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Pre-Liver Transplant Muscle Loss Is a Risk Factor for Post-Liver Transplantation Left Ventricular Systolic Dysfunction

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Background: The development of left ventricular systolic dysfunction (LVSD) after liver transplant (LT) can result in increased morbidity and mortality in the immediate period following liver transplant. The aim of this study was to evaluate low muscle mass due to chronic liver disease, as a potential risk factor for LVSD after LT.

Material/Methods: A retrospective chart review was completed for all adult patients who received a liver transplant between January 2002 and January 2015 at a single academic LT center. Collected data included patient demographics, medical history, laboratory data, radiology results, and pathology. Echocardiograms were reviewed for patients identified as having LVSD diagnosed within 1 year after LT (left ventricular ejection fraction <55%). The total psoas area (TPA), a marker of low muscle mass, was determined by measuring the average cross-sectional area of the psoas muscle on MRI or CT scans before transplant at the level of L4 vertebra.

Results: Of the 503 post-LT patients reviewed, 144 (28.6%) had pre-and post-LT echocardiograms. Of these 144 patients, 17 developed LVSD, of which 15 (88.2%) occurred within 1 year after LT. The average age at transplant of those with LVSD was 58.9±6 years, with a mean MELD score of 30.7±6. The mean TPA normalized for height for patients with LVSD was 297.68±86.99 mm^2/m^2 compared to 382.1±104.2 mm^2/m^2 for those with normal EF (p= 0.002). BMI, MELD score, and etiology of cirrhosis were not significant risk factors for post-LT LVSD in our study population. During the study period, 35.2% (n=6) of LVSD patients died within 1 year after LT.

Conclusions: Although LVSD is thought to be a rare complication after LT, those with muscle loss as predicted by mean TPA measurements normalized for height may be at highest risk.

MeSH Keywords: **Liver Transplantation • Sarcopenia • Ventricular Dysfunction, Left**

Abbreviations: **ETOH** – alcohol; **BMI** – body mass index; **CT** – computed tomography; **EF** –ejection fraction; **HCV** – hepatitis C virus; **HCC** – hepatocellular carcinoma; **LT** – liver transplantation; **LVCD** – left ventricular systolic dysfunction; **MRI** – magnetic resonance imaging; **MELD** – model for end-stage liver disease; **OLT** – orthotopic liver transplant; **TPA** – total psoas area; **TTE** – transthoracic echocardiogram

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Background

Cardiovascular complications have been identified in over 70% of orthotopic liver transplant (OLT) patients, with 3.4% developing cardiomyopathy despite a thorough preoperative cardiac evaluation [1]. The development of left ventricular systolic dysfunction (LVSD) has particularly been associated with significant morbidity after LT; however, the cause of LVSD after LT development are still unclear [2]. A study showed cardiovascular morbidity and mortality rates in the first year after transplant were 15.2% and 2.8%, respectively, and after the first were 3.9% and 2%, respectively [3]. LVSD is characterized by a reduced ejection fraction (EF), for which <45% is often used based on guidelines from American College of Cardiology Foundation/American Heart Association [4]. Previous studies have investigated the hemodynamic changes after successful OLT and found those patients to have increased systemic vascular resistance and decreased cardiac output, but further studies indicated that reduced cardiac performance could not be explained by decreased preload or excessive afterload, and is hypothesized to be due to the intrinsic depression of myocardial contractility [5,6]. Other researchers have suggested that there is a degree of reversible cardiomyopathy due to increased systemic vascular resistance after successful LT; however, this may also be due to an unmasking of cirrhotic cardiomyopathy, a distinct entity, by the physical or pharmacological strain that occurs during OLT [7,8]. A study reported abnormal cardiac response in 22.5% of 209 patients after reperfusion; as identification of this post-transplant complication was underestimated by the usual diagnostic tools, the abnormal cardiac response might be related to circulatory dysfunction with advanced liver disease [9]. Without adequate preoperative prognostication, it is impossible to identify those patients most at risk of developing cardiomyopathy after LT.

A promising avenue of investigation is the evaluation of low muscle mass, or decreased muscle mass, as a risk factor for complications after LT [10]. Low muscle mass may be accelerated in chronic medical illnesses such as end-stage liver disease, and malnutrition. One method of diagnosing low muscle mass is measuring the total psoas area (TPA), a marker of low muscle mass, determined by measuring the average cross-sectional area of the psoas muscle on MRI or CT scans before transplant at the level of L4 vertebra [10]. Our aim here was to evaluate low muscle mass as a potential risk factor for LVSD after LT. Given that CT and MRI of the abdomen are a common part of the transplant workup in our institution, we used these studies to determine the mean total psoas muscle area of a common transverse abdominal section in our patients [10–12].

