ORIGINAL RESEARCH

Renal dysfunction independently predicts muscle mass loss in patients following liver transplantation

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ABSTRACT

BACKGROUND: Liver transplantation (LT) is the only curative treatment for cirrhosis. However, the presence of complications can impact outcomes following LT. Sarcopenia, or muscle mass loss, is highly prevalent in patients with cirrhosis and is associated with longer hospitalization stays and a higher infection rate post-surgery. We aimed to identify patients at higher risk of early sarcopenia post-LT. **METHODS:** This retrospective study included 79 cirrhotic patients who underwent LT. Muscle mass was evaluated using the third lumbar spine vertebra skeletal muscle mass index (SMI) and sarcopenia was defined using established cut-off values. Computerized tomography (CT) scans performed within six-month peri-operative period (three months pre- and post-LT) were included in the study. Complications and comorbidities were collected and correlated to SMI post-LT and predictive models for SMI post-LT were constructed. **RESULTS:** The overall prevalence of sarcopenia was 46% and 62% before and after LT, respectively. Newly developed sarcopenia was found in 42% of patients. Post-LT sarcopenia was associated with longer hospital stays (54±37 vs 29±10 days, $p = 0.002$), higher number of infection (3±1 vs 1±2, $p = 0.027$), and greater number of complications (5±2 vs 3±2, $p < 0.001$) compared to absence of sarcopenia. Multivariate analyses showed that the SMI post-LT was independently associated with pre-LT renal function markers, the glomerular filtration rate (GFR) and creatinine (Model 1, GFR: $\beta = 0.33$; 95% CI = 0.04–0.17; $p = 0.003$; Model 2, Creatinine: $\beta = -0.29$; 95% CI = –0.10 to –0.02; $p = 0.009$). **CONCLUSIONS:** The present study highlights the potential role of renal dysfunction in the development and persistence of sarcopenia after LT.

KEYWORDS: cirrhosis; liver transplantation; renal dysfunction; sarcopenia

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INTRODUCTION

Sarcopenia, or muscle mass loss, is one of the most frequent complications to occur in patients with cirrhosis, affecting 40%–70% of patients on the waiting list for liver transplantation (LT) (1–4). Although LT is considered as a curative treatment for cirrhosis, the presence of complications and comorbidities, including sarcopenia pre- and post-LT, can impact the outcome and affect the health condition of patients. Accordingly, pre-transplant sarcopenia is associated with mortality, hospitalizations, duration of hospital stay, length of intensive care and intubation, infections, hepatic encephalopathy (HE), and quality of life in patients with cirrhosis (4–6). Therefore, preventing and treating sarcopenia remain an important target in the management of patients with cirrhosis.

Muscle mass loss appears concomitantly with malnutrition; resulting from inadequate food intake, altered nutrients digestion/absorption, and hypermetabolism (7,8). Muscle mass loss occurs at the rate of 2.2% per year in patients with cirrhosis which increases with severity of the disease (9,10). The waiting time on the transplant list can exceed six months (11), and thus changes in muscle mass can transpire before surgery and lead to sarcopenia which can provide an inaccurate analysis on the impact of sarcopenia on post-LT outcomes (10,12). Using the recently established sex-based cut-offs to define sarcopenia in cirrhotic patients on the transplant list (13), the aims of this study were the following: (1) to assess muscle mass status within the six-month perioperative transplant period (three months pre- and post-LT) and (2) to identify predictors pre-LT that led to sarcopenia in early post-LT period.

MATERIAL AND METHODS

Study population

This retrospective study included patients who were followed at the Centre hospitalier de l'Université de Montréal (CHUM) (Montréal, Québec) between June 5, 2012 and April 30, 2017. The inclusion criteria were subjects with cirrhosis over 18 years of age who underwent LT with available computerized tomography (CT) scan ≤ 90 days before and after surgery. Cirrhosis diagnosis was confirmed either histologically or radiologically. Exclusion criteria included acute liver failure, multivisceral transplantation, living donor LT, and hereditary and congenital diseases related to the non-functional donated liver. Ethical approval was obtained from the institutional review board at the CHUM.

Outcomes and study variables

Outcomes. The primary outcome of the study was to assess the prevalence of sarcopenia after LT. Secondary outcomes were to identify predictors for skeletal muscle index (SMI) and to evaluate the effect of early post-operative sarcopenia on one-year post-LT clinical outcomes.

