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CE Association between skeletal muscle index prior to liver transplantation and 1-year mortality posttransplant

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Abstract

Background: Liver transplantation is the only curative therapy for end-stage liver disease (ESLD). Sarcopenia is often defined as the loss of muscle quantity (skeletal muscle index [SMI]), but muscle attenuation (MA), a surrogate marker of muscle quality, is also decreased in ESLD. We assessed pre-liver transplant SMI and MA and their association with posttransplant mortality, complications, and length of intensive care unit (ICU) and hospital stay.

Methods: In 169 consecutive patients with ESLD who underwent a liver transplantation between 2007 and 2014, SMI and MA were measured on computed tomography scans at time of placement on the waiting list for liver transplantation. The primary outcome of interest was 1-year posttransplant mortality. Secondary posttransplantation outcomes of interest were complications within 30 days and length of stay in the ICU > 3 days and in the hospital >3 weeks. Logistic and Cox regression analyses were performed.

Results: MA was associated with 1-year posttransplant mortality rate (hazard ratio=0.656, 95% CI=0.464–0.921, $P = 0.015$). The highest quartile of SMI had a lower odds for the total length of stay in the hospital lasting >3 weeks (odds ratio=0.211, 95% CI=0.061–0.733, $P = 0.014$). MA was associated with a prolonged ICU stay; this was, however, not statistically significant after adjustment for age, sex, and Model for ESLD score.

Conclusion: Lower MA is associated with a longer length of ICU stay and 1-year mortality after liver transplantation, whereas low SMI was associated with a total length of hospital stay.

KEYWORDS

computed tomography, end-stage liver disease, liver cirrhosis, liver transplantation, muscle mass, myosteatosis, sarcopenia

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CLINICAL RELEVANCY STATEMENT

Liver transplantation is the only curative therapy for patients with end-stage liver disease (ESLD). Sarcopenia is often defined as the loss of muscle quantity (skeletal muscle index [SMI]), but muscle attenuation (MA) is also decreased in ESLD. We assessed pre-liver transplant SMI and muscle attenuation and their association with posttransplant mortality rate, complications, and length of intensive care unit (ICU) and hospital stay and found that MA was associated with a longer length of stay in the ICU and a 1-year mortality rate. Quartiles of SMI were associated with a longer total length of stay in the hospital. These findings confirm the clinical importance of both muscle quantity and quality in patients with ESLD. The results of our study can be used to differentiate high-risk patients for post-liver transplant complications or mortality at an early state. These patients may benefit from dietary or physical interventions to improve body composition during the waiting list period.

INTRODUCTION

Mortality rates caused by end-stage liver disease (ESLD) are rising worldwide. In 2010, liver cirrhosis caused the death of a million patients.^{1,2} Liver transplantation can be a definitive and potentially curative treatment. A common problem among patients with ESLD is the unintentional loss of muscle mass prior to liver transplantation, most likely caused by inadequate nutrition intake, impaired digestion and absorption of micronutrients and macronutrients, and diminished storage and increased demand for nutrients caused by the liver disease.^{3,4} Harimoto et al showed that sarcopenia before liver transplantation (defined by a loss of muscle mass and muscle strength) is a predictor of an increased risk of sepsis after liver transplantation, prolonged length of intensive care unit (ICU) and hospital stay, and increased 6-month mortality rate and medical costs.⁵⁻⁷

Next to the depletion of the quantity of skeletal muscle mass, muscle attenuation (MA) is a main point of interest. MA is a measure of muscle fat content and has been described as a surrogate maker of muscle quality. MA is often reduced in patients with ESLD compared with healthy controls.⁸ A reduced MA is associated with increased 5-year mortality rates in patients with cirrhosis and hepatocellular carcinoma.⁹ In a recent study, preoperative myosteatosis has been associated with 90-days mortality and respiratory and septic deaths in patients after liver transplantation. Czigany stated that myosteatosis mostly seems related to short-term outcomes after liver transplantation.¹⁰ Short-term postoperative complications after liver transplantation can be technical or medical complications, liver graft dysfunction, and infections.¹¹

