Body composition, nutritional status and clinical outcomes in end-stage liver disease

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Chapter 3

Association between skeletal muscle index prior to liver transplantation and one-year mortality post-transplant: A retrospective cohort study

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Abstract

Background and aim: Liver transplantation is the only curative therapy for end-stage liver disease (ESLD). Sarcopenia is often defined as loss of muscle quantity (Skeletal Muscle Index, SMI), but muscle radiation attenuation (MRA), a surrogate marker of muscle quality, is also decreased in ESLD. We assessed pre-liver transplant SMI and MRA and their association with mortality rate, post-liver transplant complications, length of ICU and hospital stay.

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

Results: MRA was associated one-year mortality rate (HR 0.656, 95% CI: 0.464-0.921, p-value 0.015). The highest quartile of SMI had a lower odds for total length of stay in hospital >3 weeks (OR 0.211, 95% CI: 0.061 – 0.733, p-value 0.014). MRA was associated with prolonged ICU stay. This was however not statistically significant after adjustment for age, gender and MELD score.

Conclusions: Lower MRA is associated with length of ICU stay and one-year mortality after liver transplantation, while low SMI was associated with total length of hospital stay >3 weeks.

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

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 unintentional loss of muscle mass prior to liver transplantation, most likely caused by inadequate nutritional intake, impaired digestion and absorption of micro- and macro nutrients, diminished storage and increased demand for nutrients caused by the liver disease. (3, 4) Harimoto et al. showed that pre-liver transplantation sarcopenia (defined by loss of muscle mass and loss of muscle strength), is a predictor of an increased risk of sepsis after liver transplantation, prolonged length of Intensive Care Unit (ICU) and hospital stay, increased six-month mortality rate and medical costs. (5-7)

Next to the depletion of the quantity of skeletal muscle mass, muscle radiation attenuation (MRA) is a main point of interest. MRA is a measure of muscle fat content and has been described as a surrogate maker of muscle quality. MRA is often reduced in patients with ESLD compared to healthy controls. (8) A reduced MRA is associated with increased five-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 et al. 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 analyse body composition. (12) In addition, CT analysis can also be used to quantify the different compartments of a patient's body tissue as skeletal muscle mass and adipose tissue as well as MRA. Therefore, the use of CT scan has been recommended to evaluate body composition in ESLD. (15)

The association of muscle quantity, expressed as skeletal muscle index (SMI), with post-liver transplant outcomes has been suggested by other studies, while not many data exist on the association with MRA. (15-19) Therefore, the aim of this study was to assess the association of both SMI and MRA -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 hypothesize that low SMI at time of waitlist assignment is associated with increased one year mortality following liver transplantation.

Materials and methods

Study design and population

This study was a mono-center retrospective cohort study at the Leiden University Medical Center (LUMC). Data were retrospectively collected from electronic patient files (HIX, Chipsoft, The Netherlands) until March 2018. All patients of 18 years of age or above 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 (e.g. liver and kidney) or auxiliary liver transplantation or who 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 Metical Ethical Science Committee (G16.119, May 31, 2018) of the LUMC.