Variables. Retrospective data were collected from CHUM medical records. These include demographics, radiology, operative, and laboratory reports. Data such as complications, length of hospital stay post-surgery and episodes of infections were collected. *Skeletal muscle index*. SMI was assessed with a CT scan measured at the third lumbar level vertebrae with or without the use of a contrast agent (Figure 1). Imaging was performed < 3 months before LT and up to three months after surgery. Pre-LT abdomen CT scan were mainly performed for LT evaluation, while post-LT CT scan were mainly indicated for suspected infections (Supplementary Table 1). Sequential CT scans taken within ≤ 7 days before and after LT were excluded. CT scans were analyzed with SliceOmatic V5.0 Rev-5 (Tomovision, Montréal, Québec, Canada). To calculate the SMI, skeletal muscle cross-sectional areas were defined using the Hounsfield unit threshold of –20 to +150. *Sarcopenia*. Sarcopenia was defined using cut-offs established in a population who suffered from end-stage liver disease and awaiting LT (male SMI < 50 cm^2/m^2; female SMI < 39 cm^2/m^2), according to Carey et al (13). *Length of hospital stay.* The length of hospital stay corresponds to the number of days spent in hospital after LT. *Complications.* Presence of the 13 most frequent complications (pleural effusion, dysglycemia, electrolyte imbalance, upper gastrointestinal bleeding, renal dysfunction [acute/chronic renal dysfunction, hepatorenal syndrome, acute tubular necrosis, dialysis], portal hypertension, spontaneous bacterial peritonitis, pneumonia, other respiratory issues, compromised bone health, splenomegaly, HE, and fluid retention [edema and/or ascites]) which occurred before LT and up to 12 months after LT. *Episodes of infections.* Any episode of infection which occurred before LT and up to 12 months after LT, including number of episodes of pneumonia, and spontaneous bacterial peritonitis.

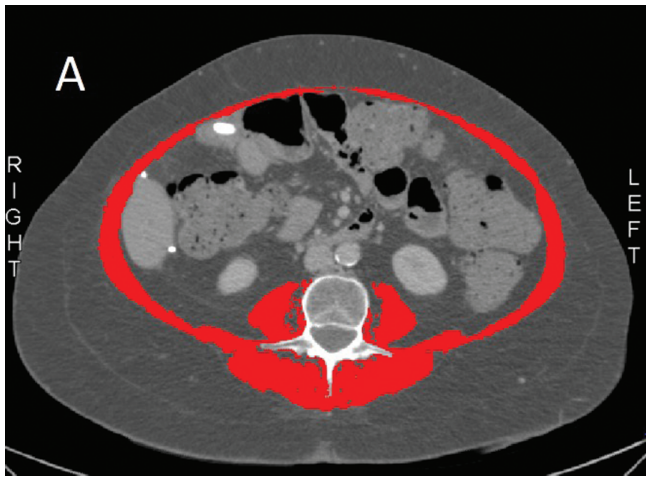

Figure 1: Cross sectional imaging

Notes: abdominal CT scan acquired in a woman at the third lumbar level; skeletal muscle index (SMI) was expressed as cross-sectional muscle area (in red)/height²; the present patient had sarcopenia with a body mass index of 30 kg/m² and SMI of 36.4 cm2/m²

Statistical analysis

Statistical analysis were performed with SPSS Statistics Version 25 software. Continuous variables were presented as means with standard deviation. Categorical variables were expressed as frequency and percentage. Chi-square test was used to compare groups and estimate the difference in percentages (with the 95% confidence interval). Differences before and after LT were assessed by paired *t*-test for SMI. Analysis of covariance was used to compare clinical outcomes between sarcopenic and non sarcopenic patients after LT, controlling for age. Pearson's correlation test was performed to analyze the relation between SMI post-LT and clinical outcomes (length of hospitalization, complications post-LT, infections post-LT). Predictive models for SMI after LT were constructed using linear regression. Variables with a p <0.20 in the univariate analysis were included in a multivariate linear regression analysis; after the collinearity test for the following pre-LT covariates: age, body mass index (BMI), Model for End-stage Liver Disease (MELD) score, SMI, total protein levels, number of common complications, number of episodes of infections, glomerular filtration rate (GFR), and creatinine. Considering collinearity between GFR and creatinine levels, two separate predictive models were run. Model 1 included all variables + GFR, while Model 2 included all variables + creatinine levels. Covariates were chosen according to their potential effect on SMI reported in literature (14,15). *P* values < 0.05 were considered significant.

