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Original article

Both muscle quantity and quality are predictors of waiting list mortality in patients with end-stage liver disease

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SUMMARY

Background and aims: Malnutrition is highly prevalent in patients with end-stage liver disease (ESLD) and associated with impaired clinical outcome. Previous studies focused on one component of body composition and not in combination with nutritional intake, while both are components of the nutritional status. We aimed to evaluate the most important risk factors regarding body composition (muscle mass, muscle quality and fat mass) and nutritional intake (energy and protein intake) for waiting list mortality in patients with ESLD awaiting liver transplantation (LTx).

Methods: Consecutive patients with ESLD listed for LTx between 2007 and 2014 were investigated. Muscle mass quantity (Skeletal Muscle Mass Index, SMI), and muscle quality (Muscle Attenuation, MA), and various body fat compartments were measured on computed tomography using SliceOmatic. Nutritional intake (e.g. energy and protein intake) was assessed. Multivariable stepwise forward Cox regression analysis was used for statistical analysis.

Results: 261 Patients (mean age 54 years, 74.7% male) were included. Low SMI and MA were found to be statistically significant predictors of an increased risk for waiting list mortality in patients with ESLD, with a HR of 2.580 (95%CI 1.055–6.308) and HR of 9.124 (95%CI 2.871–28.970), respectively. No association between percentage adipose tissue, and protein and energy intake with waiting list mortality was found in this study.

Conclusion: Both low muscle quantity and quality, and not nutritional intake, were independent risk factors for mortality in patients with ESLD.

1. Introduction

The liver plays an essential role in most metabolic pathways for both macronutrients and micronutrients [1–3]. It is therefore not surprising that malnutrition is particularly common among patients with end-stage liver disease (ESLD). Malnutrition in ESLD is characterized by loss of weight and muscle mass, with or without loss of fat mass, due to energy and protein deficiency and metabolic abnormalities [4]. Depending on the diagnostic tool used, the prevalence of malnutrition in patients with ESLD varies between 65 and 100% [5]. The only curative treatment in many of these patients is liver transplantation (LTx) [6–9]. Malnutrition is associated with poor clinical outcome due to a higher risk of complications (e.g. sepsis) and mortality after LTx [10–14]. In addition, low protein intake – i.e. less than 0.8 g per kilogram body weight – was found to be an independent predictor of mortality on the waiting list for LTx in a previous study [15].

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Abbreviations

ADL	Activities of daily living
BMI	Body Mass Index
BCAA	Branched Chain Amino Acids
BIA	Bio-Electrical Impedance
BW	Body Weight
CT	Computed Tomography
DXA	Dual energy X-ray absorptiometry
AT	Adipose Tissue
ESLD	End-Stage Liver Disease
EV	Esophageal Varices
HCC	Hepatocellular Carcinoma
HE	Hepatic Encephalopathy
HU	Hounsfield Unit
HR	Hazard Ratio
INR	International Normalized Ratio of prothrombin time
IMAT	Intramuscular Adipose Tissue
IQR	Inter Quartile Range
L3	Third lumbar vertebra
LTx	Liver Transplantation
LUMC	Leiden University Medical Center
MELD	Model for End-stage Liver Disease
MA	Muscle Attenuation
MRI	Magnetic Resonance Imaging
NASH	Non-Alcohol Steatohepatitis
REE	Resting Energy Expenditure
SAT	Subcutaneous Adipose Tissue
SBP	Spontaneous Bacterial Peritonitis
SMI	Skeletal Muscle Mass Index
SMM	Skeletal Muscle Mass
RA	Refractory Ascites
TEE	Total Energy Expenditure
US	Ultrasonography
VAT	Visceral Adipose tissue
VSFR	Visceral to Subcutaneous Fat Ratio
WHO	World Health Organisation

Nowadays, dietetic treatment in patients with ESLD is focused on a healthy body mass index (BMI) (20–25 kg/m^2), but body composition may be more important because, low skeletal muscle mass (SMM e.g. sarcopenia) and high adipose tissue are related to poor clinical outcome in patients with ESLD [10–14,16]. At this moment, graft allocation for LTx is based on the Model for End-stage Liver Disease (MELD) score in many countries. The MELD score predicts the urgency for LTx based on the predicted 3 months mortality. Interestingly, despite the association with outcome on the waiting list and in contrast to the original Child-Turcotte score, parameters measuring nutritional status including body composition are not included in the MELD [17].