Radiologic methods such as computed tomography (CT) scans have been used as a reference method to analyze body composition.¹² In addition, CT analysis can also be used to quantify the different components of a patient's body tissue as skeletal muscle mass, adipose tissue, and skeletal MA. Therefore, the use of CT scans has been recommended to evaluate body composition in ESLD.¹³

The association of muscle quantity, expressed as the skeletal muscle index (SMI), with post-liver transplant outcomes has been suggested by other studies, although not many data exist on the association with MA.¹³⁻¹⁷ Therefore, the aim of this study was to assess the association of both SMI and MA measured using CT scans—routinely performed on the waiting list for liver transplantation—with post-liver transplant mortality, complications, and length of hospital and ICU stay. We hypothesized that low SMI at the time of waitlist assignment is associated with increased 1-year mortality following liver transplantation.

MATERIALS AND METHODS

Study design and population

This study was a single center retrospective cohort study at the Leiden University Medical Center. Data were retrospectively collected from electronic patient files (HIX, Chipsoft BV) until March 2018. All patients ≥ 18 years of age with ESLD who were on the waiting list for liver transplantation with abdominal CT scan between 2007 and 2014 and who received a first orthotopic liver transplantation until February 2018 were included. Patients who received combined organ transplantations (eg, liver and kidney), received auxiliary liver transplantation, were lost to follow-up, or died during the surgical procedure were excluded. Patient inclusion is shown in Figure 1. This study was approved by the Medical Ethical Science Committee (G16.119, May 31, 2018) of the Leiden University Medical Center.

Data collection

Main determinants

Clinical data regarding primary liver disease, ESLD (MELD) score (time of assessment), presence of a hepatocellular carcinoma, date of listing on the waiting list, and date of liver transplantation were collected.

CT scans closest to the date of placement on the waiting list for liver transplantation were stored and anonymized on the hard disk for all study participants. Skeletal muscle area (SMA) and MA were determined by analysis of the transversal slice at the L3 level.^{18,19} CT images were contrast enhanced, 5 mm slice and 120 kV, in the portal venous phase, and part of the standard examinations for the evaluation for liver transplantation. Image acquisition parameters, timing during contrast, and the method of contrast administration were in accordance with standardized clinical procedures and not controlled for in this study.²⁰ Data collected from pre-liver transplant CT scans included SMA (in cm^2) and MA (in mean Hounsfield units [HUs]). The corresponding HU thresholds were -29 to 150 for SMA. The SMA analysis included the following muscles: musculus rectus abdominis, musculus transversus, musculus obliquus internus,