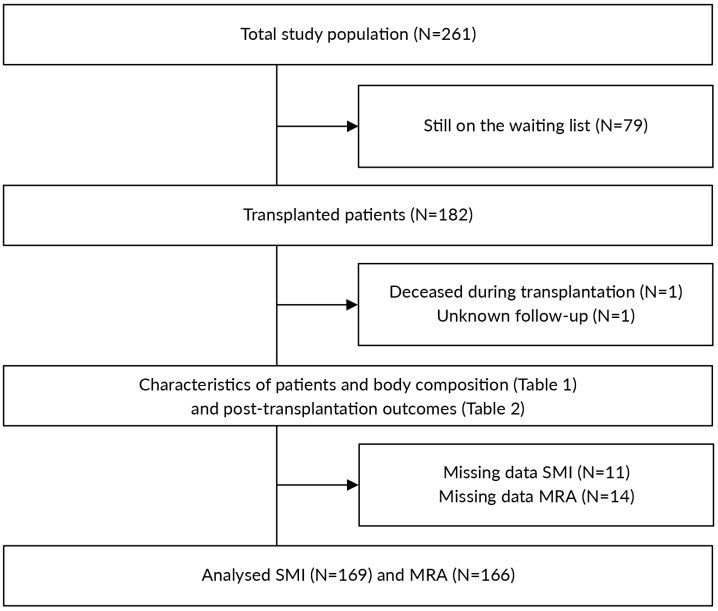

Figure 1. Study flowchart

Data collection

Main Determinants

Clinical data regarding primary liver disease, Model For End-Stage Liver Disease (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 MRA were determined by analysis of the transversal slice at L3 level. (20, 21) CT images were contrast enhanced, 5 mm slice and 120 kV and in the portal venous phase, and were part of the standard examinations for evaluation for liver transplantation. Image acquisition parameters, timing during contrast and way of contrast administration were in accordance with standardized clinical procedures and not controlled for in this study. (22) Data collected from pre-liver transplant CT scans were: skeletal muscle area (SMA, in cm^2) and MRA (mean Hounsfield Units (HU)). 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, musculus obliquus externus, musculus psoas major, musculus psoas minor, musculus erector spinae, and musculus quadratus lumborum. Four trained researchers (AD, CL, DB, MvV) analyzed the main determinants SMA and MRA through single slice contrast enhanced CT scans using SliceOmatic (Tomovision, Montreal, Canada). All researchers independently analyzed three separate CT scans prior to the study. Dissimilarities were discussed until consensus was reached, in order to optimize the inter-observer reliability. An intra-class correlation coefficient (ICC) of 0.994 ($p<0.001$; 95% CI: 0.982–0.999) was achieved. Our exposure of interest was skeletal muscle index, a measure of relative muscle mass, calculated as SMA divided by the square of patient's body height in meters (in cm^2/m^2). (20, 21, 23)

Post-transplantation outcome measures

The primary outcome of interest was one year mortality following liver transplantation. Mortality was determined by hospital records. Data on length of ICU stay, total length of hospital stay, and the post-liver transplantation complications were collected as secondary outcome measures. Post-liver transplantation complications were defined as (1) medical complications, (2) technical complications, (3) non-anastomotic biliary tract complications, (4) liver graft dysfunction and rejection and (5) infections within 30 days. (11) A more detailed description of the post-liver transplantation complications is shown in Appendix 1 (Supplementary table). (11, 24, 25)

Data Analysis

Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS Inc., Chicago, USA). 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, 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 Standard Deviation (SD). When continuous variables had a skewed distribution, the medians and Interquartile Ranges (IQR) were presented. Since 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 in ≤ 3 days and > 3 days. The outcome total length of hospital stay was dichotomized in ≤ 3 weeks and > 3 weeks.

Logistic regression analyses and Cox-regression analyses were performed to assess the association of SMI and MRA with post-liver transplantation outcomes. Results were reported as the odds ratio (OR) with 95% confidence interval (CI) and 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 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. (26) The variables age (continuous), gender (dichotomous), and MELD-score (continuous) were related to SMI and MRA, post-liver transplantation complications, mortality and length of stay in the hospital, according to previous research and checked for confounding. (27-33) To calculate the sample size, mortality data of patients with and without low SMI was 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 low SMI in 21.2% and normal SMI in 78.8% of the population. 24-months mortality rate was 36.0% in patients with normal SMI versus 60.4% in patients with low SMI. According to the sample size calculation (α = 0.05, power = 80%), 134 participants were needed for our study. (34)

Results

Study population

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 post-transplantation 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 ± 9.27 cm^2/m^2 and the mean MRA was 41.36 ± 9.67 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 (β= -0.260, 95% CI -0.495 to - 0.024, P=0.031) and MRA (β= -0.312, 95% CI -0.557 to – 0.068, P=0.013).

Table 2 shows the prevalence of post-liver transplantation complications, mortality rate and length of ICU stay longer than three days and the total length of stay in hospital longer than three 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 longer than 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 longer than 3 days after liver transplantation.

One-Year Mortality Rate

Within one year after liver transplantation twelve 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 patients within six months after liver transplantation. The mean SMI was 52.01±8.88 cm^2/m^2 in the mortality group versus 47.51±9.25 cm^2/m^2 (P=0.105) in patients who survived the first year after transplantation. Mean MRA was 36.64±8.50 in patients who died within one year versus 41.71±9.69 (P=0.080) in the remaining study population. Cox-regression showed a statistically significant association of MRA with one-year mortality rate when adjusted for age, gender 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 one-year mortality rate was reduced with 34% in patients with 5 unit higher MRA when adjusted for age, gender and MELD. SMI was not associated with one-year mortality rate.