RESULTS

Clinical and sociodemographic characteristics of the studied patient population are described in Table 1. In total, data from 79 patients with cirrhosis were included and analyzed in the study according to the flow chart in Figure 2. The cohort consisted of 62% men, the mean age was 54±11 years old, and alcohol was the most common etiology of liver disease (34%). The mean MELD score of the group was 25±5. 9% of patients were classified as Child-Pugh A, 14% as Child-Pugh B, and 61% as Child-Pugh C. Moreover, the mean BMI was 26±5 kg/m². The mean SMI was 47.9±9.1 cm²/m², whereas means for creatinine, GFR and total proteins levels were, respectively, 89±41 mmol/L, 82±26 ml/min/1.73m² and 62±11 g/L. Prevalence of common complications was as follow: 58% fluid retention (edema and/or ascites), 52% HE, 47% renal dysfunction, 46% sarcopenia, 43% electrolyte imbalance, 35% upper gastrointestinal bleeding, 35% portal hypertension, 25% spontaneous bacterial peritonitis, 22% pleural effusion, 20% pneumonia, 19% others respiratory issues, 18% splenomegaly, 13% compromised bone health, and 13% dysglycemia.

The mean time for pre-LT and post-LT CT scans was 40 days and 25 days, respectively. The presence of sarcopenia increased from 46% pre-LT to 62 % post-LT. Among patients who were sarcopenic before LT, 14% had resolved sarcopenia after LT whereas 86% remained sarcopenic. Among patients who were not sarcopenic before LT, 58% did not develop sarcopenia; however, 42% had become sarcopenic after transplantation. Apart from patients where sarcopenia was resolved (pre-LT 39.4±3.7 vs post-LT 47.6±7.7 cm²/m², p <0.02), all patients experienced a decrease of SMI after LT (persistent: pre-LT 42.2±5.8 vs post-LT 39.0±5.9 cm²/m², p = 0.0005; newly: pre-LT 50.0±7.7 vs post-LT 41.0±7.9 cm²/m², p <0.0001; never: pre-LT 55.2±8.5 vs post-LT 53.7±8.0 cm²/m², p = 0.12) (Figure 3). The presence of sarcopenia post-LT was associated with worst clinical outcomes after LT. Sarcopenic patients post-LT had longer stays in the hospital after LT (54±37 vs 29±10, p = 0.002) and experienced, at one year, greater number of complications (5±2 vs 3±2, p <0.001) and episodes of infection (3±1 vs 1±2, p = 0.027) compared to non-sarcopenic patients (Table 2). As well, SMI

Table 1: Patients' characteristics before liver transplantation

Number of patients (percentage)	79 (100%)
Men	49 (62%)
Women	30 (38%)
Age (Years)	54±11
MELD-Na Score	25±5
Child-Pugh class (A/B/C)*	7/11/48 (9%/14%/61%)
Common etiology of cirrhosis†	
ROH	27 (34%)
NASH	18 (23%)
HCV	19 (24%)
PBC	11 (14%)
PSC	7 (9%)
BMI (kg/m²)	26±5
L3 SMI (cm²/m²)	47.9±9.1
Creatinine (mmol/L)	89±41
GFR (ml/min/1.73m²)	82±26
Total protein (g/L)‡	62±11
DM	27 (35%)
CVD	37 (47%)
HCC	20 (25%)
Complications	
Fluid retention	46 (58%)
Hepatic encephalopathy	41 (52%)
Renal dysfunction	37 (47%)
Acute renal dysfunction	17 (22%)
Chronic renal dysfunction	4 (5%)
Hepatorenal syndrome	14 (18%)
Hemodialysis	2 (3%)
Sarcopenia	36 (46%)
Electrolyte imbalance	34 (43%)
Portal hypertension	28 (35%)
Upper gastrointestinal bleeding	28 (35%)
Spontaneous bacterial peritonitis	20 (25%)
Pleural effusion	17 (22%)
Pneumonia	16 (20%)
Other respiratory disorders	15 (19%)
Splenomegaly	14 (18%)
Compromised bone health	10 (13%)
Dysglycemia	10 (13%)

Note: Data are presented as mean±standard deviation and frequency (%) for continuous variables and categorical variables respectively

** Missing data for 13 patients*
† Patients may have several concurrent etiology of cirrhosis
‡ Missing data for 35 patients
BMI = Body mass index; MELD = Model for End-Stage Liver Disease, ROH = Alcohol, PBC = Primary biliary cholangitis; NASH = Non-Alcoholic steatohepatitis; PSC = Primary steatohepatitis cholangitis; HCV = Hepatitis C virus; DM = Diabetes mellitus; CVD = Cardiovascular diseases; HCC = Hepatocellular carcinoma