Material and Methods

Study Sample

This study was approved by the Thomas Jefferson University Hospital Institutional Review Board. We retrospectively reviewed the charts of 503 patients from January 2002 and January 2015 who underwent liver transplantation at Thomas Jefferson University Hospital. Only those patients with available pre-transplant cross-sectional imaging studies and transthoracic echocardiography (TTE) evaluation were included in the study population for analysis. The required imaging studies within 1 year before transplant included a computed tomography (CT) or magnetic resonance imaging (MRI) prior to transplantation with imaging at the level of the L4 vertebral body, TTE prior to LT, and TTE with EF after LT. Patients requiring repeat liver transplant were excluded.

Data collection

Collected data included patient demographics, medical history, laboratory data, radiology results, and liver pathology. We also recorded Model for End-Stage Liver Disease (MELD) scores at the time of LT. When multiple data points were available, we used imaging, laboratory data, and body mass index (BMI) calculations from the closest date prior to LT. The etiology of cirrhosis was determined by patient history, serologies, and pathology reports. The mean TPA, used as a marker of low muscle mass, was determined by a single radiologist measuring the cross-sectional area of the psoas muscles on pre-transplant MRI or CT scans at the level of the L4 vertebral body; the areas of the right and left psoas muscles were averaged to determine a mean TPA (Figure 1). The L3–L4 level is commonly used to study chronic medical illnesses, and was originally used to identify sarcopenic obesity in cancer patients [13]. During pre-transplant evaluation, these patients underwent either a CT or MRI scan, which was then archived in our electronic medical record archive. CT and MRI scans are equivalent in measuring muscle mass [14].

EF was recorded from TTE reports; for those patients in whom the post-LT EF was recorded as normal, EF was attributed to be the same as pre-transplant TTE. LVSD was defined as an EF less than or equal to 45% after transplant. BMI was determined as weight divided by height squared. TTE was only obtained after transplant if there was clinical need for this study, as it is not part of our current post-transplant protocol. Total muscle mass at the L3 vertebra on CT scan has previously been shown to be linearly related to whole-body muscle mass, which we extrapolated to the psoas muscle at the L4 level, as examined in previous studies of low muscle mass in post-LT patients, for its ease of identification and measurement at this level [10,12]. Mean TPA was then corrected for height squared (mm^2/m^2) to determine relative muscle mass due to the linear correlation of muscle mass to height squared [11].

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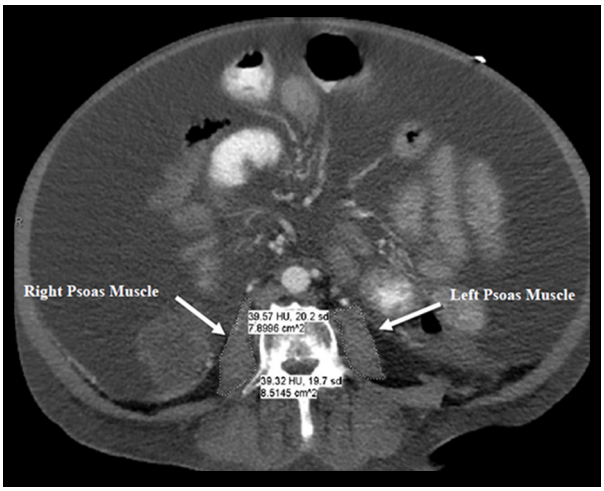

Figure 1. CT abdomen/pelvis at L4 vertebral level demonstrating patient total psoas area. The mean cross-sectional area of the left and right psoas muscle at the level of the fourth lumbar vertebra (L4) was determined. This was accomplished by first identifying the individual vertebral levels on a CT scan of the abdomen and pelvis. We then selected the individual imaging slice at the mid-portion of the L4 vertebra and outlined the borders of the left and right psoas muscle. The cross-sectional area (in mm^2) of the enclosed regions was used to calculate the mean total psoas muscle area (TPA).

Statistical analyses

We used a 2-sample *t* test to compare age, MELD score, and TPA in patients with and without LVSD. A chi-square test was used to evaluate for a significant association between specific etiologies of liver disease and LVSD. Sub-analysis was performed to determine whether there were any specific differences in the variables associated with LVSD by sex.

