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ORIGINAL ARTICLE

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Posttransplant muscle mass measured by urinary creatinine excretion rate predicts long-term outcomes after liver transplantation

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Long-term survival in orthotopic liver transplant (OLT) recipients remains impaired because of many contributing factors, including a low pretransplant muscle mass (or sarcopenia). However, influence of posttransplant muscle mass on survival is currently unknown. We hypothesized that posttransplant urinary creatinine excretion rate (CER), an established noninvasive marker of total body muscle mass, is associated with long-term survival after OLT. In a single-center cohort study of 382 adult OLT recipients, mean ± standard deviation CER at 1 year posttransplantation was 13.3 ± 3.7 mmol/24 h in men and 9.4 ± 2.6 mmol/24 h in women. During median follow-up for 9.8 y (interquartile range 6.4-15.0 y), 104 (27.2%) OLT recipients died and 44 (11.5%) developed graft failure. In Cox regression analyses, as continuous variable, low CER was associated with increased risk for mortality (HR = 0.43, 95% CI: 0.26-0.71, P = .001) and graft failure (HR = 0.42, 95% CI: 0.20-0.90, P = .03), independent of age, sex, and body surface area. Similarly, OLT recipients in the lowest tertile had an increased risk for mortality (HR = 2.69; 95% CI: 1.47-4.91, P = .001) and graft failure (HR = 2.77, 95% CI: 1.04-7.39, P = .04), compared to OLT recipients in the highest tertile. We conclude that 1 year posttransplant low total body muscle mass is associated with long-term risk of mortality and graft failure in OLT recipients.

KEYWORDS
clinical research/practice, graft survival, liver transplantation/hepatology, patient survival

1 | INTRODUCTION

Liver transplantation is the treatment of choice for patients with end-stage liver disease.[1] Over the past decades, overall 1- and 5-year survival rates after orthotopic liver transplantation (OLT) have steadily increased toward approximately 90% and 70%, respectively.[2,3] Unfortunately, long-term patient survival rates after OLT lag behind, with an overall 20-year survival rate of approximately 50%.[4] A recent study showed that at 10 years after OLT, recipients have about 20% reduced survival rate compared to the general population.[5] Furthermore, worldwide 5%-22% of the OLT recipients require retransplantation,[6,7] which is the only treatment option for patients with graft failure. Retransplantation is associated with worse outcome when compared to primary OLT.[8-10] Moreover, a liver assigned for retransplantation cannot be used for

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BSA, body surface area; CER, creatinine excretion rate; CT, computed tomography; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; OLT, orthotopic liver transplantation; γ-GT, gamma-glutamyltransferase.

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primary OLT, resulting in increased organ shortage.[11] During the past decades no large improvement in long-term patient and graft survival in OLT recipients has been achieved, therefore, greater attention should be paid to long-term follow-up after OLT.[3]

There are multiple factors that determine long-term outcome after OLT, including recipient age,[12] donor age,[1,13] primary diagnosis,[14] and disease recurrence.[15] The use of immunosuppressive medication and comorbidities including obesity, metabolic syndrome, and subsequent malignancies may also contribute to a decreased survival of OLT recipients.[16] However, the influence of many other factors on long-term survival outcomes after OLT are still unknown.

One of these factors could be muscle mass, an important source of amino acids and a key player in protein metabolism, which, in turn, is of key importance in the stress response.[17] Previous studies have shown that low muscle mass is an independent predictor of survival in several chronic diseases, including heart failure and cancer.[18,19] Moreover, it is well established that muscle mass is an indicator of nutritional status in patients who suffer from protein-energy malnutrition.[20] It has also been demonstrated that protein-energy malnutrition is associated with a higher risk of mortality in patients awaiting OLT.[21] Pretransplant muscle mass, as measured by computed tomography (CT), predicts intensive care unit (ICU) total length of stay and days of intubation after OLT.[22] However, the role of posttransplant low muscle mass has not yet been studied on long-term patient and graft survival outcomes in OLT recipients.

Creatinine is a breakdown product of creatine phosphate in muscle, which is usually produced at a constant rate depending on the amount of muscle mass.[23] Urinary creatinine excretion rate (CER) is therefore an established marker of total body muscle mass in diverse populations, including patients with wasting condition.[24-27] Low muscle mass, or sarcopenia, is an important comorbid condition in OLT recipients; however, studies investigating urinary CER have not yet been performed. We hypothesized that low urinary CER was associated with poor long-term survival after OLT. Therefore, the aim of this study was to determine whether CER is a prognostic marker of mortality and graft failure in stable OLT recipients.

2 | MATERIALS AND METHODS

2.1 | Study design and population

A single center retrospective analysis was performed in all patients aged ≥ 18 years who underwent OLT at the University Medical Center Groningen, the Netherlands, between January 1993 and December 2010. All patients received care according to a standardized protocol. Baseline was set at 1 year posttransplantation, because recipients are then considered to be stable and are less likely to develop rejection or infections. OLT recipients with missing baseline data on CER, those with a (graft) survival time less than 1 year, and those lost to follow-up were excluded.

According to the Dutch law, general consent for transplantation and organ donation includes consent for research projects. The study protocol was approved by the institutional research board (METc 2014/77) and adhered to the Declaration of Helsinki as well as to the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

2.2 | Data collection and measurements

Data were retrieved from electronic patient records. Weight, height, etiology, blood pressure, medication, and smoking status were derived from patients records. Body mass index (BMI) was defined as weight divided by height squared (kg/m^2). Body surface area (BSA) was assessed using the DuBois formula.[28] A positive cardiovascular history was defined as a previous myocardial infarction, cerebrovascular accident, and/or peripheral arterial disease. Donor characteristics were collected using the Eurotransplant database.