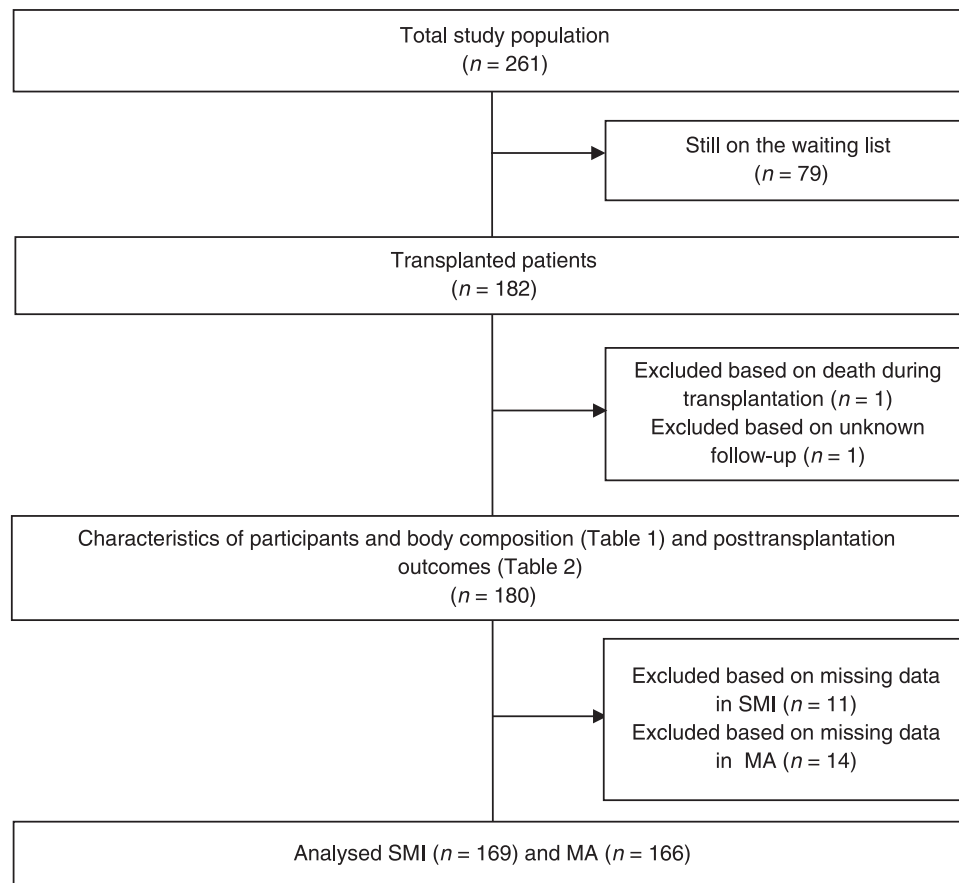


FIGURE 1 Study flowchart. MA, muscle attenuation; SMI, skeletal muscle index.

musculus obliquus externus, musculus psoas major, musculus psoas minor, musculus erector spinae, and musculus quadratus lumborum. Four trained researchers (A.D., C.L., D.B., and M.v.V.) analyzed the main determinants SMA and MA through single-slice, contrast-enhanced CT scans using SliceOmatic (TomoVision). All researchers independently analyzed three separate CT scans prior to the study. Dissimilarities were discussed until consensus was reached to optimize the interobserver reliability. An intraclass correlation coefficient of 0.994 ($P < 0.001$; 95% CI=0.982–0.999) was achieved. Our exposure of interest was the SMI, a measure of relative muscle mass, calculated as the SMA divided by the square of the patient's body height in meters (in cm^2/m^2).^{18,19,21}

Posttransplantation outcome measures

The primary outcome of interest was 1-year mortality following liver transplantation. Mortality was determined by hospital records. Data on the length of ICU stay, total length of hospital stay, and post-liver transplantation complications were collected as secondary outcome measures. Post-liver transplantation complications were defined as¹ (1) medical complications, (2) technical complications, (3) nonanastomotic biliary tract complications, (4) liver graft dysfunction and rejection, (5) and infections within 30 days.¹¹

A more detailed description of the post-liver transplantation complications is shown in Appendix 1.^{11,22,23}

Data analysis

Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS Inc). A P value < 0.05 was considered statistically significant for our primary outcome measure. For our secondary outcome measures, we corrected with the Bonferroni correction for multiplicity, and a P value < 0.017 was considered as statistically significant. Baseline and post-liver transplantation data were expressed as number and percentage or means and SD. When continuous variables had a skewed distribution, the medians and interquartile ranges (IQRs) were presented. Because the total length of hospital and ICU stay still had a positively skewed distribution after log transformation, we decided to dichotomize based on the mean value. The outcome length of ICU stay was dichotomized as ≤ 3 days and > 3 days. The outcome total length of hospital stay was dichotomized as ≤ 3 weeks and > 3 weeks.