Post-transplantation complications

Table 4 shows the results of the logistic regression analyses that examined the association of SMI and MRA with post-liver transplantation complications was found in this study. An additional analysis of the association between SMI, MRA and the separate categories of post-liver transplantation complications is reported in Appendix 2 (Supplementary table).

Total length of hospital stay

The results of the logistic regression analyses examining the association of SMI and MRA with total length of hospital stay longer than three weeks, are presented in Table 5. A statistically significant difference between the highest (54.04 – 79.29 cm^2/m^2) and lowest (25.95 – 40.48 cm^2/m^2) quartile of SMI and total length of hospital stay longer than three weeks was found. There was a significant difference in the univariate analysis (OR 0.199, 95% CI: 0.065 – 0.608, p-value 0.005) and multivariate analysis when adjusted for age, gender and MELD-score (OR 0.211, 95% CI: 0.061 – 0.733, p-value 0.014). The OR implies that the odds for a total length of stay in hospital longer than three weeks is 21.1 times lower in participants in the highest quartile of SMI compared to participants in the lowest category of SMI, when adjusted for age, gender and MELD.

Length of ICU stay

Table 5 shows the results of the logistic regression analyses that examined the association of SMI and MRA with length of ICU stay longer than three days. All quartiles of MRA showed a lower odds for ICU stay longer than three days compared to the lowest quartile in the univariate analysis, however only the highest quartile was statistically significant associated with lower odds for total ICU stay >3 days compared to the lowest quartile (OR 0.273, 95% CI: 0.105-0.708, p-value 0.008). When adjusted for age, gender and MELD-score, no statistically significant association of MRA with length of ICU stay longer than three days was found. No statistically significant association of SMI with length of ICU stay longer than three days was found in this study.

Discussion and conclusion

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

The results of this study are in line with previous findings regarding the association of SMI with total length of hospital stay after liver transplantation. (16, 26, 28) 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 favours a higher SMI. (36) In contrast to previous studies, SMI was not associated with higher one-year 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 et al. found that patients with hepatocellular carcinoma were on the waiting list for liver transplantation for a shorter period compared to patients without hepatocellular carcinoma (4.1 ± 2.9 versus 6.9 ± 6.0 months, $p<0.05$), which may result in a higher SMA and less reduced SMI and MRA. (15) A study of Hamaguchi et al. stated that MRA is an independent risk factor for mortality in patients undergoing liver transplantation, which is in line with our findings. (37, 38) 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. (36)

A strength of our study is investigating the association of post-liver transplantation outcomes with both SMI and MRA. 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 MRA on mortality, length of stay in hospital or ICU, and post-transplantation complications is limited. In addition, the muscle assessment was determined by analysing a transversal slice CT scan at L3 by trained researchers with high inter-observer 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 post-transplantation complications and in our study we analysed SMI and MRA as continuous variables instead of dichotomous variables -which other studies did based on preliminary cut-off values-. Therefore we believe that this study gives a more definitive answer regarding the relationship between MRA and SMI and the outcome measures.

A limitation of the current study is that some patients may have received more dietary advice to improve nutritional status, body composition or 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 relative low study population and low number of events of non-anastomotic biliary tract complications. As a result the adjusted analyses on the association of SMI and MRA with these biliary tract complications and the crude and adjusted analyses on the association of SMI and MRA could not be performed. Since the mean MELD score was relatively low in our study; studies in other, larger cohorts with higher MELD scores are needed to determine the generalizability of these findings.

In summary, our study confirms that not only low SMI, but also MRA is associated with higher one-year mortality rate, prolonged hospital and ICU stay following liver transplantation. The results of our study can be used to differentiate 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 muscle radiation attenuation during the waiting list prior to liver transplantation, and to evaluate how to improve both. Based on the current findings it is likely that improvement of body composition is associated with reduction in post-liver transplantation complications, mortality rate and length of hospital stay.

Table 1. Baseline Characteristics of the Participants

	Total (N=169)	Male (N=125)	Female (N=44)
Age (mean ± SD), years	54 ± 10	55 ± 10	51 ± 12
Height (mean ± SD), meters	1.75 ± 0.08	1.77 ± 0.08	1.69 ± 0.08
Weight (mean ± SD), kilograms	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%)
Auto-immune hepatitis	7 (4.1%)	2 (1.6%)	5 (11.4%)
Other[a]	27 (16.0%)	15 (12%)	12 (27.3%)
MELD-score (mean ± SD)	13 ± 6	13 ± 6	13 ± 6
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), ratio	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 [c]	147.15 ± 31.60	158.85 ± 27.07	113.91 ± 16.12
MRA (mean ± SD), mean HU [d]	41.36 ± 9.67	41.9 ± 9.11	39.80 ± 11.09
SMI (mean ± SD), SMM/m^2 [c]	47.83 ± 9.27	50.63 ± 8.79	39.87 ± 5.00

Abbreviations: HU, Hounsfield Unit; INR, International Normalized Ratio; MRA, Muscle radiation attenuation; MELD, Model for End-stage Liver Disease; SD, standard deviation; SMA, Skeletal Muscle Area; SMI, Skeletal Muscle Index; SMM, Skeletal Muscle Mass.