To obtain adequate 24 h urine samples all patients were required to adhere to a standardized protocol. All patients were instructed to start by discarding the urine void at the start of collection and to subsequently collect all urine for the next 24 hours, including a void at precisely 24 hours after the collection start. To minimize collection and measurement errors, a median of all laboratory and 24 h urinary measurements between 9 and 15 months posttransplantation was calculated (Figure S1). The median of these measurements was used for analyses. CER, urinary urea excretion, and proteinuria were assessed from 24 h urine collection. Proteinuria was defined as urinary protein excretion of > 0.5 g/day. Data on glucose, total cholesterol, triglycerides, C-reactive protein, hemoglobin levels, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyltransferase (γ-GT), alkaline phosphatase (ALP), direct and total bilirubin, serum albumin, and serum creatinine were extracted from the hospital laboratory system. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[29] To assess a potential time effect, transplantation dates were divided into 3 consecutive eras based on changes in immunosuppressive regimens. The first era was set from 1993 until 1998, the second era from 1999 until 2004, and the third era from 2005 until 2010.

2.3 | Immunosuppressive regimens and rejection

Immunosuppressive therapy was given according to a standardized protocol. Generally, from 1993 therapy consisted of a combination of prednisolone (10 mg/day), azathioprine (125 mg/day), and cyclosporin A, resulting in whole-blood levels of ~100 μg/L in the first year posttransplantation. From 1998 onwards, immunosuppressive therapy consisted of a combination of prednisolone and tacrolimus (whole-blood levels in the first year between 5-7 μg/L) or a combination of prednisolone, cyclosporin A, and azathioprine. From April 2010, the combination of prednisolone, mycophenolate mofetil, and tacrolimus was used by default. Variations in the standard regimens were present and were related to side effects or treatment of allograft rejection.[30,31.]

Acute rejection was diagnosed either clinically or confirmed with a biopsy. If acute rejection was present, initial therapy was to optimize levels of tacrolimus. If acute rejection persisted, therapy consisted of 1000 mg methylprednisolone for 3 consecutive days.

Cumulative dose of prednisolone was calculated by multiplying the prednisolone dose at baseline by the time since transplantation and adding the dose of prednisolone or methylprednisolone required for treatment of acute rejection. A conversion factor of 1.25 was used to convert methylprednisolone dose to prednisolone dose.

2.4 | Outcome measures

The primary outcome of this study was all-cause mortality. The secondary outcomes of this study were death-censored graft failure and cause-specific mortality, divided into four categories: cardiovascular, infectious, malignancy, and miscellaneous. Death-censored graft failure was defined as the requirement for retransplantation. Data on cause-specific mortality were derived from electronic patient records or, in case of missing data, requested from general practitioners. Follow-up was recorded up to 15 years after baseline, or until December 31, 2016.

2.5 | Statistical analysis

Normally distributed variables are presented as mean ± standard deviation (SD) and skewed distributed variables are presented as median (interquartile range [IQR]). Categorical variables are presented as a number (percentage). To test for differences across tertiles, 1-way analysis of variance (ANOVA) tests were used for normally distributed variables, Kruskal-Wallis tests when variables were skewed, and chi-square tests for categorical variables. Because the magnitude of muscle mass differs largely between men and woman, stratification was used to minimize a potential effect of gender in baseline analyses. All reported *P* values are 2-tailed and *P* values of ≤ .05 were considered to be statistically significant. For interaction terms a *P* value of < .05 was considered to be statistically significant. Patients were censored at date of death or lost to follow-up. Coefficients of variation (SD/mean × 100%) were calculated from the CER data obtained between 9 and 15 months after OLT.

Initial survival analysis was performed according to Kaplan-Meier with log-rank testing. Furthermore, the proportional hazards assumption was checked using Schoenfeld residuals of CER and met the criteria. We continued with Cox proportional-hazards regression analyses to study whether CER was associated with all-cause mortality. We first performed crude analysis (model 1). Subsequently, we proceeded with multivariable analyses. Model 2 was adjusted for age, sex, and BSA. Model 3 was cumulatively adjusted for eGFR, proteinuria, primary liver disease, and transplantation era. We additionally adjusted for cardiometabolic risk factors, including cardiovascular disease history, smoking, systolic blood pressure, and glucose in model 4, use of calcineurin inhibitors and cumulative prednisolone dose in model 5, liver enzymes and levels of direct bilirubin in model 6, and serum albumin and total cholesterol in model 7. For the association with death-censored graft failure, we did not adjust for model 6 and 7, because these parameters are not considered potential confounders. In continuous Cox proportional-hazards regression models, CER was log-base 2 transformed to allow for expression of the hazard ratios (HRs) per doubling of CER. In addition, CER was used as categorical variable for analyses by tertiles. Data were presented as HRs and 95% confidence intervals (CI). Furthermore, we evaluated potential effect modification by age, sex, BSA, renal function, urinary protein excretion, smoking, and serum albumin. Additionally, we have collected data on CER between 3 and 9 months posttransplantation to calculate a median urinary CER around 6 months posttransplantation and calculated CER change ($CER_{1\ year}$–$CER_{6\ months}$/$CER_{6\ months}$). To put the magnitude of CER into context additional Cox regression analyses, expressing HRs per SD change, were performed.

For visual depiction of the nonlinear relationship between CER and mortality, we made restricted cubic splines with 3 knots positioned at the 10th, 50th, and 90th percentile. To use the median of the third tertile of CER as reference in the analysis for restricted cubic splines, the standard errors of the difference in HR of each individual point compared to the reference was computed by bootstrapping by 1000 cycli.

Statistical analyses were performed using IBM Statistics SPSS version 23.0 (IBM Inc. Chicago, IL), GraphPad Prism 5 (La Jolla, CA), STATA 11.0 (STATA Corp.), and R version 3.2.3 (Vienna, Austria).

