HR, Hazard Ratio; MELD, Model for end stage liver disease; NAFLD: non-alcoholic fatty liver disease; PMI, Total psoas muscle area indexed for height at third lumbar vertebrae; RFH-GA, Royal Free Hospital Global Assessment.

Table S3. Multivariate Cox regression analysis in the female cohort for mortality, adjusting for SMI as a continuous variable

	Multivariate Cox Regression Analysis, Female Cohort		
Parameters	HR	95% C.I.	p-value
Model 1			
Age, per year	1.05	1.02-1.09	0.004
MELD score, per point	1.17	1.08-1.27	<0.001
SMI, per cm^2/m^2	1.02	0.99-1.06	0.21
RFH-GA, severe malnourished	1.86	0.76-4.57	0.18
TATI, per cm^2/m^2	1.01	1.00-1.01	0.052
Model 2			
Age, per year	1.05	1.01-1.09	0.007
MELD score, per point	1.16	1.07-1.25	<0.001
SMI, per cm^2/m^2	1.02	0.99-1.07	0.20
RFH-GA, severe malnutrition	1.76	0.72-4.35	0.22
VATI, per cm^2/m^2	1.01	1.00-1.03	0.06

Abbreviations: C.I. confidence interval; HR, Hazard Ratio; MELD, Model for end stage liver disease; SMI, Total skeletal muscle area indexed for height at the third lumbar vertebrae; RFH-GA, Royal Free Hospital Global Assessment; TATI, Total adipose tissue indexed at the third lumbar vertebrae; VATI, total visceral adipose tissue indexed at the third lumbar vertebrae.

Table S4. Multivariate Cox regression analysis in the female cohort for mortality, also adjusting for etiology

	Multivariate Cox Regression Analysis, Female cohort		
Parameters	HR	95% C.I.	p-value
Model 1			
Age, per year	1.06	1.02-1.10	0.002
MELD score, per point	1.21	1.10-1.33	<0.001
Presence of sarcopenia^{PMI}	1.35	0.56-3.27	0.50
RFH-GA, severe malnourished	2.24	0.82-6.11	0.11
TATI, per cm^2/m^2	1.01	1.00-1.01	0.06
Etiology, ref viral	--	--	0.55
ArLD	0.41	0.12-1.36	0.14
NAFLD	0.61	0.16-2.25	0.45
Cholestatic	0.63	0.24-1.67	0.35
Other	0.41	0.13-1.27	0.12
Model 2			
Age, per year	1.05	1.01-1.09	0.007
MELD score, per point	1.20	1.09-1.31	<0.001
Presence of sarcopenia^{PMI}	1.18	0.51-2.72	0.71
RFH-GA, severe malnutrition	2.40	0.87-6.65	0.09
VATI, per cm^2/m^2	1.02	1.00-1.03	0.03
Etiology, ref viral	--	--	0.37
ArLD	0.33	0.10-1.11	0.07
NAFLD	0.57	0.16-2.25	0.39
Cholestatic	0.76	0.24-1.67	0.60
Other	0.37	0.13-1.27	0.09

Abbreviations: ArLD: alcohol related liver disease; C.I. confidence interval; HR, Hazard Ratio; MELD, Model for end stage liver disease; NAFLD: non-alcoholic fatty liver disease; PMI, Total psoas muscle area indexed for height at third lumbar vertebrae; RFH-GA, Royal Free Hospital Global Assessment; TATI, Total adipose tissue indexed at the third lumbar vertebrae; VATI, total visceral adipose tissue indexed at the third lumbar vertebrae.

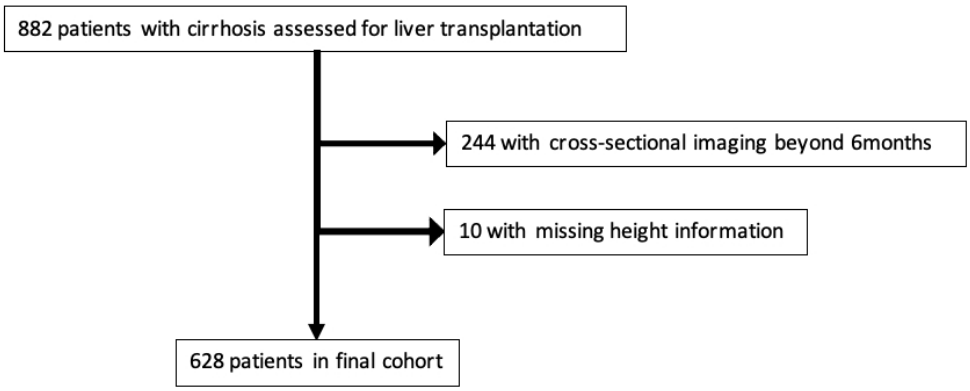

Figure 1. Patient flow chart.