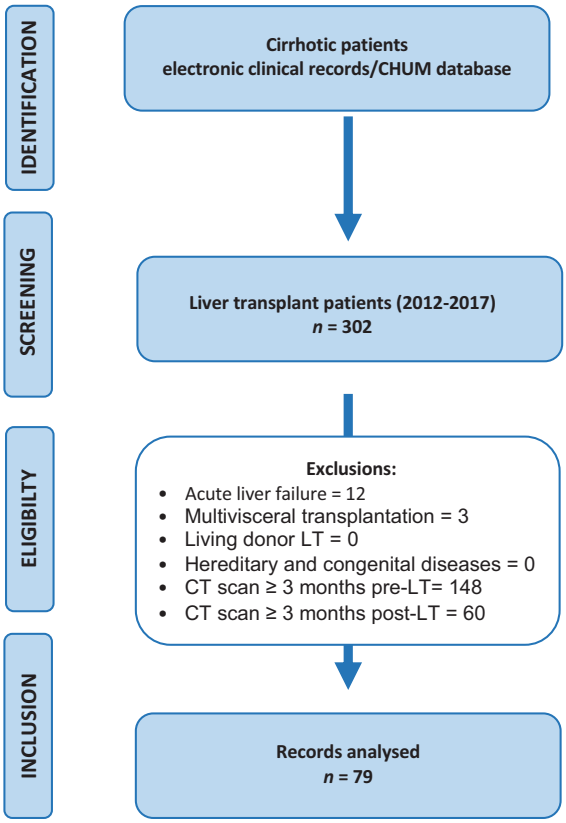

Figure 2: Flow chart of patients' recruitment

post-LT was negatively correlated with the number of complications ($r = –0.34$, $p = 0.002$), episodes of infections ($r = –0.26$, $p = 0.019$), and days of hospitalization ($r = –0.45$, $p < 0.001$) (Figure 4).

Two predictive models for SMI post-LT were constructed using multiple linear regression adjusted for pre-LT factors namely age, BMI, MELD score, SMI, total protein levels, number of common complications, number of episodes of infections; and adding GFR for Model 1 and creatinine levels for model 2 (Model 1, $R^2 = 0.71$, $p < 0.0001$; Model 2, $R^2 = 0.69$, $p < 0.0001$). The analysis showed that the SMI post-LT was independently associated with pre-LT renal function markers, GFR and creatinine (Model 1, GFR: $\beta = 0.33$; 95% CI = 0.04–0.17; $p = 0.003$; Model

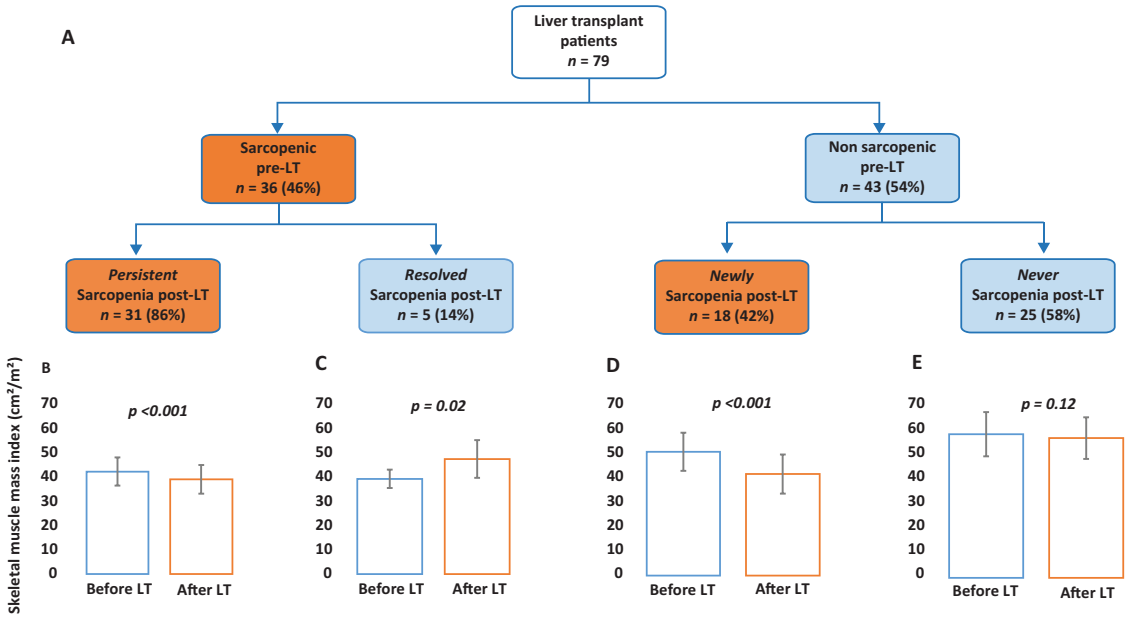

Figure 3: Evolution of skeletal muscle mass index (SMI) and sarcopenia prevalence after transplantation