3 | RESULTS

3.1 | Baseline characteristics

Between 1993 and 2010 a total of 393 patients ≥ 18 years underwent OLT. Ten OLT recipients with missing baseline data on CER or death within the first year were excluded. One recipient was lost to follow-up. Subsequently, 382 OLT recipients (58.9% men) were included for analyses with a mean age of 48.5 ± 12.5 years. Mean (of median individual) CER at 1 year posttransplant was 13.3 ± 3.7 mmol/24 h in men and 9.4 ± 2.6 mmol/24 h in women (*P* < .001). The median coefficient of variation of the CER data obtained between 9 and 15 months after liver transplantation was 19.5 (12.6-25.8)%. Baseline characteristics according to sex-stratified tertiles of CER are shown in Table 1. OLT recipients in the lowest tertile were significantly older, smoked more frequently, and were smaller when compared to OLT recipients in the highest tertile. Furthermore, patients in the lowest tertile had a lower body weight, lower BMI, lower BSA, higher total cholesterol, lower hemoglobin, and lower albumin levels when compared to patients in the highest tertile. Moreover, liver enzymes were significantly higher in OLT recipients in the lowest tertile when compared to OLT recipients in the highest tertile. Lastly, cumulative dose of prednisolone was lower in patients in the lowest tertile compared to patients in the highest tertile, whereas prednisolone dose at baseline and number of OLT recipients using prednisolone at baseline did not differ. There were no differences in renal function, transplant characteristics, and use of medication other than prednisolone. The median CER according to categories of primary liver disease for the overall OLT recipient population and according to sex stratified tertiles of CER is shown in Table 2. No material differences in CERs were observed between the primary liver diseases.

TABLE 1 Baseline characteristics of the overall OLT recipient population and according to sex-stratified tertiles of creatinine excretion rate

	Overall OLT recipients (n = 382)	T1	T2	T3	*P* value
Men (n)	221	74	73	74	
Creatinine excretion (mmol/24 h)	13.1 (10.7-15.4)	9.6 (8.6-10.7)	13.1 (12.4-13.8)	16.6 (15.4-18.9)	
Women (n)	161	51	56	54	
Creatinine excretion (mmol/24 h)	9.2 (7.7-11.1)	6.8 (5.9-7.5)	9.1 (8.5-9.9)	11.8 (11.0-13.2)	
Demographics					
Age, y	48.5 ± 12.5	49.3 ± 12.1	50.1 ± 12.6	46.2 ± 12.4	.03
Current smoker, n (%)	50 (13.1)	23 (18.4)	22 (17.1)	5 (3.9)	.005
Body composition					
Height, m	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	.001
Weight, kg	77.0 ± 14.7	73.1 ± 14.9	75.9 ± 13.4	81.8 ± 14.5	<.001
BMI, kg/m^2	25.7 ± 4.6	25.3 ± 5.2	25.2 ± 4.0	26.7 ± 4.3	.02
BSA, m^2	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	2.0 ± 0.2	<.001
Medical history					
Cardiovascular disease history, n (%)	19 (5.0)	9 (7.2)	2 (2.3)	7 (5.5)	.19
Hypertension, n (%)	231 (60.5)	70 (56.0)	84 (65.1)	77 (60.2)	.39
Circulation					
Heart rate, bpm	73.5 ± 10.1	73.4 ± 10.8	72.3 ± 10.3	74.6 ± 9.2	.35
SBP, mmHg	133.1 ± 15.4	134.8 ± 18.4	131.9 ± 14.5	132.7 ± 13.0	.32
DBP, mmHg	81.8 ± 9.2	80.9 ± 10.8	81.4 ± 8.0	82.8 ± 8.7	.24
Renal function					
eGFR, ml/min per 1.73 m^2	69.4 ± 21.9	69.6 ± 23.7	67.3 ± 20.4	71.2 ± 21.5	.36
Serum creatinine, umol/L	105.0 ± 40.0	106.2 ± 38.3	105.4 ± 27.3	103.3 ± 26.4	.74
Proteinuria, n (%)	43 (11.3)	18 (14.4)	14 (10.9)	11 (8.6)	.33
Laboratory parameters					
Triglycerides, mmol/L	1.5 (1.1-2.2)	1.6 (1.2-2.4)	1.5 (1.0-2.1)	1.5 (1.2-2.1)	.41
Total cholesterol, mmol/L	5.0 ± 1.4	5.2 ± 1.6	5.1 ± 1.4	4.8 ± 1.1	.03
HDL cholesterol, mmol/L	1.3 ± 0.5	1.1 ± 0.4	1.4 ± 0.5	1.4 ± 0.4	.11
Glucose, mmol/L	5.7 (4.7-6.6)	5.8 (4.9-6.9)	5.6 (4.8-6.9)	5.6 (4.6-6.4)	.19
HbA1C, %	6.7 (5.5-19.1)	6.7 (5.7-17.5)	6.6 (5.5-17.6)	7.0 (5.6-21.8)	.53
Hemoglobin, mmol/L	7.9 ± 1.2	7.6 ± 1.5	8.1 ± 1.0	8.1 ± 0.8	.001
Albumin, g/L	41.7 ± 4.6	40.1 ± 5.5	42.1 ± 4.3	42.7 ± 3.5	<.001
CRP, mg/L	5.0 (5.0-21.3)	8.6 (5.0-27.4)	5.0 (5.0-20.8)	5.0 (5.0-15.0)	.21
AST, U/L	26.7 (21.2-39.8)	34.0 (23.1-61.8)	26.7 (21.6-38.7)	24.2 (20.1-32.0)	<.001
ALT, U/L	28.5 (19.0-49.9)	38.0 (22.0-74.7)	28.0 (18.5-47.9)	25.2 (18.8-36.4)	<.001
γ-GT, U/L	43.6 (22.2-132.9)	84.9 (27.0-184.7)	37.8 (21.0-148.3)	33.5 (19.4-64.3)	<.001
ALP, U/L	87.4 (65.0-127.1)	113.6 (73.1-167.4)	86.0 (60.7-124.4)	73.4 (59.7-103.7)	<.001
Bilirubin total, μmol/L	16.5 (11.5-24.0)	16.7 (12.2-29.5)	16.0 (11.2-23.2)	16.0 (11.5-22.5)	.52
Bilirubin direct, μmol/L	5.8 (3.0-10.0)	6.5 (3.6-12.7)	5.9 (3.0-9.9)	5.0 (3.0-8.1)	.08
Primary liver disease					.06
Acute liver failure, n (%)	24 (6.3)	3 (2.4)	11 (8.5)	10 (7.8)	
Viral hepatitis, n (%)	55 (14.4)	25 (20.0)	16 (12.4)	14 (10.9)	
Autoimmune hepatitis, n (%)	29 (7.6)	8 (6.4)	10 (7.8)	11 (8.6)	
Primary biliary cholangitis, n (%)	33 (8.6)	12 (9.6)	8 (6.2)	13 (10.2)	
Primary sclerosing cholangitis, n (%)	75 (19.6)	16 (12.8)	23 (17.8)	36 (28.1)	