Logistic regression analyses and Cox regression analyses were performed to assess the association of SMI and MA with post-liver transplantation outcomes. Results were reported as the odds ratio

(OR) with 95% CI and the corresponding *P* value. Cox regression analyses were performed for the dichotomous time-dependent outcome mortality rate, reported as the hazard ratio (HR) with 95% CI and the corresponding *P* value. When a continuous variable was not linear to the outcome, it was divided into categories based on quartiles before the variable was added to the model. The lowest category was the reference category, as suggested by Montana-Loza et al.²⁴ The variables age (continuous), sex (dichotomous), and MELD score (continuous) were related to SMI and MA, post-liver transplantation complications, mortality, and length of stay in the hospital according to previous research and these were checked for confounding.^{25–31} To calculate the sample size, the mortality data of patients with and without low SMI were used. Outcomes from the study of Hamaguchi et al were used for sample size calculation; however, SMI in this study was analyzed as a dichotomous variable instead of a continuous outcome variable. Hamaguchi et al showed a prevalence of low SMI in 21.2% and normal SMI in 78.8% of the population. The 24-month mortality rate was 36.0% in patients with normal SMI vs 60.4% in patients with low SMI. According to the sample size calculation ($\alpha = 0.05$, power = 80%), 134 participants were needed for our study.³²

RESULTS

Study population

The data of 261 consecutive participants who were listed between 2007 and 2014 on the waiting list for liver transplantation were collected. Follow-up was until February 2018. Figure 1 shows the flowchart of the study population. Two patients who underwent a liver transplantation were excluded, one based on death during transplantation and the other for unknown follow-up, because their posttransplantation information with regard to complications, mortality, and length of stay was not available. Seventy-nine participants were still on the waiting list, and 180 patients underwent a liver transplantation by the end of the follow-up period. CT scans were missing in 11 patients, which resulted in 169 participants who were eligible for analysis. The median time on the waiting list was 234 days (IQR, 93–369 days).

The baseline characteristics of the participants, while they were on the waiting list, are presented in Table 1. The study population consisted of 125 (74.0%) men and 44 (26.0%) women with a mean age of 54 years. Alcoholic cirrhosis (33.7%) was the most frequent primary liver disease and the mean MELD score was 13 ± 6 . The mean SMI of the study population was $47.83 \pm 9.27 \text{ cm}^2/\text{m}^2$, and the mean MA was $41.36 \pm 9.67 \text{ HU}$. The mean time between the CT at placement and transplantation was 10.8 ± 0.81 months. There was a statistically significant association between MELD score and SMI ($\beta = -0.260$, 95% CI = -0.495 to -0.024 , $P = 0.031$) and MA ($\beta = -0.312$, 95% CI = -0.557 to 0.068 , $P = 0.013$).

Table 2 shows the prevalence of post-liver transplantation complications, mortality rate, length of ICU stay >3 days, and the

total length of stay in hospital >3 weeks among the participants. Medical complications and infections were the post-liver transplantation complications that occurred most frequently, in 80 (47.3%) and 88 (52.1%) participants, respectively. The median total length of hospital stay was 15 days (IQR, 11–26 days), and 51 (30.2%) patients were admitted for >3 weeks. The median length of ICU stay was 1 day (IQR, 1–4 days), and 53 (31.4%) patients were admitted to the ICU for >3 days after liver transplantation.

One-year mortality rate

Within 1 year after liver transplantation, 12 participants (7.1%) died. All of these patients were male and the mean age was 52 ± 9.95 years. Three patients (25%) died within the first 30 days after liver transplantation and one patient within 6 months after liver transplantation. The mean SMI was $52.01 \pm 8.88 \text{ cm}^2/\text{m}^2$ in the mortality group vs $47.51 \pm 9.25 \text{ cm}^2/\text{m}^2$ ($P = 0.105$) in patients who survived the first year after transplantation. Mean MA was 36.64 ± 8.50 in patients who died within 1 year vs 41.71 ± 9.69 ($P = 0.080$) in the remaining study population. Cox regression showed a statistically significant association of MA with the 1-year mortality rate when adjusted for age, sex, and MELD (HR = 0.656, 95% CI = 0.464–0.921, $P = 0.015$), as shown in Table 3. This HR shows that the hazard of 1-year mortality rate was reduced with 34% in patients with five-unit higher MA when adjusted for age, sex, and MELD. SMI was not associated with the 1-year mortality rate.