Malnutrition can be defined as “a state resulting from lack of uptake or intake of nutrition leading to altered body composition and body cell mass leading to diminished physical and mental function and impaired clinical outcome of disease” [18]. Body weight and BMI are inaccurate as markers of nutritional status in patients with ESLD because of the incapability differentiating body composition. The presence of ascites and high adipose tissue mass may mask the loss of SMM and altered body composition in patients with ESLD [19]. Computed tomography (CT) is considered as one of the reference methods for analysing body composition with low inter- and intra-observer variability [20–24]. Other techniques to analyse the body composition are Dual energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI) and ultrasonography (US). DXA is not accurate in differentiating between different types of adipose tissue and US has poor reproducibility and accuracy in general. MRI and CT scans are both accurate methods, but MRI is expensive and limited accessible. CT scan is part of diagnostic evaluation of the patients during the screening for LTx. With the use of CT, both SMM, as well as other compartments of the body tissue, including different types of adipose tissue can be evaluated independently with a high accuracy [25].

No previous studies have been performed on the association between the combination of nutritional data with all components of body composition, including SMI (a measure of muscle quantity), muscle attenuation (MA, a measure of muscle quality), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), intramuscular adipose tissue (IMAT), and visceral to subcutaneous fat ratio (VSFR) with mortality on the waiting list for LTx. This study aims to evaluate if and which of the aforementioned parameters of body composition and nutritional intake are risk factors for mortality in patients with ESLD on the waiting list for LTx.

2. Materials and methods

2.1. Study design

This was a single-centre cohort study with patients from the Leiden University Medical Center (LUMC), Leiden, the Netherlands, a tertiary referral centre for liver disease and LTx. Data were retrospectively collected from electronic patient files (HIX, Chipsoft, The Netherlands) until 31 December 2016.

2.2. Study population

For this study, medical and dietetic records of 261 consecutive patients with ESLD listed between 2007 and 2014 at the LUMC for LTx were used, derived from the Eurotransplant registry [26]. The inclusion criteria for participants in this study were: a minimum age of 18, the presence of chronic liver disease, and being on the waiting list for LTx. Excluded from this study are patients who needed multiple organ transplantations, suffered from acute liver failure, had re-transplantations, or had a missing abdominal CT. Transplantation, mortality, or removal from the transplantation waiting list for other (medical) reasons terminated the follow-up period, with censoring in the analysis. The science committee of the Department of Gastroenterology and Hepatology of the LUMC and the Medical Ethical Committee approved this study and because of the retrospective study on existing data a waiver for informed consent was granted.

2.3. Study parameters

2.3.1. Clinical and laboratory assessment

Patient characteristics comprise age, gender, and clinical data such as primary liver disease and indication for LTx, body weight (BW, in kilogram), height (in centimeter), date of listing, date of transplantation or removal from the transplantation waiting list and laboratory assessments, which include International Normalized Ratio of prothrombin time (INR), bilirubin, creatinine and MELD score $(((0.957 * \ln(\text{Creatinine in mg/dL})) + (0.378 * \ln(\text{Bilirubin in mg/dL})) + (1.12 * \ln(\text{INR}))) + 6.43)$. Smoking and activity of

daily living (ADL) dependency were gathered from electronic patient files.

2.3.2. Body composition

Body composition was determined with single slice contrast abdominal CT images using SliceOmatic (Tomovision, Montreal, Canada) [20]. CT was performed with three types of CT scanners: Toshiba 64-slice, Aquillion One (16 cm detector), and Aquillion One Genesis (16 cm detector). All 4-phase CT scans were made for diagnostic reasons with contrast using one strict protocol. The axial abdominal CT closest to the date of placement (maximum 3 months) on the waiting list for liver transplantation was used. All CT images were analysed by four trained researchers blinded for clinical outcomes (AD, CL, DB, MvV). Before analysing the CT scans, the four researchers examined three identical CT scans independently and discussed differences until consensus was reached to maximize the inter-observer reliability. The intra-class correlation coefficient between the four researchers was 0.99 (C.I. 0.98–1.00, $P < 0.001$).

Different body tissues were studied in the cross-sectional areas of in the middle of the third lumbar vertebra (L3) level with CT scan (surface in cm^2: SMM, MA, IMAT, SAT and VAT) [16]. SMM was corrected for height by calculation the Skeletal Muscle Mass Index (SMI). Based on the density of the different types of body tissues, using Hounsfield Units (HU), the tissue of interest was assessed. Furthermore, the CT scans were analysed by examining the density of different types of body tissues. The corresponding HU thresholds were −29 to 150 for SMM, −190 to −30 for IMAT, −190 to −30 for SAT and −150 to −50 for VAT [22,27–29]. MA is an indirect method for measuring the infiltration of fat into the SMM and a method for analysing the quality of the SMM. MA (e.g. myosteatosis) was assessed using mean HU of the skeletal muscle area at L3 level [30]. VSFR was calculated by the ratio of the VAT area to the SAT area [27,31].