(Continues)

TABLE 1 (Continued)

	Overall OLT recipients (n = 382)	T1	T2	T3	*P* value
Cryptogenic cirrhosis + NASH, n (%)	46 (12.0)	19 (15.2)	17 (13.2)	10 (7.8)	
Alcohol cirrhosis, n (%)	47 (12.3)	18 (14.4)	17 (13.2)	12 (9.4)	
Storage disorders, n (%)	21 (5.5)	4 (3.2)	9 (7.0)	8 (6.3)	
Other, n (%)	52 (13.6)	20 (16.0)	18 (14.0)	14 (10.9)	
Transplant characteristics					
Cold ischemia time, h	8.1 (6.9-10.0)	8.3 (6.7-10.1)	7.9 (6.7-10.2)	8.0 (7.0-9.9)	.77
Warm ischemia time, min	48.0 (41.0-57.0)	48.0 (41.0-56.0)	48.0 (41.0-58.3)	48.5 (42.0-57.3)	.91
Age donor, y	43.7 ± 14.5	43.7 ± 14.3	43.5 ± 15.3	43.8 ± 14.0	.98
Donation after brain death, n (%)	342 (89.5)	106 (84.8)	117 (90.7)	119 (93.0)	.09
Transplantation era, n (%)					.83
1993-1998	118 (30.9)	42 (33.6)	35 (27,1)	41 (32.0)	
1999-2004	133 (34.8)	43 (34.4)	47 (36.4)	43 (33.6)	
2005-2010	131 (34.3)	40 (32.0)	47 (36.4)	44 (34.4)	
Transplant complications					
Acute rejection, n (%)	159 (41.6)	51 (40.8)	53 (41.1)	55 (43.0)	.93
Relaparotomy, n (%)	57 (14.9)	22 (17.6)	21 (16.3)	14 (10.9)	.24
Length of intensive care stay, d	3.0 (1.0-7.0)	3.0 (2.0-8.5)	3.5 (2.0-8.8)	2.0 (1.0-5.0)	.11
Pretransplant MELD score	14.2 (10.0-22.2)	14.2 (8.8-19.7)	14.8 (10.4-24.2)	13.5 (10.3-21.4)	.64
Medication					
Calcineurin inhibitor, n (%)					
Cyclosporine	160 (41.9)	48 (38.4)	54 (41.9)	58 (45.3)	.57
Tacrolimus	200 (52.4)	67 (53.6)	68 (52.7)	65 (50.8)	.87
Proliferation inhibitor, n (%)					
Azathioprine	169 (44.2)	51 (40.8)	56 (43.4)	62 (48.4)	.50
Mycophenolate mofetil	62 (16.2)	20 (16.0)	22 (17.1)	20 (15.6)	.94
Prednisolone, n (%)	328 (85.9)	109 (87.2)	109 (84.5)	110 (85.9)	.83
Prednisolone dose, mg/d	10.0 (7.5-10.0)	10.0 (5.0-10.0)	10.0 (7.5-10.0)	10.0 (7.5-10.0)	.08
Cumulative prednisolone dose, g	3.7 (3.0-5.5)	3.7 (2.7-5.5)	3.7 (2.8-4.5)	3.9 (3.6-6.6)	.02
Antidiabetics, n (%)	77 (20.2)	30 (24.0)	22 (17.1)	25 (19.5)	.37
Antihypertensives, n (%)	217 (48.7)	54 (43.5)	67 (52.3)	65 (50.8)	.33
Statins, n (%)	34 (8.9)	10 (8.0)	11 (8.5)	13 (10.2)	.83

Data are represented as mean±SD, median (interquartile range) or n (%). Differences were tested by ANOVA or Kruskal-Wallis for continuous variables and with χ^2- test for categorical variables. Cardiovascular disease history was defined as myocardial infarction, cerebrovascular accident and/or peripheral arterial disease. BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-cholesterol, high-density lipoprotein; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma-glutamyltransferase; ALP, alkaline phosphatase; NASH, non-alcoholic fatty liver disease. Storage disorders include Wilson's disease, hemochromatosis and alfa-1-antitrypsin deficiency. Hypertension was defined as a SBP ≥ 140 mmHg and/or a DBP ≥ 90 mmHg and/or the use of antihypertensive drugs; Antidiabetics include oral agents and insulin.

3.2 | Association of CER with all-cause mortality and graft failure

During a median follow-up for 9.8 (6.4-15.0) years, 104 (27.2%) OLT recipients died, and 44 (11.5%) OLT recipients developed death-censored graft failure. Over sex-stratified tertiles of CER, 43 (33.9%) OLT recipients died in the first tertile, 35 (27.3%) died in the second tertile, and 26 (20.5%) died in the third tertile (Figure 1A, log-rank test: $P = .009$). For death-censored graft failure, 17 (13.4%) OLT recipient needed retransplantation in the first tertile, whereas 17 (13.3%) and 10 (7.9%) OLT recipients needed retransplantation in respectively the second and third tertile (Figure 1B, log-rank test: $P = .09$).