Notes: (A) shows prevalence of sarcopenia expressed as frequencies and percentages; (B-E) show the comparison of SMI before and after LT; paired t-test was performed to compare SMI before LT vs SMI after LT, difference considered significant at p < 0.05

Table 2: Adjusted comparison of clinical outcomes by sarcopenia status after LT

	Sarc-	Sarc+	*p* value
Post-LT complications	3±2	5±2	< 0.001
Post-LT Episodes of infection	1±2	3±2	0.027
Post-LT Length of hospital stay (days)*	29±10	54±37	0.002

Notes: Data are presented as mean and standard deviation; analysis of covariance was used to assess the effect of sarcopenia on clinical outcomes, controlling for age; significance considered at p <0.05
** Missing data for four patients*
Sarc- = Non-Sarcopenic; Sarc+ = Sarcopenic

2, Creatinine: β = –0.29; 95% CI = –0.10 to –0.02; p = 0.009). In both models, the baseline SMI pre-LT was the greatest predictor of SMI post-LT (Model 1, β = 0.52, 95% CI = 0.22–0.84, p = 0.001; Model 2, β = 0.60, 95% CI= 0.29–0.94, p <0.001) (Table 3). In agreement with our predictive models, patients who had renal dysfunction before LT showed lower SMI post-LT (p = 0.043) and were at higher risk of developing sarcopenia (RR = 3.11, 95% CI= 1.19–8.16, p = 0.021). In addition, post-LT sarcopenic patients had a lower baseline GFR (91±23 vs 75±28 ml/min/1.73m^2, p = 0.003) and higher baseline creatinine levels (75±25 vs 106±75 mmol/L, p = 0.018) compared to non-sarcopenic patients (Figure 5).

DISCUSSION

To date, LT is the only curative treatment for patients with cirrhosis. Receiving a new liver is a rare privilege, so it is important to optimize recovery of patients following LT by identifying factors pre-LT that could promote negative outcomes. Using the cut-offs specific to the cirrhosis population on the transplant waiting list, we demonstrated that the prevalence of sarcopenia post-LT (62%) was higher than that of sarcopenia pre-LT (46%). Moreover, we observed newly onset sarcopenia in 42% patients within a three-month post-operative period. After adjusting for confounding variables, SMI and renal failure markers (GFR and creatinine) were found to be independent predictors for SMI post-LT. In addition, we showed that patients with renal dysfunction pre-LT were at higher risk of developing sarcopenia post-LT. Together, we demonstrated that renal dysfunction was associated with the development as well as the persistence of sarcopenia in patients following LT.

Imaging by CT scan is still the most well-validated method to assess sarcopenia in patients with cirrhosis (16,17). In the present study, L3 SMI cut-offs were used as follow: male SMI < 50 cm^2/m^2;