2.3.3. Nutritional intake

Assessment of nutritional status was performed prospectively at screening for LTx and included not only assessment of body composition but also assessment of daily nutritional intake by a dietician. Dietary consultation was performed at the time of screening for LTx by two experienced dieticians and was performed according to the Dutch dietary treatment protocol liver diseases [32]. This included measuring of body weight and height, structured assessment of nutritional intake and difficulties eating. Data on dietary intake was collected from the electronic patient files and recalculated for intake of energy (kilocalories) and protein (gram) with the use of the Dutch Nutrition File ('eetmeter') from The Netherlands Nutrition Centre [33,34]. Dietary intake of energy and protein was compared to the dietary recommendations. If the exact amount consumed was not reported in the electronic patient files, we used standardized portion sizes. The individual energy needs were calculated with the World Health Organization (WHO) equation for resting energy expenditure (REE) with an additional 30% to account for physical activity and disease based on a patient's age, BW (estimated dry weight if ascites was present), and height to calculate the total energy expenditure (TEE) [35]. The protein intake was calculated as gram per kilogram body weight (dry weight if ascites was present). The protein recommendation for patients with liver cirrhosis was set at 1.2 g per kilogram (dry weight if ascites was present) BW [36,37]. All patients received individual nutritional advise based on their nutritional needs by the dietician.

2.4. Outcome measures

Data regarding mortality, which is the main outcome variable of this study, transplantation, or other reasons for removal from the waiting list were obtained from the electronic patient files and the Eurotransplant Registry. Other reasons for removal from the waiting list had been recorded, such as improved clinical status, or being non-transplantable (e.g. due to a non-curative malignancy).

2.5. Statistical analyses

Descriptive analysis of baseline characteristics was performed for the population (N (%), mean (sd)) or median (Interquartile range). The main outcome of this study was mortality during the waiting list period (dichotomous). The main determinants in this study comprised all the components of body composition and nutritional intake: SMI, VAT, SAT, and IMAT, MA, VSFR, protein intake (gram/kg BW) and energy intake (as percentage of requirements). All determinants were analysed as continuous variables and were checked for linearity before the analysis. Dummy variables based on quartiles were made if there was no linearity based on the optimal reference categories e.g. lowest category for IMAT, SAT, VAT and VSFR and the highest category for SMI, MA, protein and energy intake. Time was measured in days from date of listing until transplantation, when mortality occurred, or until the end of data collection on 31 December 2016. Likewise, LTx caused censoring, but this was not counted as an event. If patients were removed from the waiting list because of reasons other than transplantation or mortality, the reason for removal was used for categorizing these patients. Consequently, patients who were removed because of their degenerated clinical status were analysed as non-survivors, while those who were removed because of their stable or improved clinical status were considered as survivors.

A prediction model was made to predict the risk of waiting list mortality including the continuous data of body composition and nutritional data in the analysis. General and disease-specific data were added also to the model. Multivariable stepwise forward Cox regression analysis was used and parameters were checked for co-linearity. All variables with a p-value <0.20 in univariable analysis were included in multivariable analysis. Age (continuous), sex (dichotomous), smoking (categorical), ADL dependency (dichotomous), and MELD score (continuous) were checked for confounding by adding these determinants into the model. These factors were related based on previous research to an individual's body composition and mortality risk [38–40]. In order to check if these missing data resulted in different outcomes, we included a sensitivity analysis with only complete cases. A p-value <0.05 was considered significant in the final model. All analyses were performed using IBM statistics SPSS version 23 [41].

3. Results

3.1. Baseline characteristics

Three hundred forty five patients were listed for LTx in the observed period. In total, 261 (75.6%) patients were included based. Fig. 1 shows a flowchart with the division of survivors and non-survivors. 60 patients were scored as non-survivors of whom 37 died during the waiting list period and 23 were removed from the waiting list because of a worsened clinical status (progression HCC (N = 5), not anymore meeting the Milan criteria (N = 15),

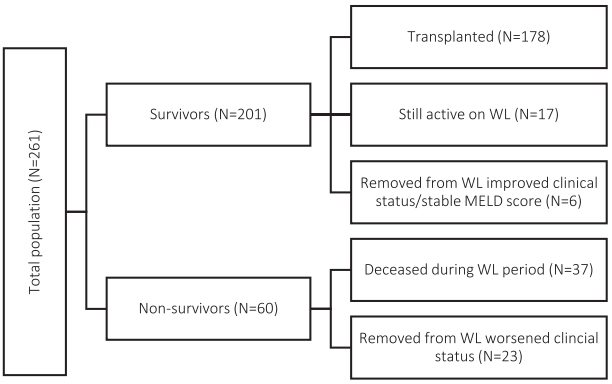

Fig. 1. Distribution of survivors and non-survivors.

cholangiocarcinoma (N = 1) and for unknown reasons (N = 1)). The mean time on the waiting list for survivors was 275 days versus 171 days for non-survivors. Table 1 presents the population characteristics at the moment of screening for LTx. Baseline characteristics in both groups were comparable. The mean time between CT scan and the date of listing for liver transplantation was fifty days. The mean time between the consultation with the dietician and the listing for transplantation was fifty days.