We proceeded with Cox regression analyses and checked for potential interactions of CER with age, sex, BSA, renal function, urinary protein excretion, smoking, and serum albumin. For both

TABLE 2 Creatinine excretion rate according to categories of primary liver disease

	Overall OLT recipients (n = 382)	T1	T2	T3
Primary liver disease				
Acute liver failure	11.8 (10.2-13.9)	[a]	11.9 (9.9-14.1)	11.8 (11.3-17.6)
Viral hepatitis	11.3 (8.6-14.3)	8.6 (6.6-9.6)	12.6 (11.6-13.7)	15.7 (14.9-16.9)
Autoimmune hepatitis	10.8 (8.6-13.4)	8.1 (7.8-9.6)	10.2 (8.9-12.6)	13.4 (11.5-19.1)
Primary biliary cholangitis	10.5 (8.0-12.5)	7.7 (6.6-8.2)	9.2 (8.4-12.4)	12.3 (10.9-13.5)
Primary sclerosing cholangitis	13.0 (10.3-15.4)	9.8 (7.9-10.7)	12.2 (9.7-13.4)	15.4 (14.7-18.6)
Cryptogenic cirrhosis + NASH	11.0 (8.9-13.3)	9.7 (6.7-10.9)	11.7 (9.0-12.9)	16.0 (14.1-18.0)
Alcohol cirrhosis	10.4 (8.3-13.8)	7.3 (6.3-9.2)	12.0 (8.9-13.2)	15.4 (13.0-17.6)
Storage disorders	12.9 (10.1-15.7)	9.3 (9.2-9.9)	12.9 (11.3-14.3)	15.9 (12.6-18.0)
Other	10.4 (8.1-13.1)	7.8 (6.8-8.5)	10.2 (9.4-12.3)	14.3 (12.7-18.4)

Data are represented as median (interquartile range) CER according to categories of primary liver disease. CER, creatinine excretion rate.
[a]Not enough variables for reliable presentation.

all-cause mortality and death-censored graft failure no significant interactions were identified (all $P \geq .05$), when adjusted for age, sex, and BSA.

Cox regression analyses for CER as log-transformed continuous variable showed a significant association with all-cause mortality (HR = 0.43 per doubling of CER; 95% CI: 0.26-0.71, $P = .001$), and death-censored graft failure (HR=0.42 per doubling of CER; 95% CI: 0.20-0.90, $P = .03$), independent of age, sex, and BSA (Tables 3 and 4, model 2). These associations are graphically depicted in nonlinear restricted cubic splines (Figure 2). Further adjustment for eGFR, proteinuria, primary liver disease, and transplantation era did not materially change the association of CER with all-cause mortality (HR = 0.47; 95% CI: 0.28-0.81, $P = .006$) and graft failure (HR = 0.40; 95% CI: 0.19-0.84, $P = .02$) (Table 3-4, model 3). Adjusting for cardiovascular disease history, smoking, systolic blood pressure, glucose, calcineurin inhibitors, cumulative prednisolone dose, liver enzymes, direct bilirubin, serum albumin, and total cholesterol did not materially change the results for all-cause mortality (Table 3, models 4-7) or death-censored graft failure (Table 4, models 4-5).

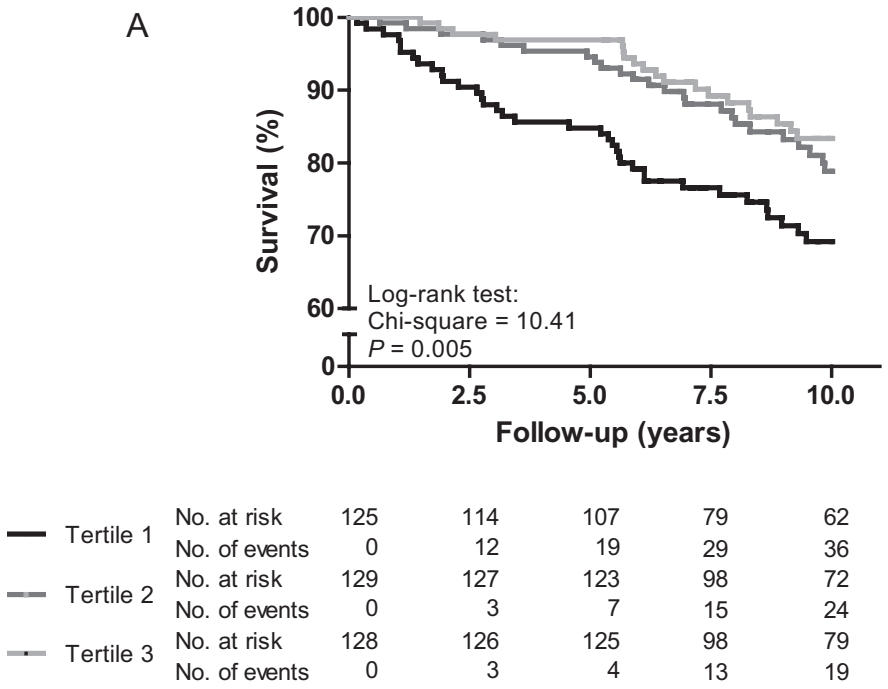
We continued with Cox proportional-hazards models to study the associations according to tertiles of CER. OLT recipients with low CER levels (first tertile) appeared to be at an approximately 2.5-fold higher risk of all-cause mortality (HR = 2.58; 95% CI: 1.35-4.93, $P = .004$), and 3-fold higher risk of graft failure (HR = 3.20; 95% CI: 1.21-8.44, $P = .02$), when compared to OLT recipients in the third tertile, independent of potential confounders including age, sex, BSA, eGFR, proteinuria, primary liver disease, and transplantation era (Table 3, model 3). Adjusting for other potential confounders did not materially change the results for all-cause mortality and graft failure (Table 3, models 4-7; Table 4, models 4-5).

To investigate the association of CER with cause-specific mortality, we performed additional Cox regression analyses (Table S1). We found a significant association of CER with cardiovascular mortality (model 3, HR 0.77; 95% CI 0.66-0.89, $P < .001$). No statistically significant associations were found for CER with infectious, malignant, and miscellaneous mortality. Furthermore, there was a significant association of CER around 6 months posttransplantation with all-cause mortality (model 3, HR: 0.54; 95% CI: 0.33-0.88, $P = .01$), which was independent of age, sex, BSA, eGFR, proteinuria, primary liver disease, and transplantation era. We did not find a significant association of CER around 6 months after transplantation with graft failure (Table S2). Additional analyses were performed to assess the association of change in CER with all-cause mortality and death-censored graft failure (Table S3). Change in CER was not predictive for all-cause mortality, whereas CER measured at 1 year posttransplant and 6 months posttransplant were. However, change in CER was predictive for graft failure, whereas CER at 6 months posttransplant was not. When comparing the magnitude of CER with other potential variables of interest additional Cox regression analyses revealed muscle mass to have a similar magnitude for the association with mortality as glucose and BMI (Table S4).