[a] *Includes non-alcoholic fatty liver disease, cryptogenic, hemochromatosis, and other not specified diseases with liver cirrhosis*

[b] *Data of 7 patients were missing*

[c] *Data of 11 patients were missing*

[d] *Data of 14 patients were missing*

Table 2. Descriptive Statistics of Outcomes of Interest

	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)
Post-Transplantation Complications within 30 days, ***n*** (%)*			
Medical complications	80 (47.3%)	61 (48.8%)	19 (43.2%)
Technical complications	53 (31.4%)	42 (33.6%)	11 (25.0%)
Non-anastomotic biliary tract complications	5 (3.0%)	3 (2.4%)	2 (4.5%)
Liver graft dysfunction & 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.

** Medical 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 MRA with one-year mortality

	Univariate analysis			Multivariate analysis SMI (adjusted for age, gender and MELD)			Multivariate analysis MRA (adjusted for age, gender and MELD)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
SMI (5 cm^2/m^2)	1.048	0.957-1.689	0.098	1.187	0.879-1.614	0.270			
MRA (5 unit mean HU)	0.782	0.599-1.040	0.085				0.656	0.464-0.921	**0.015**
Age (years)	0.982	0.935-1.032	0.478	0.974	0.927-1.023	0.291	0.942	0.889-0.998	0.044
Gender	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

CI = Confidence interval; HR, Hazard ratio; HU, Hounsfield Unit; MRA, Muscle radiation attenuation; SMI, Skeletal Muscle Index. P<0.05 was considered statistically significant.

Table 4. Logistic Regression on the Association of SMI and MRA with Post-liver transplantation Complications

	Univariate analysis			Multivariate SMI (adjusted for age, gender and MELD)			Multivariate MRA (adjusted for age, gender and MELD)		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
SMI (cm^2/m^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			
MRA (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	0.551
42.23 – 47.81	0.806	0.303-2.144	0.666				0.813	0.282-2.342	0.701
47.84 – 66.09	1.000	0.368-2.740	1.000				1.126	0.349-3.630	0.843
Age (years)	1.003	0.969-1.038	0.865	1.001	0.966-1.038	0.955	1.003	0.963-1.045	0884
Gender	0.657	0.303-1.426	0.288	0.885	0.346-2.268	0.799	0.637	0.281-1.445	0.281

** Presence of at least one of the following post-liver transplantation complications: medical complications, technical complications, non-anastomotic biliary tract complications, liver graft dysfunction and rejection or infections. Abbreviations: CI, Confidence interval; HU, Hounsfield Unit; MRA, Muscle radiation attenuation; MELD, Model for End-stage Liver Disease; OR, Odds ratio; SMI, Skeletal Muscle Index. P-value <0.05 was considered statistically significant.*

Table 5. Logistic Regression on the Association of SMI and MRA with Total Length of Stay in Hospital >3 Weeks and Length of Stay in ICU >3 Days

	Univariate analysis			Multivariate SMI (adjusted for age, gender and MELD)			Multivariate MRA (adjusted for age, gender 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/m^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**			
MRA (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
Gender	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/m^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			

	Univariate analysis			Multivariate SMI (adjusted for age, gender and MELD)			Multivariate MRA (adjusted for age, gender and MELD)		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
MRA (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
Age (years)	1.047	1.008-1.088	0.018	1.052	1.012-1.094	0.011	1.036	0.991-1.082	0.115
Gender	1.029	0.492-2.154	0.939	1.448	0.570-3.682	0.436	1.012	0.453-2.262	0.977
MELD	1.048	0.993-1.106	0.088	1.063	1.003-1.126	0.040	1.050	0.90-1.113	0.105

Abbreviations: CI, Confidence interval; HU, Hounsfield Unit; MRA, Muscle radiation attenuation; MELD, Model for End-stage Liver Disease; OR, Odds ratio; SMI, Skeletal Muscle Index.
P-value <0.05 was considered statistically significant