3.2. Body composition and nutrient intake

Table 2 shows the results of CT scan body composition analysis and nutritional intake for survivors and non-survivors. The groups were comparable, regarding energy and protein intake and body composition as measured with CT at the liver transplantation screening. Mean MA, was significantly higher in the survivors, whereas VAT was significantly higher in the non-survivors. SMI was higher in the survivor group, although this was not statistically significant.

3.3. Univariable and multivariable analysis

The results of the univariable and multivariable analysis for the total study population are shown in Table 3. Significant results in univariable analysis were found in SMI, MA and IMAT. The lowest quartiles of SMI and MA showed an increased risk of mortality during the waiting list compared to the highest quartile. The highest quartile of IMAT was in the univariable analysis also found as a statistically significant predictor of waiting list mortality compared to the lowest quartile. In the multivariable analysis, we found SMI, MA and IMAT to be statistically significant predictors of waiting list mortality. The first quartile with the lowest SMI (<70.8 cm^2/m^2) was found to be a significant predictor of mortality during the waiting list period with a HR of 2.580 (95%C.I. 1.06–6.31) compared with the highest quartile (>94.02 cm^2/m^2). Also in the MA, the lowest quartile (<34.0) had a higher risk of waiting list mortality compared to the highest quartile (>47.8) with a HR of 9.12 (95%C.I. 2.87–28.97). Moderate IMAT between 6.02 and 8.97 cm^2 on L3 level was found as a negative predictor of waiting list mortality in our cohort with a HR of 0.41 (95%C.I. 0.15–1.17). The results in the multivariable analysis were adjusted for age, gender, MELD score, ADL dependency, and smoking as confounders.

Table 1
Baseline population characteristics at the moment of screening for liver transplantation.

	Total (N = 261)	Survivors (N = 201)	Non-survivors (N = 60)	P-value
Age (years)	54.0 (10.1)	53.7 (10.05)	55.2 (10.39)	0.31
Gender Male (%)	195 (74.7)	148 (73.6)	47 (78.3)	0.45
Primary liver disease				0.84
Alcoholic Cirrhosis	88 (33.7)	66 (32.8)	22 (36.7)	
Cholestatic Disease	37 (14.2)	30 (14.9)	7 (11.7)	
Hepatocellular Cancer	36 (13.8)	25 (12.4)	11 (18.3)	
Hepatitis C	31 (11.9)	24 (11.9)	7 (11.7)	
Hepatitis B	19 (7.3)	13 (6.5)	6 (10.0)	
NASH	16 (6.1)	13 (6.5)	3 (5.0)	
Auto-immune hepatitis	9 (3.4)	8 (4.0)	1 (1.7)	
Biliary Cholangitis	8 (3.1)	7 (3.5)	1 (1.7)	
Metabolic disease	8 (3.1)	8 (4.0)	0 (0)	
Cryptogenic	5 (1.9)	4 (2.0)	1 (1.7)	
Other not specified	3 (1.1)	2 (1.0)	1 (1.7)	
Hemochromatosis	1 (0.4)	1 (0.5)	0 (0)	
HCC (yes)	104 (39.8)	78 (38.8)	26 (43.3)	0.55
Complications before listing				
SBP (yes)	44 (17.1)	32 (16.1)	12 (21.1)	0.38
RA (yes)	41 (16.1)	31 (16.0)	10 (17.2)	0.80
HE (yes)	66 (26.0)	43 (21.8)	23 (40.4)	<0.01*
EV (yes)	169 (66.0)	131 (65.8)	38 (66.7)	0.89
MELD score	13.2 (6.4)	13.3 (6.5)	12.8 (6.0)	0.54
Bilirubin (μmol/L)	84.2 (149.8)	67.5 (114.0)	140.1 (225.1)	<0.01*
INR (ratio)	1.3 (0.4)	1.2 (0.3)	1.4 (0.5)	0.02*
Creatinine (μmol/L)	83.6 (38.0)	82.7 (38.3)	86.6 (37.1)	0.47
ADL independent (yes)	225 (90.0)	170 (88.1)	55 (96.5)	0.06
Smoking				0.39
Current	75 (37.9)	60 (32.3)	15 (26.3)	
Never	92 (30.9)	72 (38.7)	20 (35.1)	
Former[a]	76 (31.3)	54 (29.0)	22 (38.6)	

Population characteristics at the moment of screening for liver transplantation are presented in total population, persons who survived the waiting list, and persons who died during waiting list period. Results are given in N (%) or mean (sd). Abbreviations and acronyms: cm = centimeter, m = meter, m^2 = squared meter, kg = kilogram, g = gram, L = liter, NASH = non-alcoholic steatohepatitis, HCC = hepato-cellular carcinoma, SPB = spontaneous bacterial peritonitis, RA = refractory ascites, HE = hepatic encephalopathy, EV = Esophageal varices, ADL = activity of daily living, WL = waiting list.
*P < 0.05 was considered significant.
[a] Former smoker, if person quit smoking more than 4 weeks before screening.