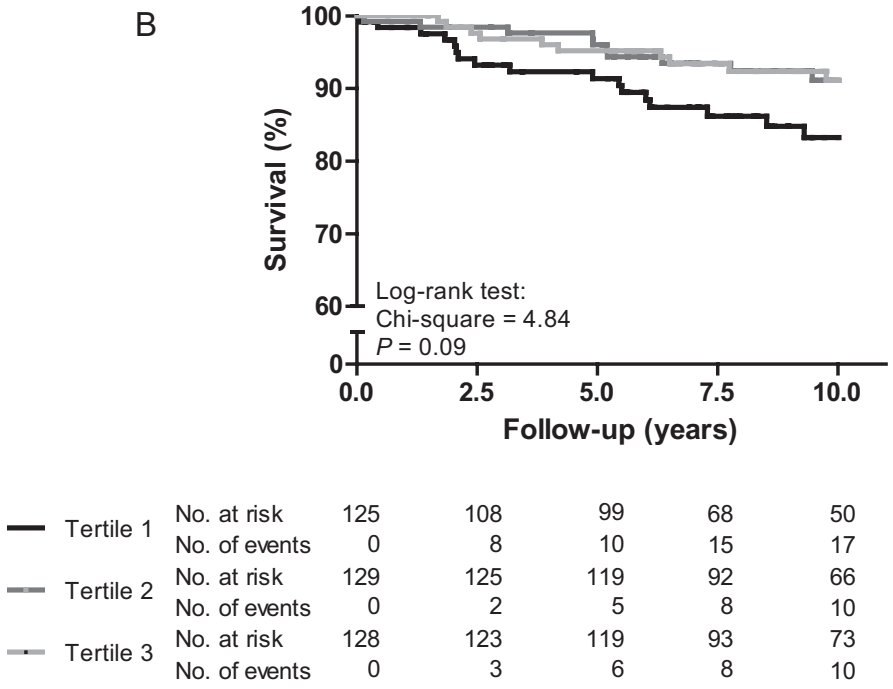
4 | DISCUSSION

In this study, we demonstrated that a low posttransplant total body muscle mass, as measured by urinary CER, was inversely associated with an increased risk of long-term all-cause mortality and graft failure in OLT recipients. The risk for all-cause mortality was more than 2.5-fold higher and the risk for death-censored graft failure was 3-fold higher in the lowest tertile when compared to the highest tertile of CER. The current results underline the importance of an adequate posttransplant total body muscle mass on long-term survival post-OLT.

To the best of our knowledge, we are the first to investigate the association of posttransplant total body muscle mass, as reflected by urinary CER, with long-term all-cause mortality and graft failure in OLT recipients. Urinary CER is an inexpensive, accessible,



Tertile 1	No. at risk	125	114	107	79	62
	No. of events	0	12	19	29	36
Tertile 2	No. at risk	129	127	123	98	72
	No. of events	0	3	7	15	24
Tertile 3	No. at risk	128	126	125	98	79
	No. of events	0	3	4	13	19



Tertile 1	No. at risk	125	108	99	68	50
	No. of events	0	8	10	15	17
Tertile 2	No. at risk	129	125	119	92	66
	No. of events	0	2	5	8	10
Tertile 3	No. at risk	128	123	119	93	73
	No. of events	0	3	6	8	10

FIGURE 1 Kaplan-Meier curves for all-cause mortality (A) and graft failure (B) according to sex-stratified tertiles of CER in 382 OLT recipients. CER, creatinine excretion rate [Correction added after online publication on June 5, 2018: Missing text from figure legend has been added.]

and reliable marker in stable patients and in patients with wasting conditions, without the need for invasive procedures or exposure to radiation.[23,27]

Muscle mass, as reflected by CER, has been associated with the development of cardiovascular disease and all-cause mortality in the general population.[24] As mentioned, OLT recipients have about 20% reduced survival rates when compared to the general population.[5] This magnitude of survival rate was similar for OLT recipients in the third tertile in our study. However, a decrease of almost 30% in survival rate was observed in OLT recipients in the first tertile, emphasizing the importance of muscle mass for OLT recipients.

Results in the general population are consistent with the results from other populations, namely that CER has been associated with mortality, independently of age and sex in patients with coronary artery disease, type 2 diabetes, and heart failure.[26,32,33] In addition, CER has been shown to predict all-cause mortality and graft failure in renal transplant recipients, implicating the importance of muscle mass posttransplantation.[25]

TABLE 3 Association of creatinine excretion rate with all-cause mortality (12-mo)

	CER as continuous variable (log-base^2)		Tertiles of CER (mmol/24 h)				
			T1		T2		T3
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	Reference
All-cause mortality, no. of events	104		43		35		26
Model 1	0.61 (0.41-0.90)	.01	1.79 (1.10-2.92)	.02	1.29 (0.78-2.15)	.32	1.00
Model 2	0.43 (0.26-0.71)	.001	2.69 (1.47-4.91)	.001	1.82 (1.04-3.18)	.04	1.00
Model 3	0.47 (0.28-0.81)	.006	2.58 (1.35-4.93)	.004	1.77 (1.00-3.14)	.05	1.00
Model 4	0.48 (0.25-0.90)	.02	2.46 (1.21-5.00)	.01	1.28 (0.65-2.53)	.47	1.00
Model 5	0.44 (0.24-0.80)	.007	2.91 (1.36-6.23)	.006	2.12 (1.11-4.05)	.02	1.00
Model 6	0.45 (0.25-0.79)	.006	2.92 (1.47-5.82)	.002	1.93 (1.07-3.49)	.03	1.00
Model 7	0.46 (0.26-0.83)	.009	2.39 (1.21-4.71)	.01	1.49 (0.81-2.73)	.20	1.00