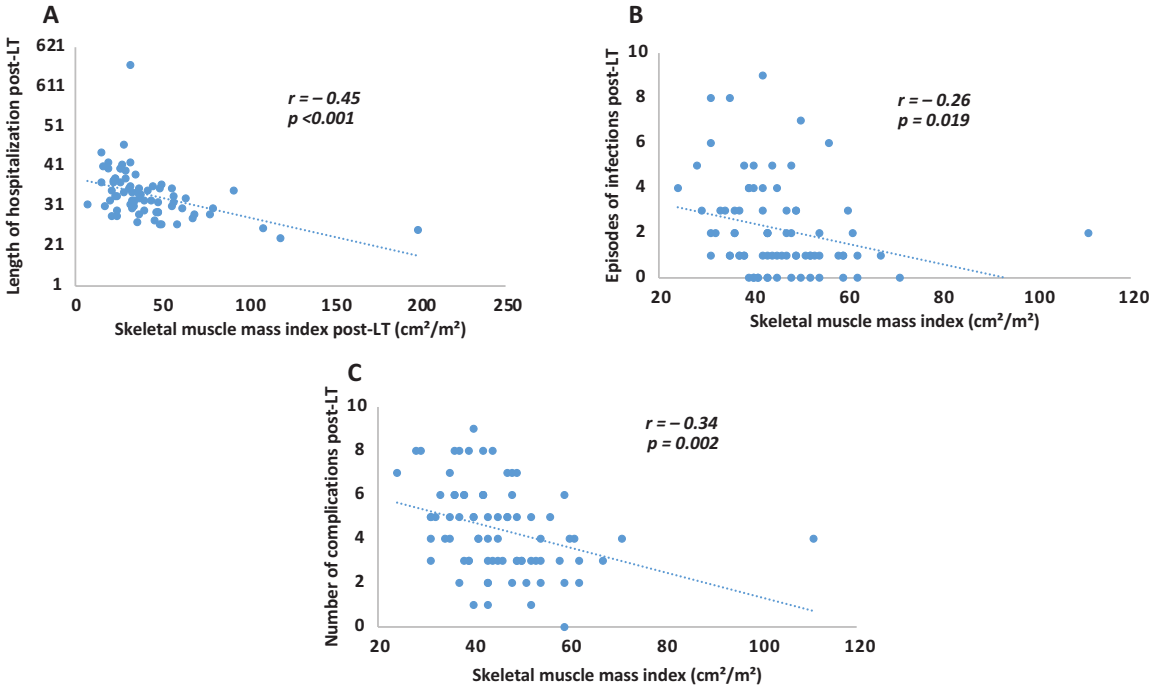

Figure 4: Pearson correlation analysis between skeletal muscle index (SMI) and clinical outcomes post-LT

Notes: Figure 4 illustrates distribution of points, each point representing each patient; (A), (B) and (C) show the relation between the SMI and the length of hospitalization, number of episodes of infections post-LT and the number of complications occured post-LT, respectively; a negative Pearson's coefficient r indicates a negative relation between variables; correlation was considered significant at p < 0.05

Table 3: Multivariate regression analyses to predict skeletal muscle index after liver transplantation

	Model 1			Model 2		
	Beta	95% CI	*p* value	Beta	95% CI	P value
Age	0.10	–0.110 to 0.281	0.382	0.021	–0.180 to 0.216	0.852
BMI	–0.01	–0.46 to 0.43	0.946	–0.020	–0.499 to 0.423	0.867
MELD-Na	0.01	–0.37 to 0.42	0.917	–0.026	–0.450 to 0.362	0.827
Total Protein	–0.04	–0.22 to 0.16	0.749	–0.038	–0.228 to 0.166	0.748
SMI (pre-LT)	0.52	0.22–0.84	0.001	0.602	0.294–0.936	<0.001
Complications	–0.19	–0.19 to –1.44	0.159	–0.197	–1.660 to 0.297	0.166
Infections	–0.08	–2.09 to 1.00	0.478	–0.082	–2 .172 to 1.039	0.482
GFR	0.33	0.04–0.17	0.003			
Creatinine				–0.285	–0.104 to –0.016	0.009

Notes: Multivariate regression was performed with a sample of 44 patients; significance considered at p *<0.05*
BMI = Body mass index; MELD = Model for End-Stage Liver Disease; SMI = Skeletal muscle index; GFR = Glomerular filtration rate; LT = Liver transplantation

female SMI < 39 cm^2/m^2 as defined Carey et al and recommended by the European Association for the Study of the Liver (EASL) (13,18). We included patients who received a CT scan (to evaluate SMI) within six-months peri-operative period (three months pre- and post-LT). Three months is a key period of time in nutrition assessment which distinguishes acute from chronic phase of malnutrition. Acute malnutrition appears and installs in less than three months and is commonly associated

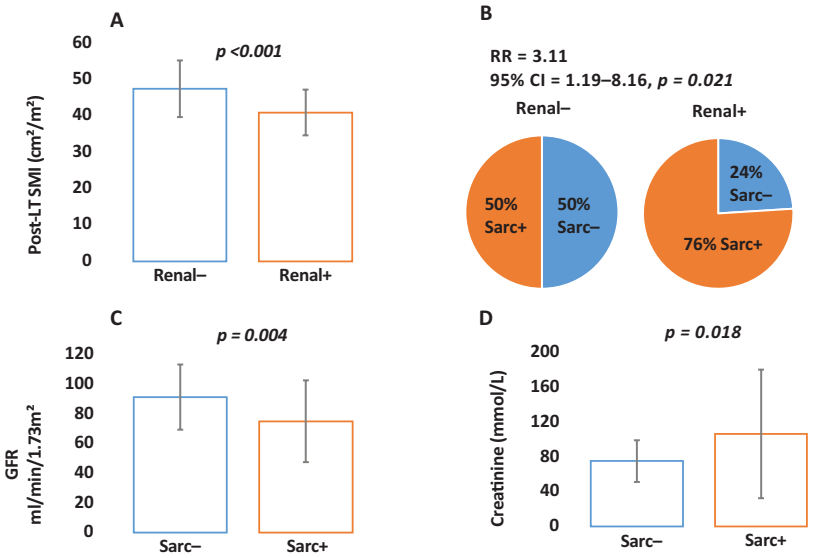

Figure 5: High prevalence of sarcopenia after LT in patients with pre-transplant renal dysfunction