Table 2
Body composition and nutritional data at screening.

	Survivors (N = 201)	Non-Survivors (N = 60)	P-value
Skeletal Muscle Mass Index (cm^2/m^2)	84.23 (17.2)	77.9 (14.0)	0.20
Muscle Attenuation (mean HU)	42.0 (9.2)	37.4 (10.7)	0.01*
Intramuscular Fat (cm^2)	7.3 (6.3)	8.1 (6.6)	0.78
Visceral Fat (cm^2)	102.33 (77.7)	114.0 (92.8)	0.03*
Subcutaneous fat (cm^2)	145.5 (91.4)	147.8 (92.7)	0.86
Visceral to Subcutaneous Fat Ratio (ratio)	0.8 (0.6)	0.9 (0.6)	0.13
Energy intake (% of requirements)	90.5 (26.6)	87.2 (28.6)	0.34
Protein intake (gr/kg BW)	1.1 (0.4)	1.1 (0.6)	0.10

Results of nutritional data and body composition analysis with computed tomography per group of survivors and non-survivors during waiting list period. Results are given in mean (sd). Abbreviations: cm^2 = square centimeter, gr = gram, kg = kilogram, BW = body weight, HU= Hounsfield unit.
*P < 0.05 was considered significantly different.

3.4. Sensitivity analysis

The results of the sensitivity analysis are presented in Table 4. In the multivariable sensitivity analysis, a significantly increased risk for waiting list mortality was found in the lowest quartile of SMI with a HR op 2.55 (95%CI 0.90–7.28) compared to the highest quartile. In MA all quartiles had a significantly increased risk of waiting list mortality compared to the reference quartile which was set on the highest density of the muscle mass, respectively a HR of 8.88 (95%CI 1.95–40.41) for the first quartile, the second quartile a HR 3.65 (95%CI 0.91–14.68) and a HR of 3.67 (95%CI 1.10–12.20). IMAT was not found statistically significantly related with mortality during the waiting period for LTx.

Table 3
Univariable and multivariable Cox-regression analysis for risk factors for waiting list mortality in patients with end-stage liver cirrhosis.

	Univariable analysis			Multivariable analysis (N = 219)[a]		
	Regression coefficient (Standard Error)	Hazard Ratio (Confidence Interval)	P-value	Regression coefficient (Standard Error)	Hazard Ratio (Confidence Interval)	P-value
Skeletal Muscle Mass Index (cm^2/m^2) (N = 244)						
1st quartile: <70.8 cm^2/m^2	0.57 (0.38)	1.77 (0.84–3.70)	0.13*	0.95 (0.46)	2.58 (1.06–6.31)	0.04*
2nd quartile: 70.8–83.2 cm^2/m^2	0.24 (0.39)	1.27 (0.59–2.76)	0.54	0.45 (0.46)	1.56 (0.64–3.83)	0.33
3rd quartile: 83.2–94.0 cm^2/m^2	−0.05 (0.41)	0.96 (0.43–2.13)	0.91	−0.18 (0.44)	0.84 (0.36–1.97)	0.68
4th quartile: > 94.0 cm^2/m^2	Reference	Reference		Reference	Reference	
Muscle Attenuation (mean HU) (N = 244)						
1st quartile: <34.1	1.39 (0.40)	4.01 (1.84–8.77)	<0.01*	2.21 (0.59)	9.12 (2.87–28.97)	<0.01*
2nd quartile: 34.1–42	0.55 (0.44)	1.73 (0.73–4.12)	0.22	1.03 (0.57)	2.81 (0.93–8.53)	0.22
3rd quartile: 42.1–47.8	0.43 (0.42)	1.53 (0.64–3.64)	0.34	0.80 (0.50)	2.22 (0.83–5.93)	0.18
4th quartile: > 47.8	Reference	Reference		Reference	Reference	
Intramuscular Fat (cm^2) (N = 244)						
1st quartile: < 3.3 cm^2	Reference	Reference		Reference	Reference	Reference
2nd quartile: 3.3–6.0 cm^2	0.29 (0.38)	1.34 (0.64–2.82)	0.44	0.08 (0.43)	1,09 (0.47–2.54)	0.85
3rd quartile: 6.0–9.0 cm^2	−0.50 (0.49)	0.61 (0.23–1.61)	0.32	−0.88 (0.53)	0.41 (0.15–1.17)	<0.01*
4th quartile: > 9.0 cm^2	0.58 (0.35)	1.78 (0.89–3.56)	0.10*	−0.58 (0.48)	0.56 (0.22–1.43)	0.23
Visceral Fat (cm^2) (N = 243)						
1st quartile: <40.2 cm^2	Reference	Reference				
2nd quartile: 40.2–84.2 cm^2	0.21 (0.38)	1.23 (0.58–2.60)	0.59			
3rd quartile:84.2–146.8 cm^2	−0.19 (0.40)	0.83 (0.38–1.81)	0.64			
4th quartile: > 146.8 cm^2	0.14 (0.38)	1.15 (0.55–2.43)	0.71			
Subcutaneous fat (cm^2) (N = 203)						
1st quartile: <83.8 cm^2	Reference	Reference				
2nd quartile: 83.8–127.7 cm^2	0.40 (0.42)	1.49 (0.65–3.41)	0.34			
3rd quartile: 127.7–193.9 cm^2	0.23 (0.43)	1.25 (0.54–2.90)	0.60			
4th quartile: > 193.9 cm^2	−0.12 (0.46)	0.89 (0.36–2.18)	0.79			
VSFR (ratio) (N = 203)						
1st quartile: <0.4	Reference	Reference				
2nd quartile: 0.4–0.7	0.25 (0.43)	1.29 (0.56–2.99)	0.55			
3rd quartile: 0.7–1.0	0.30 (0.42)	1.34 (0.59–3.07)	0.48			
4th quartile: > 1.0	0.32 (0.42)	1.38 (0.60–3.14)	0.45			
Energy intake (% of requirements)						
<50% (N = 11)	0.45 (0.64)	1.56 (0.44–5.52)	0.49			
50–75% (N = 64)	0.16 (0.38)	1.18 (0.560–2.47)	0.67			
75–100% (N = 77)	0.11 (0.37)	1.12 (0.54–2.30)	0.77			
>100% (N = 70)	Reference	Reference				
Protein intake (g/kg BW)						
<0.8 g/kg/day (N = 49)	0.37 (0.38)	1.45 (0.70–3.06)	0.33			
0.8–1.2 g/kg/day (N = 87)	0.25 (0.34)	1.28 (0.66–2.50)	0.47			
>1.2 g/kg/day (N = 86)	Reference	Reference				