Cox proportional-hazards regression analysis was performed to assess the association of creatinine excretion rate with all-cause mortality.
Model 1: crude.
Model 2: adjustment for age, sex, and body surface area.*
Model 3: model 2 + adjustment for eGFR, proteinuria, primary liver disease, and transplantation era.
Model 4: model 3 + adjustment for cardiovascular disease history, smoking*, SBP, and glucose.
Model 5: model 3 + adjustment for use of calcineurin inhibitors and cumulative prednisolone dose.
Model 6: model 3 + adjustment for liver enzymes (AST, ALT, γ-GT, and ALP) and direct bilirubin.
Model 7: model 3 + adjustment for serum albumin and total cholesterol.
eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma-glutamyltransferase; ALP, alkaline phosphatase. *Less than 95% of data of the variable available.

TABLE 4 Association of creatinine excretion rate with death-censored graft failure (12-mo)

	CER as continuous variable (log-base^2)		Tertiles of CER (mmol/24 h)				
			T1		T2		T3
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	Reference
Graft failure, no. of events	44		17		17		10
Model 1	0.58 (0.32-1.05)	.07	1.94 (0.89-4.25)	.10	1.73 (0.79-3.78)	.17	1.00
Model 2	0.42 (0.20-0.90)	.03	2.77 (1.04-7.39)	.04	2.18 (0.91-5.19)	.08	1.00
Model 3	0.40 (0.19-0.84)	.02	3.20 (1.21-8.44)	.02	2.55 (1.03-6.32)	.04	1.00
Model 4	0.28 (0.11-0.67)	.004	4.30 (1.37-13.44)	.01	2.23 (0.74-6.76)	.16	1.00
Model 5	0.35 (0.14-0.82)	.02	3.10 (1.11-8.67)	.03	2.48 (0.97-6.34)	.06	1.00

Cox proportional-hazards regression analysis was performed to assess the association of creatinine excretion rate with death-censored graft failure.
Model 1: crude.
Model 2: adjustment for age, sex, and body surface area.*
Model 3: model 2 + adjustment for eGFR, proteinuria, primary liver disease, and transplantation era.
Model 4: model 3 + adjustment for cardiovascular disease history, smoking*, SBP, and glucose.
Model 5: model 3 + adjustment for use of calcineurin inhibitors and cumulative prednisolone dose.
eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure. *Less than 95% of data of the variable available.

To date, focus has predominantly been on pretransplant muscle mass and its effect on adverse outcomes post-transplantation. Yet, we would advocate that attention on muscle mass, the anabolic influence of dietary interventions, and physical activity on longer term posttransplantation is warranted. Regrettably, CT is usually not part of routine posttransplantation follow-up. Moreover, it requires exposure to radiation, is expensive, and like magnetic resonance imaging (MRI), does not allow for whole body muscle mass measurement, which is reflected by CER. In addition, CT and MRI measurements may lead to over- or underestimation of muscle mass. CT and MRI lack the capability for specific tissue differentiation between edema and fatty infiltration in muscle mass, which could lead to overestimation. On the other hand, in wasting conditions connective, neural, and vascular tissue do not atrophy as much as muscle mass, which in turn could lead to underestimation.[23,34]