Posttransplantation complications

Table 4 shows the results of the logistic regression analyses that examined the association of SMI and MA with post-liver transplantation complications. No statistically significant association of SMI and MA with post-liver transplantation complications was found in this study. An additional analysis into the association between SMI, MA, and the separate categories of post-liver transplantation complications is reported in Appendix 2.

Total length of hospital stay

The results of the logistic regression analyses examining the association of SMI and MA with the total length of hospital stay >3 weeks are presented in Table 5. A statistically significant difference between the highest (54.04 – $79.29 \text{ cm}^2/\text{m}^2$) and lowest (25.95 – $40.48 \text{ cm}^2/\text{m}^2$) quartile of SMI and total length of hospital stay >3 weeks was found. There was a significant difference in the univariate analysis (OR = 0.199, 95% CI = 0.065–0.608, $P = 0.005$) and multivariate analysis when adjusted for age, sex, and MELD score (OR = 0.211, 95% CI = 0.061–0.733, $P = 0.014$). The OR implies that the odds for a total length of stay in the hospital >3 weeks is 21.1

TABLE 1 Baseline characteristics of the participants (N = 169).

	Total (N = 169)	Male (n = 125)	Female (n = 44)
Age (mean ± SD), y	54 ± 10	55 ± 10	51 ± 12
Height (mean ± SD), m	1.75 ± 0.08	1.77 ± 0.08	1.69 ± 0.08
Weight (mean ± SD), kg	82.2 ± 15.9	85.4 ± 15.5	73.3 ± 13.6
Primary liver disease, n (%)			
Alcoholic cirrhosis	57 (33.7)	50 (40.0)	7 (15.9)
Cholestatic disease	24 (14.2)	14 (11.2)	10 (22.7)
Viral hepatitis	34 (20.1)	30 (24.0)	4 (9.1)
Hepatocellular cancer	20 (11.8)	14 (11.2)	6 (13.6)
Autoimmune hepatitis	7 (4.1)	2 (1.6)	5 (11.4)
Other ^a	27 (16.0)	15 (12)	12 (27.3)
MELD score (mean ± SD)			
Bilirubin (mean ± SD), μmol/L	69 ± 119	69 ± 119	70 ± 119
Creatinine (mean ± SD), μmol/L	83 ± 40	84 ± 34	79 ± 55
INR (mean ± SD)	1.3 ± 0.3	1.2 ± 0.3	1.3 ± 0.5
Smoking, n (%) ^b			
Current	51 (30.2)	40 (32.0)	11 (25.0)
Never	59 (34.9)	39 (31.2)	20 (45.4)
Former (>1 month)	52 (30.8)	44 (35.2)	8 (18.2)
Body composition			
SMA (mean ± SD), cm ²	147.15 ± 31.60	158.85 ± 27.07	113.91 ± 16.12
MA (mean ± SD), mean HU	41.36 ± 9.67	41.9 ± 9.11	39.80 ± 11.09
SMI (mean ± SD), SMM/m ^{2c}	47.83 ± 9.27	50.63 ± 8.79	39.87 ± 5.00

Abbreviations: INR, international normalized ratio; MA, muscle attenuation; MELD, Model for End-Stage Liver Disease; SMA, skeletal muscle area; SMI, skeletal muscle index; SMM, skeletal muscle mass.

^aIncludes nonalcoholic fatty liver disease, cryptogenic cirrhosis, hemochromatosis, and other nonspecified diseases with liver cirrhosis.

^bThe data of seven patients were missing.

^cSMI = SMA/square of length in meters.

times lower in participants in the highest quartile of SMI compared with participants in the lowest category of SMI, when adjusted for age, sex, and MELD.

Length of ICU stay

Table 5 shows the results of the logistic regression analyses that examined the association of SMI and MA with length of ICU stay >3 days. All quartiles of MA showed a lower odds for ICU stay >3 days compared with the lowest quartile in the univariate analysis; however, only the highest quartile was statistically significantly associated with lower odds for total ICU stay >3 days compared with the lowest quartile (OR=0.273, 95% CI=0.105–0.708, P=0.008). When adjusted for age, sex, and MELD score, no statistically significant association of MA with length of ICU stay >3 days was found anymore. No statistically significant association of SMI with length of ICU stay >3 days was found in this study.