Results of Cox-regression analysis with univariable analysis and multivariable analysis for waiting list mortality. Abbreviations: HU = Hounsfield Unit, cm^2 = square centimeter, g = gram, kg = kilogram, BW = body weight, HU= Hounsfield unit, VSFR = visceral to subcutaneous fat ratio.
*In univariable analysis P < 0.2 and in multivariable analysis a P < 0.05 were considered significant.
[a] Multivariable analysis adjusted for age, gender, MELD score, smoking and ADL independency.

Table 4
Univariable and multivariable Cox-regression sensitivity analysis of risk factors for waiting list mortality in patients with end-stage liver cirrhosis in complete cases (N = 159).

	Univariable analysis			Multivariable analysis[a]		
	Regression coefficient (Standard Error)	Hazard Ratio (Confidence Interval)	P-value	Regression coefficient (Standard Error)	Hazard Ratio (Confidence Interval)	P-value
Skeletal Muscle Mass Index (cm^2/m)						
1st quartile: <70.8 cm^2/m^2	0.70 (0.450)	2.01 (0.83–4.85)	0.12*	0.94 (0.54)	2.55 (0.90–7.28)	0.08
2nd quartile: 70.8–83.2 cm^2/m^2	0.09 (0.518)	1.09 (0.40–3.01)	0.87	0.30 (0.54)	1.35 (0.43–4.20)	0.61
3rd quartile: 83.2–94.0 cm^2/m^2	0.01 (0.500)	1.01 (0.38–2.70)	0.98	−0.03 (0.52)	0.97 (3.50–2.69)	0.95
4th quartile: > 94.0 cm^2/m^2	Reference	Reference		Reference	Reference	
Muscle Attenuation (mean HU)						
1st quartile: <34.1	1.59 (0.528)	4.89 (1.74–13.75)	<0.01*	2.184 (0.77)	8.88 (1.95–40.41)	0.005*
2nd quartile: 34.1–420.	0.92 (0.559)	2.51 (0.84–7.50)	0.10*	1.295 (0.71)	3.65 (0.91–14.68)	0.07*
3rd quartile: 42.1–47.8	1.02 (0.562)	2.77 (0.92–8.33)	0.07*	1.299 (0.61)	3.67 (1.10–12.20)	0.03*
4th quartile: > 47.8	Reference	Reference		Reference	Reference	
Intramuscular Fat (cm^2)						
1st quartile: < 3.3 cm^2	Reference	Reference		Reference	Reference	
2nd quartile: 3.3–6.0 cm^2	0.20 (0.505)	1.23 (0.46–3.30)	0.69	0.049 (0.55)	1.05 (0.36–3.07)	0.93
3rd quartile: 6.0–9.0 cm^2	−0.31 (0.63)	0.73 (0.21–2.51)	0.62	−0.907 (0.72)	0.40 (0.10–1.69)	0.21
4th quartile: > 9.0 cm^2	0.83 (0.45)	2.30 (0.94–5.59)	0.07*	0.064 (0.67)	1.07 (0.29–3.98)	0.92
Visceral Fat (cm^2)						
1st quartile: <40.2 cm^2	Reference	Reference				
2nd quartile: 40.2–84.2 cm^2	0.34 (0.46)	1.40 (0.57–3.48)	0.46			
3rd quartile:84.2–146.8 cm^2	−0.07 (0.50)	0.94 (0.35–2.51)	0.89			
4th quartile: > 146.8 cm^2	0.11 (0.46)	1.12 (0.45–2.76)	0.81			
Subcutaneous fat (cm^2)						
1st quartile: <83.8 cm^2	Reference	Reference				
2nd quartile: 83.8–127.7 cm^2	0.54 (0.48)	1.71 (0.67–4.36)	0.26			
3rd quartile: 127.7–193.9 cm^2	0.29 (0.49)	1.34 (0.51–3.52)	0.56			
4th quartile: > 193.9 cm^2	−0.37 (0.54)	0.69 (0.24–1.97)	0.49			
VSFR (ratio)						
1st quartile: <0.4	Reference	Reference				
2nd quartile: 0.4–0.7	0.06 (0.49)	1.06 (0.41–2.74)	0.91			
3rd quartile: 0.7–1.0	0.21 (0.47)	1.24 (0.49–3.14)	0.65			
4th quartile: > 1.0	0.17 (0.48)	1.19 (0.46–3.08)	0.73			
Energy intake (% of requirements)						
<50% (N = 7)	−0.48 (1.05)	0.62 (0.08–4.80)	0.64			
		1.05 (0.45–2.48)				
50–75% (N = 41)	0.05 (0.44)	1.02 (0.46–2.25)	0.91			
75–100% (N = 57)	0.02 (0.40)	Reference	0.96			