Notes: (A) shows the comparison of skeletal muscle index (SMI) post-LT between patients with and without renal disease. In (B) are shown prevalence of sarcopenia expressed as percentages and categorized by absence or presence of renal disease, respectively; (C) and (D) Represent estimated GFR and creatinine levels in non sarcopenic vs sarcopenic patients RR = Relative risk; LT = Liver transplantation; Renal– = No renal disease; Renal+ = Renal disease; Sarc– = Non sarcopenic; Sarc+ = Sarcopenic; GFR = Glomerular filtration rate

with illness or temporary situation affecting food intake (19,20). Malnutrition is known to be related to muscle weakness and loss (21). However, malnutrition is a reversible risk factor, so early detection is important. The peri-operative period, referred to as pre-, intra-, and post-operative phases, is a critical and an important period in order to reduce complications and improve outcomes post-surgery (highlighted by the Enhanced Recovery After Surgery [ERAS] program) (22,23). In the context of LT, the pre-operative phase consists in prioritization and identification of patients at high risk and involves multiple biochemical analyses which require fasting (24,25). The frequency of these tests increases as the disease progresses and LT approaches. Moreover, invasive procedures such as varices ligation also require fasting and contribute to inadequate dietary intake, which may promote acute malnutrition and increase the prevalence of sarcopenia at the time of LT (26). The post-operative phase is also important in peri-operative medicine as it determines potential future complications. Unfortunately, liver transplant recipients may also experience acute malnutrition in the early post-operative phase due to surgical stress and complications, immunosuppression therapy, surgery related hypermetabolism, or more fasting clinical tests, exposing them to early muscle wasting and other complications (24). Of note, in our study, 86% of CT scans after LT were performed less than one month after surgery allowing us to have accurately describe the muscle status post-LT. In our cohort, 46% of patients were sarcopenic before LT, similar to findings observed in other studies which reported 41% to 48% of pre-LT sarcopenia (4,6,15).

Interestingly, the majority of patients in our cohort developed a decline in muscle mass (ie, SMI) resulting in higher number of patients with sarcopenia post-LT (62%). Furthermore, 42% of patients who were non-sarcopenic before LT, became sarcopenic within three months post-LT. This finding supports our hypothesis of possible acute malnutrition related muscle wasting. Other studies have reported newly developed sarcopenia in patients but were assessed one year after LT (12,27). Using the psoas muscle area to define sarcopenia, Tsien et al reported an increase in the onset of sarcopenia from 62.3% to 86.8% (27), while Jeon et al observed an increase from 36% to 46% (12). However, it is unclear whether sarcopenia developed as early as three months or was due to factors occurring greater than three months post-LT. Few previous studies have addressed the onset of early sarcopenia (within three months post-LT). Some studies evaluated muscle function and showed early improvements in muscle function within six months after LT (28–30). In a prospective study measuring both muscle mass and function, it was demonstrated that improvement in hand grip values

occurred independently to improvement in muscle mass, three months after LT (31). Our study is the first to describe acute muscle wasting post LT which is critical to identify in order to prevent sarcopenia and manage related negative outcomes.

Pathogenesis of sarcopenia is a complex and multifactorial system. In patients with cirrhosis, in addition to age and malnutrition, increased catabolic state is one of the main causes of sarcopenia. Hypermetabolism increases consumption of amino acids as energy sources and decreases protein synthesis, resulting in muscle wasting and sarcopenia (2,32,33). In the present study, a multivariate analysis after adjusting for age, BMI, MELD score, complications, and infections revealed that SMI, and GFR and creatinine levels pre-LT were independent predictors for SMI post-LT. In this regard, lower SMI pre-LT predicted lower SMI post-LT consistent with a high rate of persistent sarcopenia in our cohort (86%). This finding is in agreement with previous studies in literature that reported persistent sarcopenia in patients after LT (4,27).