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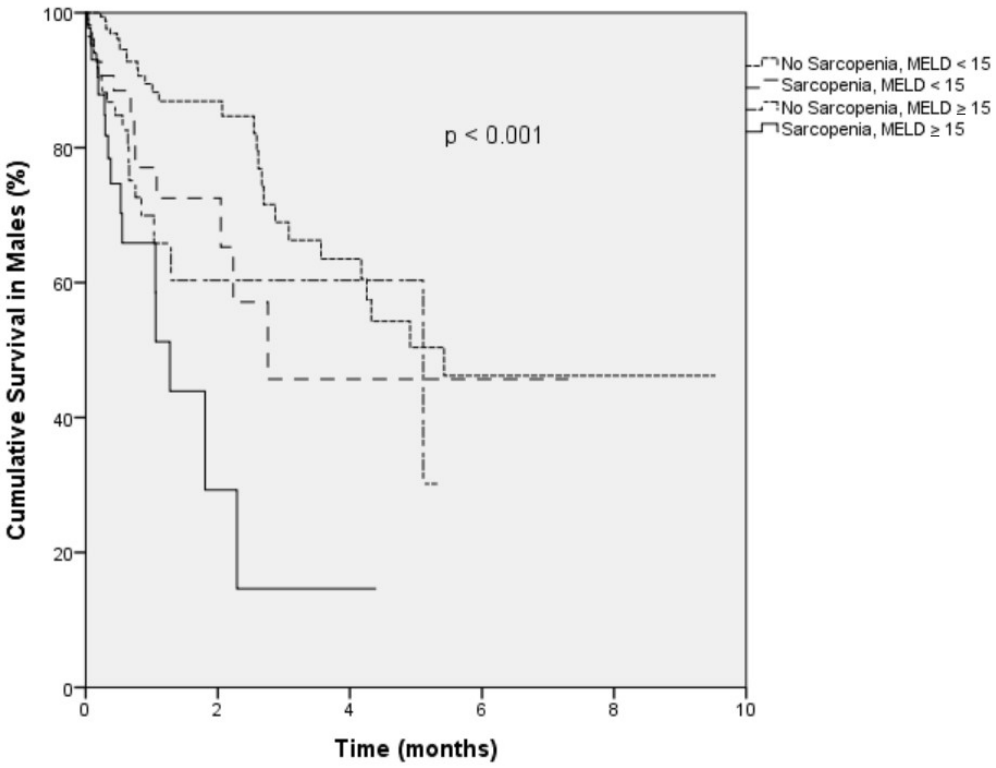

Figure 2. Kaplan Meier curve of male patients stratified by SarcopeniaPMI and MELD status.

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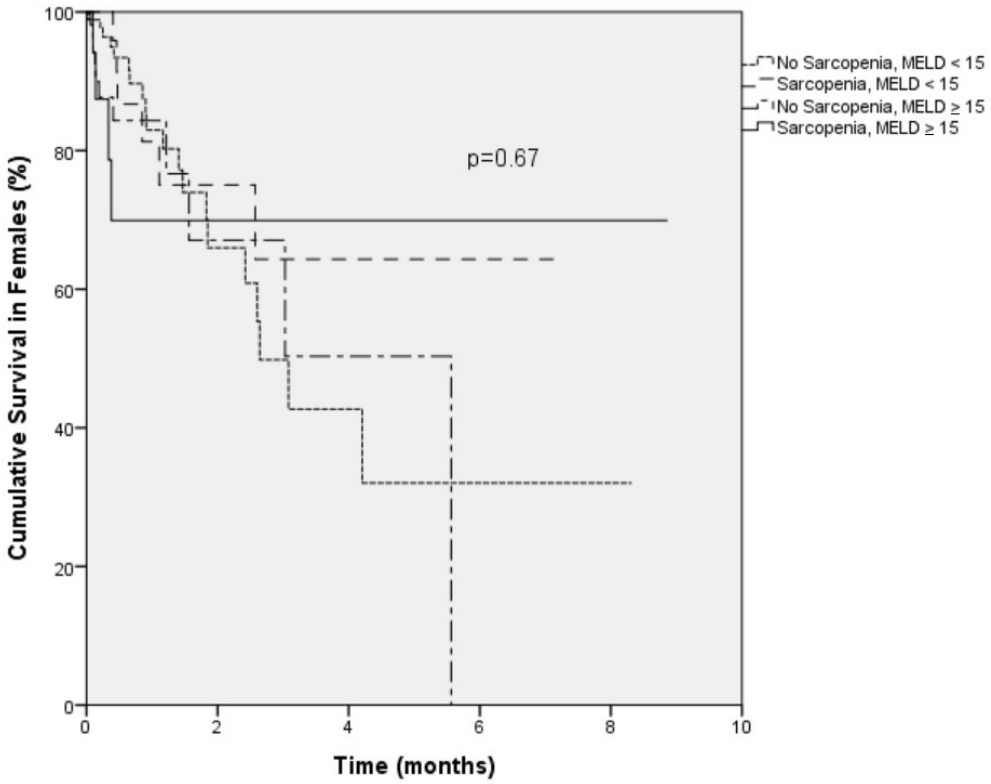

Figure 3. Kaplan Meier curve of female patients stratified by SarcopeniaPMI and MELD status.

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