Supplementary table - Appendix I

Table 6. Post-Transplantation Complications Within 30-days After Transplantation

Complication	Description	
Medical complications (9)	Hemodynamic complications	Hypertension, cardiac arrhythmia (bradycardia), supraventricular arrhythmias
	Respiratory changes	Reduced ventilation capacity, pleural leakage, interstitial edema and acute pulmonary edema, atelectasis, pneumo- or hemothorax and mechanical ventilation.
	Renal dysfunction	Serum creatinine level > 2-3 mg/dL and/or an increase in the basal serum creatinine >50%. Oliguria, diuresis < 0.5 mL/kg/h, electrolytic changes, ascites, edema and acid/base disorders with increases in the levels of creatinine.
	Neurological complications	Intracranial hemorrhage, anoxic ischemic encephalopathy, convulsions and disorientation with episodes of agitation and confusion
Technical complications (9)	Postoperative hemorrhage	Hemorrhagic abdominal drainages, hemodynamic instability, serial determination of the hematocrit/hemoglobin
	Vascular complications	Hepatic artery thrombosis, portal vein thrombosis, hepatic venous obstruction
	Biliary tract complications	Bile leak, fistula, biliary stricture and anastomotic stenosis
Non-anastomotic biliary tract complications (9,33)		Cholelithiasis (gallstone), intrahepatic stenosis, non-anastomotic strictures/ stenosis, ischemia/ reperfusion injury
Liver graft dysfunction & Rejection (9,20,34)	Primary poor function	One or more of the following variables were present: (1) bilirubin ≥10 mg/dL; (2) INR ≥1.6; (3) aminotransferase level (alanine aminotransferase or aspartate aminotransferase) >2000IU/mL.
	Acute cellular rejection	Graft rejection usually within the first three months
	Rejection	Treatment of the rejection
Infections (9,21)		Bacterial infections, viral infections, fungal infections

Abbreviations: INR, International Normalized Ratio

Supplementary table – Appendix II

Table 7. Sub-analysis Logistic Regression on the Association of SMI and MRA with Post-Transplantation Complications specified by complication

	Univariate analysis			Multivariate SMI (adjusted for age, gender and MELD)			Multivariate MRA (adjusted for age, gender and MELD)		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Medical complications									
SMI (cm²/m²)									
25.95 – 40.48	Ref			Ref					
40.51 – 46.82	0.823	0.346-1.956	0.659	0.912	0.363-2.289	0.844			
46.98 – 53.63	1.529	0.650-3.596	0.330	1.665	0.601-4.611	0.327			
54.04 – 79.29	1.100	0.467-2.595	0.827	1.142	0.410-3.182	0.800			
MRA (mean HU)									
12.90 – 34.74	Ref						Ref		
35.01 – 42.15	0.826	0.350-1.947	0.662				1.124	0.451-2.800	0.802
42.23 – 47.81	0.718	0.306-1.686	0.447				1.105	0.432-2.828	0.835
47.84 – 66.09	0.508	0.213-1.214	0.127				1.057	0.381-2.929	0.915
Age (years)	1.053	1.018-1.090	0.003	1.055	1.019-1.093	0.003	1.057	1.015-1.100	0.007
Gender	0.797	0.39-1.593	0.521	1.140	0.481-2.704	0.766	0.953	0.453-2.006	0.899
MELD	1.027	0.975-1.081	0.318	1.043	0.986-1.103	0.146	1.039	0.983-1.099	0.178
Technical complications									
SMI (cm²/m²)									
25.95 – 40.48	Ref			Ref					
40.51 – 46.82	0.401	0.153-1.048	0.062	0.326	0.117-0.904	**0.031**			
46.98 – 53.63	0.637	0.260-1.561	0.324	0.417	0.145-1.200	0.105			
54.04 – 79.29	0.735	0.302-1.79	0.498	0.475	0.165-1.367	0.167			
MRA (mean HU)									
12.90 – 34.74	Ref						Ref		
35.01 – 42.15	1.239	0.499-3.076	0.644				1.126	0.438-2.895	0.806
42.23 – 47.81	0.967	0.384-2.432	0.943				0.834	0.308-2.258	0.721
47.84 – 66.09	0.892	0.350-2.275	0.811				0.774	0.263-2.274	0.641
Age (years)	0.999	0.967-1.031	0.928	0.994	0.962-1.028	0.736	0.991	0.955-1.028	0.633