A novel observation from our results is that high creatinine levels predicted low post-LT SMI, while low GFR predicts low post-LT SMI. Moreover, patients with renal dysfunction were at higher risk of having sarcopenia within three months after LT. Renal impairment is commonly observed in patients with cirrhosis (34,35) (47% of patients exhibited renal dysfunction in our study) and creatinine levels are carefully considered in the calculation of MELD score to predict survival after LT (34,36). The relationship between renal function and sarcopenia in patients with cirrhosis has not been thoroughly studied; however, a recent French study recently reported high rate of 72% sarcopenic in patients undergoing simultaneous liver and kidney transplantation using the same Carey's criteria (37). Sarcopenia is commonly observed in patients with chronic renal disease, affects 11% to 29% in early stages of renal disease, and can reach over 65% in patients requiring dialysis (38–40). Furthermore, several studies reported associations between sarcopenia and low GFR (41), high proteinuria (39,42), and albuminuria (43) in renal patients. Mechanisms underlying these observations are not clear. De Souza et al proposed a role of inflammation in the development of sarcopenia in patients suffering from renal dysfunction and reported high levels of hs-CRP and low levels of IL-4 in patients with renal dysfunction and sarcopenia (39). This is in agreement with a meta-analysis which included 3,072 sarcopenic patients and stated significant high levels of inflammatory marker CRP in patients with sarcopenia than in controls. In addition, other studies highlighted the role of mitochondria in the pathogenesis of sarcopenia in the context of renal dysfunction (40,44). Impaired mitochondrial function, which plays an important energy metabolism and amino acid metabolism, results in muscle function impairment and consequently muscle mass loss (45). Indeed, amino acids are necessary for the activation of the mammalian target of rapamycin (mTOR) signalling pathway which is required for the stimulation of human skeletal muscle protein synthesis (46). Besides, Plank et al reported a loss of 10% of total body protein from skeletal muscle during the first 10 days after LT (31). Muscle constituting a major reservoir of total body protein (47), a reduction in total body protein would be associated with reduction in muscle mass. Overall, renal dysfunction may lead to changes in mitochondria metabolism leading to an increase in oxidative stress and inflammation. Conversely, inflammation and oxidative stress may induce mitochondria damage in patients with renal dysfunction resulting in muscle wasting (45,48). Alcohol consumption could explain the relationship between sarcopenia and renal impairment in the context of cirrhosis. Alcohol abuse induces liver inflammation and has been associated with myopathy (49–51). A recent study by de Silva et al suggested a role of the inducible nitric oxide synthase in ethanol-induced oxidative stress and pro-inflammatory cytokines production in the kidney (51). These findings could explain our results since alcohol was the main cause of liver disease. However, alcohol-induced oxidative and inflammatory state on kidney function merits to be properly investigated. Taken together, acute malnutrition with impaired metabolism linked to renal dysfunction may synergistically contribute to muscle mass loss in the early stage of post-transplant recovery.

The prognostic value of sarcopenia in cirrhotic patients undergoing LT has attracted increasing interest in recent years. Previous studies have reported the role of sarcopenia on clinical outcomes after LT (52). However, in comparison to our study, those studies assessed sarcopenia at the listing time for LT (4,15,53). As our results showed that muscle mass was subject to changes during a six-month peri-operative period of time, it would be important to reconsider the timing for sarcopenia

assessment and schedule CT scan for all patients within three months post-LT. Indeed, many patients become sarcopenic early following LT and might be at higher risk of long-term negative outcomes. Accordingly, we demonstrated that early (< 3 months) post-transplant sarcopenia was associated with an increased number of complications, infections and longer hospital stays after LT. The association between sarcopenia and clinical outcomes post-LT is difficult to explain. Though, some explanations can be proposed. Sarcopenia is correlated to frailty and physical limitations (54). Yet, sedentary lifestyle is common in liver transplant recipients especially in the early post-operative period (52,55). Both sarcopenia and physical inactivity may progress together after surgery leading to negative clinical outcomes such as metabolic disorders, including diabetes and cardiovascular diseases.

Study limitations

We acknowledge limitations of our study due to retrospective and cross-sectional design. In line with this, we recognize the following limitations: (1) small size of our cohort because of missing data and reliance on available CT scans acquired according to clinical indications, (2) the retrospective nature did not allow us to evaluate physical performance (For a thorough evaluation of muscularity, the four following criteria should be considered: quantity [SMI], quality [myosteatosis], strength, and functional capacity), and (3) statistical analyses were also limited due to retrospectively missing data. Thus, some confounding factors were not considered in multivariate analysis. Though, our predictive models were able to predict more than 68% variation of SMI.

CONCLUSION

This is the first study to evaluate the course and impact of sarcopenia within three months of the post-operative period. We demonstrated that 42% of our cohort who were non-sarcopenic before LT became sarcopenic within three months after LT. A novel finding of this study is the potential role of renal dysfunction in the development and persistence of sarcopenia after LT. Hence, further studies are needed to elucidate pathophysiological mechanisms underlying the relationship between renal impairment and sarcopenia in the context of cirrhosis.

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CONTRIBUTIONS:

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ETHICS APPROVAL: The study been reviewed by Comité d'éthique à la recherche (CÉR) du CHUM.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: CT scan medical indication

Pre-LT CT scan indications	Frequency
LT evaluation	36 (46%)
Thrombosis surveillance	10 (13%)
HCC surveillance	7 (9%)
Abdominal pain	6 (8%)
Others	20 (25%)
Post-LT CT scan indications	
Suspected infections (collections, abscess)	38 (48%)
Vascular assessment (thrombosis, abdominal bleeding)	23 (29%)
Others	18 (23%)