DISCUSSION

With the present study we demonstrate that not only skeletal muscle quantity (reflected by SMI) but also MA assessed at screening for liver transplantation is associated with post-liver transplantation outcomes. We found a low MA to be associated with higher 1-year mortality and prolonged ICU stay after liver transplantation. Also, the lowest quartile of SMI is associated with prolonged length of hospital stay compared with the highest quartile.

The results of this study are in line with previous findings regarding the association of SMA (muscle quantity) with the total length of hospital stay after liver transplantation.^{14,24,26} In addition, a recent meta-analysis demonstrated the association of SMI with post-liver transplantation survival with a pooled HR of 0.98 (95% CI=0.96–1.00), which favors a higher SMI.³³ In contrast to previous studies, SMI was not associated with higher 1-year posttransplant mortality in our study. This might be explained by the relatively low sample size and the higher prevalence of patients with hepatocellular carcinoma. A study by Tsien

TABLE 2 Descriptive statistics of outcomes of interest (N = 169).

	Total (N = 169)	Male (n = 125)	Female (n = 44)
Time on waiting list, median (IQR), days	234 (93–369)	243 (105–356)	198 (59–442)
Posttransplantation complications within 30 days, n (%) ^a			
Medical complications	80 (47.3)	61 (48.8)	19 (43.2)
Technical complications	53 (31.4)	42 (33.6)	11 (25.0)
Nonanastomotic biliary tract complications	5 (3.0)	3 (2.4)	2 (4.5)
Liver graft dysfunction and rejection	27 (16.0)	18 (14.4)	9 (20.5)
Infections	88 (52.1)	63 (50.4)	25 (56.8)
Mortality, n (%)			
Within 1 year	12 (7.1)	12 (9.6)	0 (0.0)
Length of stay in ICU, median (IQR), days	1 (1–4)	1 (1–4)	1 (1–6)
Length of stay in ICU > 3 days, n (%)	53 (31.4)	39 (31.2)	14 (31.8)
Total length of stay in hospital, median (IQR), days	15 (11–26)	15 (11–25)	16 (12–30)
Total length of stay in hospital > 3 weeks, n (%)	51 (30.2)	35 (28.0)	16 (36.4)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

^aMedical complications: hemodynamic complications, respiratory changes, renal dysfunction, and neurological complications. Technical complications: postoperative hemorrhage, vascular complications, and biliary tract complications. Liver graft dysfunction: primary poor function, rejection, and recurrent viral hepatitis. Infections: bacterial, viral, and fungal.

TABLE 3 Cox regression on the association of SMI and MA with 1-year mortality.

	Univariate analysis			Multivariate analysis SMI (adjusted for age, sex, and MELD)			Multivariate analysis MA (adjusted for age, sex, and MELD)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
SMI (5 cm ²)	1.048	0.957–1.689	0.098	1.187	0.879–1.614	0.270			
MA (5-unit mean HU)	0.782	0.599–1.040	0.085				0.656	0.464–0.921	0.015
Age, y	0.982	0.935–1.032	0.478	0.974	0.927–1.023	0.291	0.942	0.889–0.998	0.044
Sex	0.030	0.000–6.775	0.205	0.000	0.000–9.233	0.959	0.000	0.000–9.233	0.959
MELD	1.069	0.993–1.151	0.075	1.087	1.004–1.177	0.041	1.040	0.959–1.127	0.345

Note: P < 0.05 was considered statistically significant.