	Univariate analysis			Multivariate SMI (adjusted for age, gender and MELD)			Multivariate MRA (adjusted for age, gender and MELD)		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Gender	0.659	0.303-1.432	0.292	0.450	0.171-1.186	0.106	0.628	0.280-1.406	0.258
MELD	1.006	0.953-1.062	0.825	0.997	0.942-1.055	0.922	1.003	0.948-1.061	0.917
Non-anastomotic biliary tract complications									
SMI (cm^2/m^2)									
25.95 – 40.48	Ref			Ref					
40.51 – 46.82	0.650	0.103-4.104	0.647	0.528	0.073-3.819	0.527			
46.98 – 53.63	-	-	-	-	-	-			
54.04 – 79.29	-	-	-	-	-	-			
MRA (mean HU)									
12.90 – 34.74	Ref						Ref		
35.01 – 42.15	0.488	0.043-5.595	0.564				0.143	0.006-3.189	0.219
42.23 – 47.81	0.976	0.131-7.265	0.981				0.227	0.015-3.537	0.290
47.84 – 66.09	-	-	-				-	-	-
Age (years)	0.936	0.876-1.001	0.054	0.942	0.877-1.012	0.103	0.893	0.816-0.978	0.014
Gender	1.937	0.313-11.991	0.477	0.520	0.070-3.892	0.525	1.441	0.187-11.117	0.726
MELD	1.072	0.952-1.207	0.254	1.035	0.916-1.171	0.578	1.033	0.904-1.180	0.637
Liver graft dysfunction and rejection									
SMI (cm^2/m^2)									
25.95 – 40.48	Ref			Ref					
40.51 – 46.82	0.708	0.223-2.254	0.559	0.851	0.253-2.861	0.795			
46.98 – 53.63	0.436	0.121-1.576	0.205	0.724	0.167-3.135	0.666			
54.04 – 79.29	1.159	0.399-3.366	0.786	2.052	0.548-7.687	0.286			

	Univariate analysis			Multivariate SMI (adjusted for age, gender and MELD)			Multivariate MRA (adjusted for age, gender and MELD)		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
MRA (mean HU)									
12.90 – 34.74	Ref						Ref		
35.01 – 42.15	1.412	0.444-4.493	0.559				1.481	0.431-5.093	0.533
42.23 – 47.81	1.167	0.357-3.813	0.799				1.279	0.337-4.843	0.718
47.84 – 66.09	1.000	0.295-3.395	1.000				0.998	0.236-4.218	0.997
Age (years)	0.980	0.944-1.018	0.299	0.983	0.945-1.023	0.405	0.986	0.43-1.032	0.553
Gender	1.529	0.630-3.709	0.348	1.766	0.571-5.464	0.323	1.490	0.581-3.822	0.406
MELD	1.069	1.004-1.139	0.037	1.070	1.003-1.142	0.040	1.067	1.000-1.139	0.051
Infections									
SMI (cm^2/m^2)									
25.95 – 40.48	Ref			Ref					
40.51 – 46.82	0.559	0.235-1.334	0.190	0.615	0.246-1.537	0.296			
46.98 – 53.63	0.587	0.248-1.393	0.227	0.755	0.274-2.084	0.588			
54.04 – 79.29	0.615	0.258-1.466	0.273	0.791	0.283-2.21	0.655			
MRA (mean HU)									
12.90 – 34.74	Ref						Ref		
35.01 – 42.15	0.750	0.317-1.772	0.512				0.783	0.313-1.960	0.601
42.23 – 47.81	0.594	0.252-1.400	0.234				0.661	0.257-1.701	0.391
47.84 – 66.09	1.000	0.421-2.373	1.000				1.114	0.405-3.065	0.835
Age (years)	0.989	0.959-1.019	0.452	0.994	0.963-1.025	0.686	0.995	0.960-1.031	0.791
Gender	1.295	0.648-2.587	0.464	1.163	0.491-2.753	0.732	1.180	0.563-2.473	0.661
MELD	1.090	1.028-1.156	0.004	1.088	1.024-1.155	0.006	1.090	1.026-1.157	0.005

Abbreviations: CI, Confidence interval; HU, Hounsfield Unit; MRA, Muscle radiation attenuation; MELD, Model for End-stage Liver Disease; OR, Odds ratio; SMI, Skeletal Muscle Index. P-value <0.05 was considered statistically significant.

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