>100% (N = 54)	Reference					
Protein intake (g/kg BW)						
<0.8 g/kg/day (N = 29)	0.08 (0.47)	1.08 (0.43–2.73)	0.86			
0.8–1.2 g/kg/day (N = 61)	0.29 (0.37)	1.34 (0.65–2.79)	0.43			
>1.2 g/kg/day (N = 69)	Reference	Reference				

Results of Cox-regression analysis with univariable analysis and multivariable analysis for waiting list mortality, including only complete cases. Abbreviations: HU = Hounsfield Unit, cm^2 = square centimeter, g = gram, kg = kilogram, BW = body weight, HU = Hounsfield unit, VSFR = visceral to subcutaneous fat ratio.
*In univariable analysis P < 0.2 and in multivariable analysis a P < 0.05 were considered significant.
[a] Multivariable model adjusted for age, gender, MELD score, smoking and ADL independency.

4. Discussion

Our study indicates that both a lower muscle quality, represented by MA, and muscle quantity, represented by SMI are independently related to increased risk of mortality in patients with end-stage liver disease on the waiting list for LTx. In addition, intramuscular adipose tissue (IMAT) might be a negative predictor of mortality, however this result was not confirmed in the sensitivity analysis. Other components of body composition or nutritional intake were not significantly associated with waitlist mortality. Visceral adipose tissue was higher in the non-survivor group as compared to the survivor group at the time of screening, but was not found to be predictive for waitlist mortality in the final model.

Our findings on muscle quantity are in line with multiple other studies demonstrating that sarcopenia, defined as low SMI, is strongly associated with negative outcome prior to and after LTx [16,42]. In addition to these studies, we found that the quality of the skeletal muscle mass is also statistically associated with mortality. The etiology of abnormal muscle quality in patients with ESLD has not been fully explained yet, but it seems to be related to the metabolic abnormalities caused by liver failure. Gluconeogenesis, glycogenolysis, ketogenesis, and dysregulation of fat oxidation might result in muscle abnormalities [43]. Muscle wasting is an important complication of ESLD and multicausal. It can be explained by a reduced nutrient intake due to the illness and dietary restrictions, but also several important mechanism contribute to muscle wasting in ESLD. Multiple metabolic hepatic pathways can be deranged and may contribute to malnutrition. High protein catabolism, insulin resistance, increased fat turnover and increased energy expenditure contribute to a hypermetabolic state. Skeletal muscle autophagy is enhanced in liver cirrhosis and potentially mediated by hyperammonaemia or hepatic encephalopathy [10].

In our study, SMI was found to be significantly associated with an increased risk of waiting list mortality, but only in the lowest quartile. This might be explained by the fact that SMI at the beginning of the waiting list period was relatively high in our population, compared to the cut-off points for SMI which were established for oncology patients [30].