Abbreviations: HR, hazard ratio; HU, Hounsfield unit; MA, muscle attenuation; MELD, Model for End-Stage Liver Disease; SMI, skeletal muscle index.

et al found that patients with hepatocellular carcinoma were on the waiting list for liver transplantation for a shorter period compared with patients without hepatocellular carcinoma (4.1 ± 2.9 vs 6.9 ± 6.0 months, $P < 0.05$), with a higher SMA and less reduced SMI and MA.¹³ A study of Hamaguchi et al stated that MA is an independent risk factor for mortality in patients undergoing liver transplantation, which is in line with our findings.^{34,35} In two studies included in a systematic review, the risk of post-liver transplantation complications was significantly increased in patients with a low muscle mass.³³

A strength of our study is investigating the association of post-liver transplantation outcomes with both SMI and MA. Most studies investigated the association between sarcopenia and mortality or post-liver transplantation complications. However, the

number of studies investigating the effect of both SMI and MA on mortality, length of stay in the hospital or ICU, and posttransplantation complications is limited. In addition, the muscle assessment was determined by analyzing a transversal slice CT scan at L3 by trained researchers with high interobserver reliability. This method improved the comparability with other studies and is the reference for body composition analyses. Finally, in our study, we investigated the association between body composition and a wide range of posttransplantation complications. We analyzed SMI and MA as continuous variables instead of dichotomous variables, which other studies based on preliminary cutoff values did. Therefore, we believe that this study gives a definitive answer regarding the relationship between MA and SMI and the outcome measures.

TABLE 4 Logistic regression on the association of SMI and MA with post-liver transplantation complications.

		Post-liver transplantation Complications ^a					
		Univariate analysis		Multivariate SMI (adjusted for age, sex and MELD)		Multivariate MA (adjusted for age, sex and MELD)	
		OR	95% CI	OR	95% CI	OR	95% CI
			p value		p value		p value
SMI cm ²							
25.95 – 40.48	Ref			Ref			
40.51 – 46.82	0.563	0.218-1.455	0.235	0.572	0.212-1.541		0.269
46.98 – 53.63	1.367	0.480-3.891	0.558	1.438	0.432-4.785		0.554
54.04 – 79.29	1.562	0.532-4.593	0.417	1.632	0.474-5.623		0.438
MA mean HU							
12.90 – 34.74	Ref					Ref	
35.01 – 42.15	1.371	0.480-3.915	0.556			1.389	0.465-4.208
42.23 – 47.81	0.806	0.303-2.144	0.666			0.813	0.282-2.342
47.84 – 66.09	1.000	0.368-2.740	1.000			1.126	0.349-3.630
Age y	1.003	0.969-1.038	0.865	1.001	0.966-1.038	1.003	0.963-1.045
Sex	0.657	0.303-1.426	0.288	0.885	0.346-2.268	0.637	0.281-1.445
MELD	1.054	0.984-1.129	0.132	1.063	0.990-1.142	1.055	0.983-1.132

Abbreviations: HU, Hounsfield unit; MA, muscle attenuation; MELD, Model for End-Stage Liver Disease; OR, odds ratio; Ref, reference; SMI, skeletal muscle index.
^aThe presence of at least one of the following post-liver transplantation complications: medical complications, technical complications, nonanastomotic biliary tract complications, liver graft dysfunction and rejection, or infections. A P value < 0.05 was considered statistically significant.

TABLE 5 Logistic regression on the association of SMI and MA with total length of stay in hospital >3 weeks and length of stay in ICU > 3 days.

