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MYOSTEATOSIS AS A RISK FACTOR FOR HEPATOCELULAR CARCINOMA RECURRENCE AFTER DECEASED DONOR LIVER TRANSPLANTATION

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ABSTRACT

INTRODUCTION: Sarcopenia is defined as loss of muscle mass. Besides, myosteatosis is characterized by increased proportion of intermuscular and intramuscular fat. We aimed evaluate the impact of sarcopenia and myosteatosis in hepatocellular carcinoma (HCC) recurrence after liver transplantation.

METHODS: Retrospective study of consecutive patients with HCC who underwent liver transplantation in a single institution. Right psoas attenuation (PAt) was measured in Hounsfield units at the level of the third lumbar vertebra. Partial volume of the right psoas (PV) was measured up to the level of the iliac crest. Sarcopenia was defined based on the median values found in each measured parameter.

RESULTS: Our study sample included 206 patients. The median follow-up was 4.83 years (IQR 2.35–7.82 years). Overall survival was 84% at 1 year and 75% at 3 years. There were 16 patients (7.76%) with HCC recurrence. Sarcopenia had no impact on overall survival ($p<0.68$) or disease-free survival ($p<0.679$). The continuous value of psoas attenuation was negatively associated with the risk of HCC recurrence ($p=0.017$). Univariate analysis for HCC recurrence identified micro- and macrovascular invasion, preoperative AFP greater than 200, pathological staging beyond Milan Criteria and presence of myosteatosis as significant risk factors. Multivariate analysis only confirmed myosteatosis as an independent risk factor for recurrence (HH 5.88, 95% CI 1.52; 25, and $p=0.005$).

CONCLUSIONS: Myosteatosis was associated with HCC recurrence after liver transplantation.

Keywords: liver transplantation, hepatocellular carcinoma

Introduction

Sarcopenia is defined as muscle wasting associated with impaired function. It reflects the nutritional status of the patients and has a role in the natural history of several chronic illness[1,2]. It has been explored as a prognostic factor in many liver diseases, such as cirrhosis or malignancies, and also in prognosis and outcomes related to these conditions[3-5].

In the context of liver transplantation (LT), the initial report by Englesbe et al. revealed a strong association between psoas area and post-transplant mortality (HR=3.7 per 1000 mm^2) decrease in psoas area ($p<0.0001$) in a series of 163 patients[6]. Other authors have published similar findings showing sarcopenia as an independent risk factor of poor survival in living donor liver transplantation (LDLT)[7-9]. It is worth mentioning that many methods have been used to determine sarcopenia in these studies, such as psoas diameter or area at level of third lumbar vertebra and even bioelectrical impedance analysis; some of them with measurements height-normalized[7].

Recurrence of hepatocellular carcinoma (HCC) related to sarcopenia is another outcome which has been explored in the last years. Kim et al. showed 9% increase in recurrence per unit decrease in psoas muscle thickness after LDLT. All patients had advanced HCC beyond Milan Criteria[9]. Besides muscle mass quantity, which was the initial and most obvious measurable parameter, it seems that quality and function also play an important role in the outcome of liver transplantation. In this context, the term myosteatosis is used to characterize an increased proportion of intermuscular and intramuscular fat. Myosteatosis are often present in cirrhotic patients, and it is independently associated with a higher long-term mortality in cirrhosis[10]. Hamaguchi et al. explored this hypothesis and showed intramuscular fat accumulation was an independent risk factor for poor survival after LDLT (OR=3,898 p< 0,001)[8].

Regarding methods, more sophisticated and time-consuming imaging techniques have been recently introduced aiming to identify sarcopenia more accurately. The main approaches that are currently being used are cross section area (CSA) of psoas muscle at level of L3, CSA of all truncal muscles at level of L3, total psoas volume (TPV), some of them associated with measurement of muscle density (Hounsfield Units) aiming to asses muscle quality[11]. However, despite many data being published about sarcopenia, there is still debate about its role in the recurrence rate of HCC in deceased donor liver transplantation (DDLT) recipients and also if more complex imaging techniques of measurements could add information about overall prognosis.

Therefore, we evaluated the relationship between sarcopenia and outcomes after DDLT in a large series of patients with HCC according to Milan Criteria. A secondary goal was to investigate if different imaging techniques for measuring sarcopenia, including mass quantity and function, can have better performance than the classical approach of CSA of the psoas muscle area.

Material and Methods

We screened the records of all adult recipients undergoing LT at the Department of Gastroenterology at the University of Sao Paulo Medical School (FMUSP), during the period June 2008 to December 2018. Among 871 LT we found 285 patients preoperatively diagnosed with HCC. Exclusion criteria were LT performed with partial grafts (split liver or living donors); patients with 30day mortality; and loss of follow up; no radiological images digital records; or radiological follow up longer than 3 months before LT. After exclusion criteria, we had 206 patients preoperatively diagnosed with HCC within Milan Criteria enrolled in this study (figure 1).

Data were collected from prospective database including recipient and tumor characteristics: age, race, sex, etiology of liver disease, MELD score components, body mass index (BMI), pre and post treatment alpha-fetoprotein. Histological features of the explant were obtained from post-operative

pathological reports. Post-transplant mortality and patients' status were investigated in computadorized medical records or medical consultation. Hepatocellular carcinoma recurrence was defined on the basis of radiological evidence. This study was approved by the Ethics Committee of the São Paulo University and was conducted in accordance with the Declaration of Helsinki of 1996.