The study of Fujiwara showed that low intramuscular fat deposition in the muscle was an independent predictor of survival in patients with HCC [44]. In our study, only the third quartile of

IMAT was found as a statistically significant predictor for waiting list mortality; however, our study population of patients with ESLD was more heterogeneous. Besides, despite the high intra-class correlation coefficient among the four observers, we expected that IMAT content analysed with CT might be less accurate because this is only a small part of the CT image and is therefore sensitive to inter-observer differences, as is found in studies with MRI body composition analysis [45,46].

Protein and energy malnutrition is often described as a negative prognostic factor in patients awaiting LTx; however, this is mostly measured with screening tools for malnutrition without objective dietary intake measurements such as dietary history or food diaries. In the current study, protein intake has not been found to be a significant predictor of waiting list mortality, although the direction of the regression coefficient indicates a lower mortality risk in patients with higher protein intake; this is in contrast with the study of Ney et al., who found a significant association between protein intake and higher risk of mortality with low protein intake during the waiting list period [15]. An explanation for this difference might be the method for assessing the protein intake in these studies. Ney et al. recorded protein intake by a two-day recall, while in the current study, protein intake was obtained from dietary consultations just before placement on the waiting list. Few people in the Netherlands have inadequate intake of protein because of the high proportion of meat, dairy, and cheese common in the Dutch food pattern [47]. Since muscle mass is related to protein intake, this might result in a relatively high skeletal muscle mass in our study population compared to other populations; however, the mean protein intake in our population was lower than the recommendations in patients with ESLD [36,37]. In addition, protein intake can be influenced by dietetic or nutritional advice patients received before the moment of waiting list screening, for example in referring hospitals; however, these data is lacking in our cohort. Since the relatively high intake of energy and protein in our study population, we expect that many patients received nutritional advise prior to the screening, including advice to frequently use small meals with an evening-snack and a good breakfast [48]. The type of protein or amino-acid was also not included in our study. Some literature suggests that protein intake, especially Branched Chain Amino Acids (BCAA) and leucine, might have a positive effect on muscle anabolism and protein synthesis [49,50]. In a recent trial in patients with liver cirrhosis, the intervention group with a high protein and fibre diet, combined with BCAA supplementation showed an increase in muscle mass and a decrease in FM compared with the control group, but the effects on muscle attenuation were not described [51].

Our study is limited by the fact that energy recommendations were calculated with equations to predict the energy needs of individuals, while measuring the REE with indirect calorimetry is recommended in patients with ESLD. Due to the retrospective design of our study, no indirect calorimetry data was available. Objective data regarding physical activity and sports at the moment of screening were also lacking. Muscle quantity and quality are correlated with the level of physical activity, but physical activity levels are lower in patients with liver cirrhosis compared to healthy subjects [52,53]. Resistance training might increase muscle attenuation in elderly, but this is not confirmed in liver cirrhosis patients yet [40]. Nevertheless increase of muscle mass has been found in two intervention studies with exercise programs in patients with liver cirrhosis [54,55]. All previously mentioned studies did not analyse the effects of physical activity on muscle quality. Intervention studies measuring this effect in patients with ESLD are therefore needed.

To the best of our knowledge, our study is the first study which combines nutritional data and body composition data. Both reduced muscle quantity and quality, increased the risk of mortality in patients with ESLD during the waiting list period for LTx. Besides, a moderate IMAT was associated with a decreased risk of mortality. Due to the homogenous character of our population and the consecutive inclusion, the results of this study can be generalized to other ESLD patients who are listed for LTx. Therefore, body composition analysis, especially SMI, MA and IMAT, may have an added value in identifying patients who are at risk for mortality during the waiting list period. Since all patients have a CT scan during their screening period standard analysis for SMI, MA and IMAT is relatively easy to implement. More research into the causal relationships and improving the body composition during the waiting list period is needed to give specific recommendations for our patient population and in order to reduce their mortality risk. In addition, the added value of adding data from body composition analysis for graft allocation in combination with MELD-scores should be evaluated.

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Authors contribution

Daphne Bot: Participated in research design, writing the paper, performance of research, data collection and data analysis. Anneke Droop: Participated in research design, performance of research and data collection. Claudia J. Lucassen: Participated in data collection.

Mariëlle E. van Veen: Participated in data collection.

Jeroen L.A. van Vugt: Participated in research design and data collection.

Shirin Shahbazi Feshtali: Participated in data collection.

Eva Leistra: Participated in research design, writing the paper, performance of research, data collection and data analysis.

Maarten E. Tushuizen: Participated in writing the paper.

Bart van Hoek: Participated in research design, writing the paper, performance of research, data collection and data analysis.

Declaration of competing interest

The Authors declare that there is no conflict of interest.

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