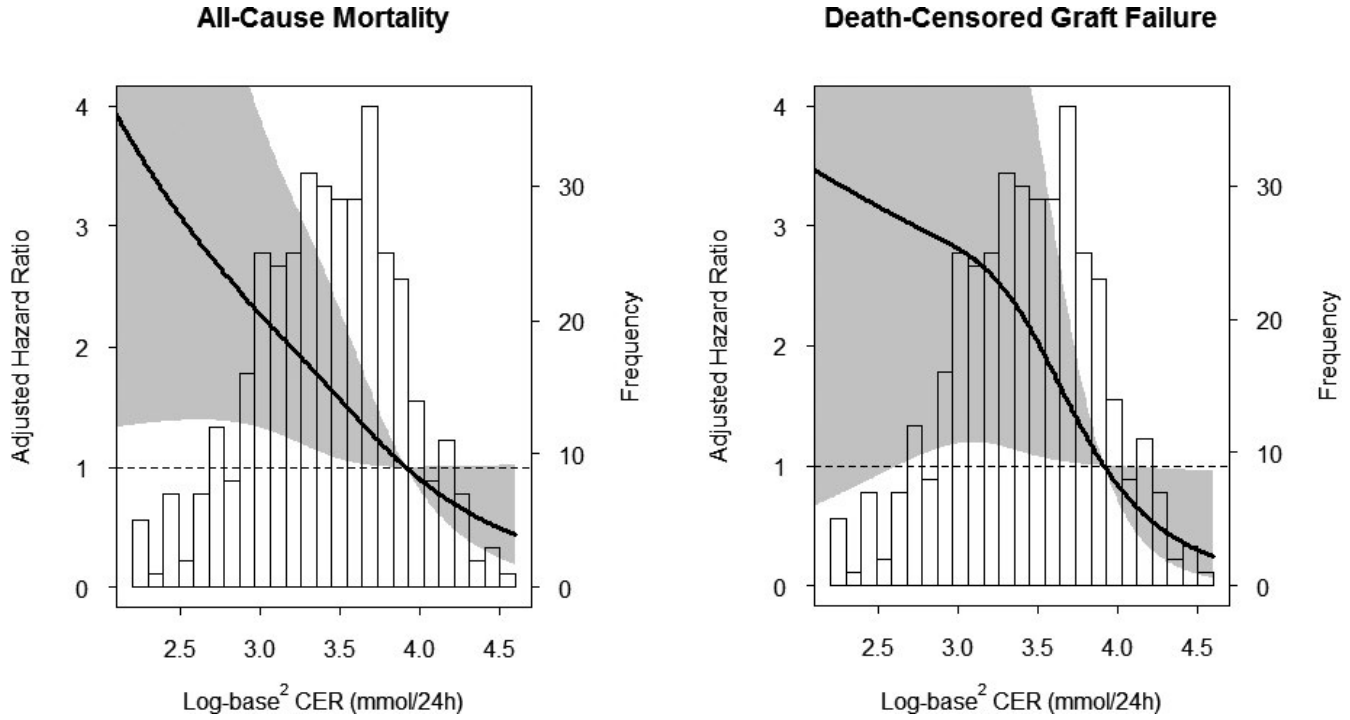


FIGURE 2 Association of log-transformed (HR per doubling of) CER on all-cause mortality and graft failure in 382 OLT recipients. Data were fit by a Cox proportional-regression model with time-varying covariates based on restricted cubic splines with 3 knots. Adjusted for age, sex, and BSA. Reference standard was the median CER of the third tertile (ie, 3.9 mmol/24 h log-transformed per doubling of CER equivalent to a CER of 15.1 mmol/24 h). The gray area represents the 95% confidence interval (CI)

Sarcopenia or loss of skeletal muscle mass is the major component of malnutrition and is a frequent complication in chronic liver disease and cirrhosis that adversely affects clinical outcomes.[35] Because etiology and severity of the underlying liver disease may significantly contribute to the severity of loss of skeletal muscle mass,[35] it could be hypothesized that these patients have different levels of urinary CER posttransplantation. In our study, levels of posttransplant CER did not differ across categories of primary liver disease, indicating that disease etiology was not associated with skeletal muscle mass status, as measured by urinary CER 1 year posttransplantation.

Liver transplantation is expected to abolish the abnormalities in nutritional status and in dietary intake. By restoring liver function, maintenance of protein synthesis and the liver's ability to regulate energy metabolism is recovered, presumably eliminating the metabolic alterations involved in the pathophysiology of malnutrition in cirrhotic patients.[36] Nonetheless, status after transplantation is associated with accelerated senescence, making OLT recipients prone to muscle wasting.[37] Unfortunately, meticulous evaluation of mechanisms responsible for loss of muscle mass has not yet been performed. As a result, protein-energy malnutrition can still be observed in OLT recipients, greatly increasing recipients risks for mortality.[21,38] Although the impact of posttransplantation malnutrition on graft failure has not yet been studied in OLT recipients and a potential mechanism is unknown, protein-energy malnutrition has been associated with graft loss in renal transplant recipients.[39] In this study, causal pathway analyses revealed muscle mass to be an explanatory component. Therefore, we hypothesize that protein-energy malnutrition may also increase the risk for graft loss in OLT recipients.

Although muscle mass is often not regained posttransplantation, a substantial increase in body weight can be observed. Most OLT recipients gain an average of 5.1 kg, in the first year posttransplantation.[40] This gain of mostly fat mass increases in subsequent years and is accelerated by poor lifestyle factors, including an approximately doubled fat intake compared to pretransplantation, reduced physical activity, and immunosuppressive medication.[40-42] As a result, an increased prevalence of obesity and new onset diabetes after transplantation, and an increased risk of metabolic syndrome and mortality in OLT recipients can be observed.[40,43,44]

As mentioned, OLT recipients have reduced levels of physical activity compared with age-predicted levels in healthy populations.[45,46] Physical activity has a large impact on weight management and is known to improve exercise capacity and muscular strength.[46] The latter has been shown to be inversely associated with hypertension in OLT recipients and mortality in cirrhotic patients.[47,48] Furthermore, the same entities that could lead to a poor muscle mass are suspected to give rise to low physical activity. Hence, muscle mass could be an indirect measure of physical activity and therefore explain the results found in this study. Management of impaired muscle mass should ideally be initiated as soon as possible after recovery from transplantation. However, to the best of our knowledge, studies on nutritional and physical-activity-based

interventions to regain muscle mass and improve long-term outcome are lacking.[49] Nevertheless, there are some studies that show the effects of nutrition and physical activity on short-term outcomes. A previous retrospective study showed that perioperative nutritional therapy improved short-term survival in patients with sarcopenia who underwent living donor liver transplantation.[50] Furthermore, a randomized clinical trial in OLT recipients showed that combined intervention of home-based exercise and dietary modification improved exercise capacity (measured by VO2peak) and self-reported general health.[51] Future studies focusing on interventions to improve muscle mass and long-term clinical outcomes posttransplantation are warranted.

A valuable strength of this study is that CER was measured multiple times over a 6-month period. Utilizing the median of multiple measurements reduces the influence of measurement errors. Other strengths of this study are its sizable population, the long median follow-up of 9.8 years, and a loss to follow-up group composed of only 1 patient.

The current study has some limitations. Previous studies have speculated on the role of nutrition in preventing muscle loss in OLT recipients.[36,46] Unfortunately, in this study 24 h urinary urea excretion, as a marker for protein intake, was available only in 17.2% of OLT recipients, discarding its utility for analyses. Other limitations are the lack of assessments of muscle mass before and right after transplantation and that data on noncompliance and physical activity were not available. Furthermore, liver biopsies to assess the distribution of fibrosis or cirrhosis were not routinely performed. The fact that our study is a single-center cohort study could limit external validity of its findings.

In conclusion, lower posttransplant urinary CER was inversely associated with an increased risk of both all-cause mortality and graft failure in OLT recipients. In addition, we are the first to show a more than 2.5-fold higher risk for all-cause mortality and a 3-fold higher risk for graft failure in the lowest tertile when compared to the highest tertile of CER. Further research is warranted to investigate possible mechanisms responsible for loss of muscle mass after liver transplantation.

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AUTHOR CONTRIBUTION

SPS and MCJO analyzed the data and wrote the first draft of the paper. MFE, HB, APB, SJLB, and VEM contributed to the interpretation of the results and provided important advice and intellectual content. SPS, MCJO, HB, APB, and SJLB collaborated in the data collection. All authors had access to the data, contributed to critical revision of the manuscript, and approved the final version of the manuscript.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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SUPPORTING INFORMATION

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

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