	Univariate analysis			Multivariate SMI (adjusted for age, sex and MELD)			Multivariate MA (adjusted for age, sex and MELD)		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Total length of stay in hospital >3 weeks									
SMI (cm ²)									
25.95 – 40.48	Ref			Ref					
40.51 – 46.82	0.735	0.302-1.790	0.498	0.814	0.321-2.062	0.664			
46.98 – 53.63	0.788	0.327-1.898	0.595	0.883	0.314-2.478	0.813			
54.04 – 79.29	0.199	0.065-0.608	0.005	0.211	0.061-0.733	0.014			
MA (mean HU)									
12.90 – 34.74	Ref						Ref		
35.01 – 42.15	0.473	0.189-1.187	0.111				0.545	0.207-1.434	0.219
42.23 – 47.81	0.644	0.266-1.557	0.328				0.826	0.312-2.188	0.700
47.84 – 66.09	0.314	0.117-0.839	0.021				0.409	0.132-1.269	0.122
Age (years)	1.019	0.985-1.055	0.279	1.029	0.993-1.066	0.121	1.012	0.972-1.054	0.557
Sex	1.469	0.710-3.042	0.300	1.092	0.450-2.653	0.846	1.502	0.689-3.276	0.306
MELD	1.054	0.998-1.113	0.059	1.054	0.995-1.117	0.074	1.051	0.993-1.113	0.084
Length of stay in ICU >3 Days									
SMI (cm ²)									
25.95 – 40.48	Ref			Ref					
40.51 – 46.82	0.892	0.350-2.275	0.811	1.095	0.405-2.964	0.858			
46.98 – 53.63	1.077	0.432-2.685	0.874	1.420	0.473-4.259	0.532			
54.04 – 79.29	1.115	0.446-2.788	0.815	1.440	0.476-4.355	0.518			
MA (mean HU)									
12.90 – 34.74	Ref						Ref		
35.01 – 42.15	0.400	0.162-0.986	0.047				0.486	0.188-1.254	0.135
42.23 – 47.81	0.344	0.138-0.857	0.022				0.468	0.174-1.262	0.134
47.84 – 66.09	0.273	0.105-0.708	0.008				0.450	0.150-1.352	0.155

TABLE 5 (Continued)

	Univariate analysis		Multivariate SMI (adjusted for age, sex and MELD)		Multivariate MA (adjusted for age, sex and MELD)	
	OR	p-value	OR	95%CI	OR	p-value
Age, y	1.047	0.018	1.052	1.012-1.094	1.036	0.115
Sex	1.029	0.939	1.448	0.570-3.682	1.012	0.977
MELD	1.048	0.088	1.063	1.003-1.126	1.050	0.105

Note: P values < 0.05 were considered statistically significant.

Abbreviations: HU, Hounsfield unit; ICU, intensive care unit; MA, muscle attenuation; MELD, Model for End-Stage Liver Disease; OR, odds ratio; Ref, reference; SMI, skeletal muscle index.

A limitation of the current study is that some patients may have received more dietary advice to improve nutrition status and body composition, or they may have had more physical exercise prior to liver transplantation. No data were available on the number of sessions and intensity of dietary consultation or physical therapy and physical performance status before screening for liver transplantation. A second limitation is the relatively low study population and the low number of events of nonanastomotic biliary tract complications. As a result, the adjusted analyses on the association of SMI and MA with these biliary tract complications and the crude and adjusted analyses on the association of SMI and MA could not be performed. Because the mean MELD score was relatively low in our study, larger cohorts with higher MELD scores are needed to determine the generalizability of these findings.

CONCLUSION

In summary, our study confirms that not only low SMI but also MA is associated with a higher 1-year mortality rate, prolonged hospital stay, and prolonged ICU stay following liver transplantation. The results of our study can be used to identify high-risk patients for post-liver transplantation complications or mortality at an early state. These patients may benefit from more dietary or physical interventions to improve body composition during the waiting list period. Further research is needed to evaluate the dynamics of skeletal muscle quantity and MA during the waiting list prior to liver transplantation and to evaluate how to improve both. Based on the current findings, it is likely that the improvement of body composition is associated with a reduction in post-liver transplantation complications, mortality rate, and length of hospital stay.

AUTHOR CONTRIBUTIONS

Daphne Bot, Suzanne Klerks, and Bart van Hoek contributed to the conception and design of the research. Daphne Bot, Suzanne Klerks, and Eva Leistra contributed to the design of the research. Daphne Bot, Suzanne Klerks, Maarten E. Tushuizen, and Bart van Hoek contributed to the acquisition and analysis of the data. Daphne Bot, Suzanne Klerks, Maarten E. Tushuizen, and Bart van Hoek contributed to the interpretation of the data. Daphne Bot, Suzanne Klerks, Maarten E. Tushuizen, and Daphne Bot drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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DISCLOSURES

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

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

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