Results

Among 503 patients who were transplanted between January 2002 and January 2015, 144 patients (28.6%) had pre-and post-LT echocardiograms and imaging at the level of the L4 vertebral body. LVSD was identified in 17 of these patients. Of the patients with LVSD, the average age at transplant was 58.9±6 years, with a mean MELD score at time of LT of 30.7±6. Most of the patients were males (75.6%). Seven of the 17 patients with LVSD had cardiac catheterization completed after development of LVSD was discovered with no significant coronary artery disease found. There were no significant differences between those with LVSD and those without LVSD in terms of age, MELD score at time of LT, etiology of cirrhosis, and presence of HCC (Table 1). Most patients with LVSD had hepatitis C-related disease (58.8%), followed by combined HCV/alcohol (17.6%),

Table 1. Total patient population comparison between normal Ejection fraction (EF) and Left ventricular systolic dysfunction (LVSD) patients.

	Normal EF patients (EF >45%)	LVSD patients (EF ≤45%)	p value
Variable			
Number of patients	127	17	N/A
Mortality within 1 year of transplant	17 (13.3%)	6 (35.3%)	N/A
Age	56±8.5	58.9±6	0.18
MELD	28.9±7.6	30.7±6	0.32
Male sex	64.7% (96)	75.6% (11)	0.34
HCC	39.3%(50)	23.5%(4)	0.21
Etiology of cirrhosis			
Hepatitis C	65 (51.2%)	10 (58.8%)	0.56
Alcohol	17 (13.4%)	1 (5.9%)	0.3
Hepatitis C and alcohol	12 (9.4%)	3 (17.6%)	0.38
Nonfulminant or drug induced	122 (96.1%)	16 (94.1%)	0.89
Fulminant or drug induced	5 (3.9%)	1 (5.9%)	0.71
BMI	29.59±6.46 kg/m^2	27.01±4.45 kg/m^2	0.11
Mean TPA/m^2	382.1±104.2 mm^2/m^2	297.68±86.99 mm^2/m^2	**0.002**

MELD – Model for end stage liver disease; HCC – hepatocellular carcinoma; BMI – body mass index; TPA – total psoas area.

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Table 2. Male population comparison between normal Ejection fraction (EF) and Left ventricular systolic dysfunction (LVSD) patients.

	Normal EF patients (EF >45%)	LVSD patients (EF ≤45%)	p Value
Number of patients	96	11	N/A
Age	56±8.5	58.2±6.3	0.40
MELD	29±7.4	32.5±5.5	0.13
Etiology of cirrhosis			
Hepatitis C	53 (55.2%)	7 (64%)	0.60
Alcohol	14 (14.6%)	1 (9.1%)	0.62
Hepatitis C and alcohol	12 (12.5%)	2 (18.2%)	0.60
Fulminant or drug induced	2 (2.1%)	1 (9.1%)	0.19
BMI			
Mean TPA/m^2	1241.70±318.80 mm^2/m^2	993.78±301.08 mm^2/m^2	**0.017**

MELD – Model for end stage liver disease; HCC – hepatocellular carcinoma; BMI – body mass index; TPA – total psoas area.

Table 3. Female population comparison between normal Ejection fraction (EF) and Left ventricular systolic dysfunction (LVSD) patients.

	Normal EF patients (EF >45%)	LVSD patients (EF ≤45%)	p Value
Number of patients	31	6	n/a
Age	56.3±8.8	60.3±4.9	0.29
MELD	28.2±8.3	27.5±6.5	0.82
Etiology of cirrhosis			
Hepatitis C	12 (38.7%)	3 (50%)	0.62
Alcohol	3 (9.7%)	0	N/A
Hepatitis C and alcohol	0	1 (16.7%)	N/A
Fulminant or drug induced	3 (9.7%)	0	N/A
BMI	29.59±6.46 kg/m^2	27.01±4.45 kg/m^2	0.11
Mean TPA/m^2	327.30±89.60 mm^2/m^2	254.32±61.68 mm^2/m^2	**0.065**

MELD – Model for end stage liver disease; HCC – hepatocellular carcinoma; BMI – body mass index; TPA – total psoas area.

alcohol (5.9%), and fulminant or drug-induced (5.9%). Mean BMI was similar between those without LVSD and those with LSVD, at 29.59±6.46 kg/m^2 and 27.01±4.5 kg/m^2, respectively.

The only statistically significant difference between those with normal heart function and those with LVSD after LT was a significantly lower mean TPA. Specifically, the mean TPA normalized for height for patients with LVSD was 297.68±86.99 mm^2/m^2 compared to 382.1±104.2 mm^2/m^2 for those with normal EF (p=0.002). Additionally, of the patients with LVSD, 35.2% (n=6) died within 1 year after LT.

Subgroup analysis by sex

Among 107 male patients in our cohort with echocardiographic correlation, 11 (10%) developed LVSD after LT (Table 2). Males without LVSD had a mean TPA 1241.70±318.80 mm^2/m^2 compared with 993.78±301.08 mm^2/m^2 for patients with LVSD, (p=0.017). There were no other significant differences between these 2 groups.

Among 37 female patients in our cohort with echocardiographic correlation, 6 (16%) developed LVSD after LT (Table 3). There were no other significant differences between these 2 groups. Females with LVSD had lower mean TPA values than those without LSVD, with a trend towards significance (p=0.065). There were no other significant differences between these 2 groups.

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Discussion

Loss of muscle mass or low muscle mass prior to LT has been shown to be a predictor of numerous outcomes, such as infection and mortality, in post-LT patients [10,15,16]. Our study adds to the already well-established importance of the role of low muscle mass in end-stage liver disease, as we demonstrate that those with post-LT LVSD had a significantly lower mean TPA when normalized for height, as compared to those patients who did not develop LVSD. In addition, we found no significant differences based on age, MELD, or HCC, or when comparing the etiologies of cirrhosis, including HCV, HCV/ETOH, and ETOH, between these 2 groups.

Recent studies have shown that low muscle mass is an independent risk factor for mortality in patients with cirrhosis, which is not correlated with the degree of liver dysfunction as measured by standard scoring systems [17]. To the best of our knowledge, there is no literature on the effect of low muscle mass on heart function after LT. Nasraway et al. demonstrated that reduced cardiac performance could not be explained by decreased preload or increased afterload, and is instead related to the intrinsic depression of myocardial contractility [5]. Specifically, it was hypothesized nonsurvivors of LT have less pre-transplant cardiac reserve, and postoperatively they demonstrate early myocardial depression and subsequently lower levels of cardiac index and oxygen delivery. Patients who develop these hemodynamic patterns are more prone to organ failure and death [5]. A possible explanation for our identification of low muscle mass as a risk factor for LVSD is that low muscle mass may be an objective indicator of cardiac reserve.

With further subgroup analysis of men and women, we identified a significant difference in mean TPA normalized for height in men only. This may be due to the high percentage of men in our study for both normal EF and LVSD groups, at 64.7% (n=96) and 75.6%(n=11), respectively. There was a trend towards significance for mean TPA in women, but the sample size was limited. In addition to the sample size being limited, our study was retrospective, which may introduce selection bias and misclassification.

Malnutrition, systemic inflammation, endocrine imbalances, and oxidative stress appear to connect low muscle mass and LVSD. At the muscular level, alterations of the ubiquitin proteasome system, myostatin signaling, and apoptosis have been described in both low muscle mass and LVSD and could play a role in the loss of muscle mass and function [18]. Protein energy malnutrition is a known prognostic indicator of end-stage liver disease patients after LT [19], but typical measures of estimation by biological markers (e.g., albumin, or body composition with BMI) are misleading in this patient population. The production of albumin in these patients is decreased due to their liver failure, and the BMI is artificially inflated due to fluid overload (i.e., peripheral edema and ascites). Muscle forms the largest reservoir of protein in the body and may be objectively measured using CT or MRI to provide an easily reproducible method of determining nutritional status. Imaging studies allow for direct visualization and differentiation of muscle mass from fat and visceral organs. CT and MRI of the abdomen and pelvis are a common part of the workup for liver transplantation patients with end-stage liver disease and, as such, provide a method of determining nutritional status without additional testing [20].

Our study was limited by the small percentage of patients who were identified with LVSD. This was further limited by the heterogeneity in our patient population, and there may have been other factors we did not identify that act separately or in concert with low muscle mass in being associated with LVSD. This population may indeed be larger; however, post-LT echocardiography is not a standard of care at our institution, which explains why only 28.6% of patients had post-LT echocardiograms available. Due to the limited studies available, selection bias may affect the results. Routine post-LT surveillance echocardiograms to monitor EF would allow for better assessment of LVSD. In addition to detecting more cases of LVSD, routine echocardiography could also help identify the time frame of development of LVSD and its natural history, which would allow for preemptive therapies with the goal of decreasing morbidity. However, additional prospective studies are needed before additional recommendation of routine post-transplant echocardiography can be made.

Conclusions

This study adds to a growing body of literature demonstrating the importance of adequate nutrition in LT. Since the United States switched to a MELD-based liver allocation system in February 2002, patients with more severe liver disease have been prioritized for LT [21]. Limitations of the Model for End-Stage Liver Disease (MELD) score include its failure to assess the nutritional and functional status of cirrhotic patients. With further research, low muscle mass continues to be a potentially modifiable factor that could improve the mortality and morbidity of LT patients. As we continue to identify areas affected by low muscle mass, future studies could develop a more rigorous and complete scoring system to identify those patients at highest risk in the post-operative period, and potentially improve our ability to effectively allocate resources.

Conflicts of interest

None.

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