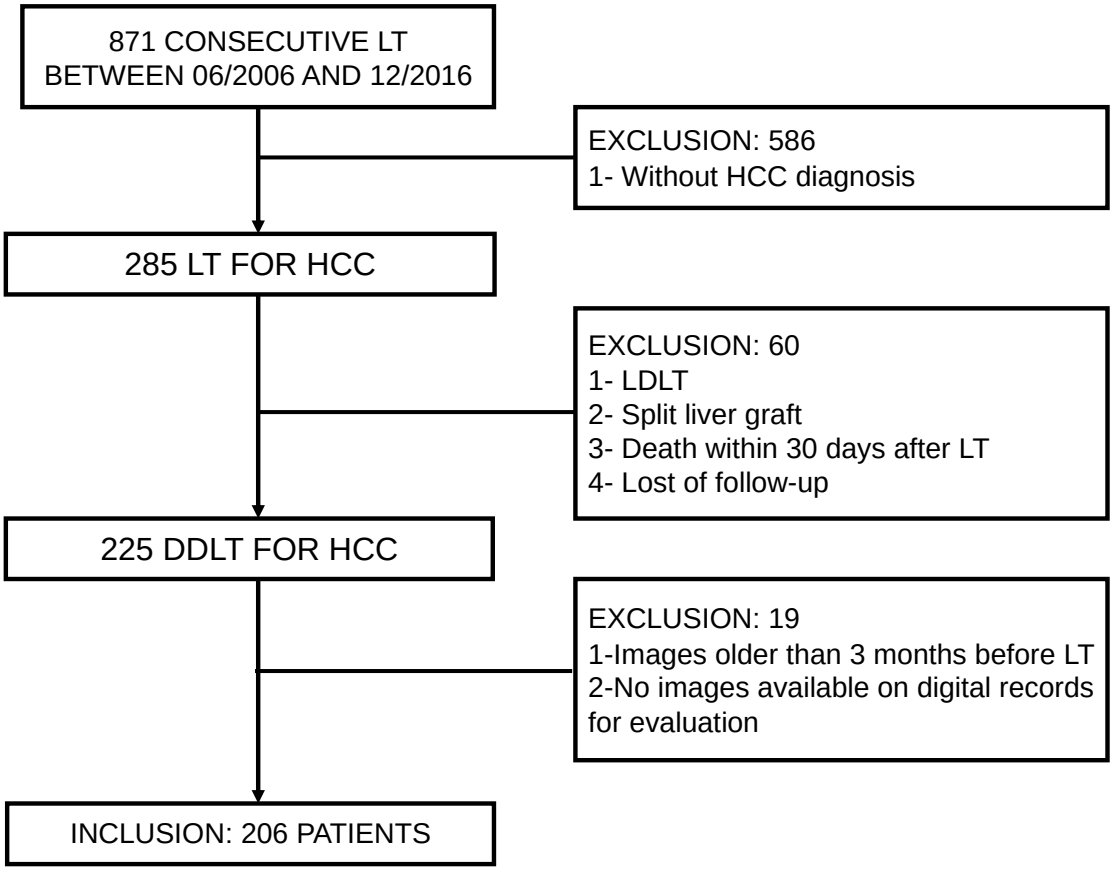

Figure 1 – Study flowchart.

Imaging Analysis

All radiological Images were analyzed using a workstation (*Philips*, Medical Imaging, Best, Netherlands) by one radiologist (G.C.) with 2 years of experience in abdominal imaging and a body imaging fellow (L.T.). Imaging analysis was supervised by an experienced radiologist with 15-year experience in liver imaging and dubious cases were decided by consensus.

Right psoas attenuation (PAt) was measured in Hounsfield units at the level of third lumbar vertebra. Partial right psoas volume (PV) was measured up to the level of the iliac crest because this is captured in superior abdomen images. Sarcopenia and myosteatosis were defined based on median values found in each measured parameter.

All images from thorax, abdomen and pelvis after liver transplantation, including MRI, MDCT, bone scintigraphy and also the corresponding reports were reviewed to detect possible sites of metastatic diseases.

Data Analysis

Descriptive statistics included absolute and relative frequencies for qualitative variables and mean and standard deviation for quantitative variables. The measures of PV (cm^3) was adjusted for height squared and gender; and PAt was adjusted just for gender. Median values of PV and PAt was employed as cutoff in order to categorize patients as sarcopenic and myosteatosis, respectively. Interaction effect between risk factors for HCC recurrence and sarcopenia were tested by means of subgroup analysis. Quartile

values of transformed measures were stratified by gender. Estimates of general survival and free disease survival including a 95% confidence interval (95% CI) and a bidirectional α of 0.05 were calculated using Kaplan-Meier. In order to test the hypothesis that the different factors had no impact on these estimates, a log rank statistic was used. Cox regression was used to evaluate the multiple influences of the factors on the general survival. Backward selection procedure including p=0.05 to enter and p=0.10 to drop variables was the selection method adopted for the model regression.

Results

Our study sample included a cohort of 206 deceased-donor liver transplantation recipients for HCC (158 men, 48 women) with mean age of 57.70 ± 9.85. The primary etiologies of HCC were HCV (63.6%), alcohol (28.2%) and HBV (9.7%). The mean functional MELD was 14.67 ± 6.85 and 42.2% of patients were pathologic outside of Milan Criteria. Clinical characteristic and other relevant features are described in Table 1. The median follow-up duration was 4.83 years (IQR 2.35–7.82 years; minimum 0.1 year and maximum 11.20 years). Overall survival was 84% in 1year e 75% in 3years (Figure 2). Radiological evaluation of sarcopenia and myosteatosis is displayed in table 2.

There were 16 patients (7.76%) with HCC recurrence. Univariable analysis for HCC recurrence identified micro and macrovascular invasion, preoperative AFP higher than 200, HCC size, pathologic outside MC, and myosteatosis as significant risk factors (table 3). Multivariate analysis confirmed only myosteatosis as an independent risk factor, HH 5.88, IC95% of 1.52 ; 25, and p=0.005 (table 4).

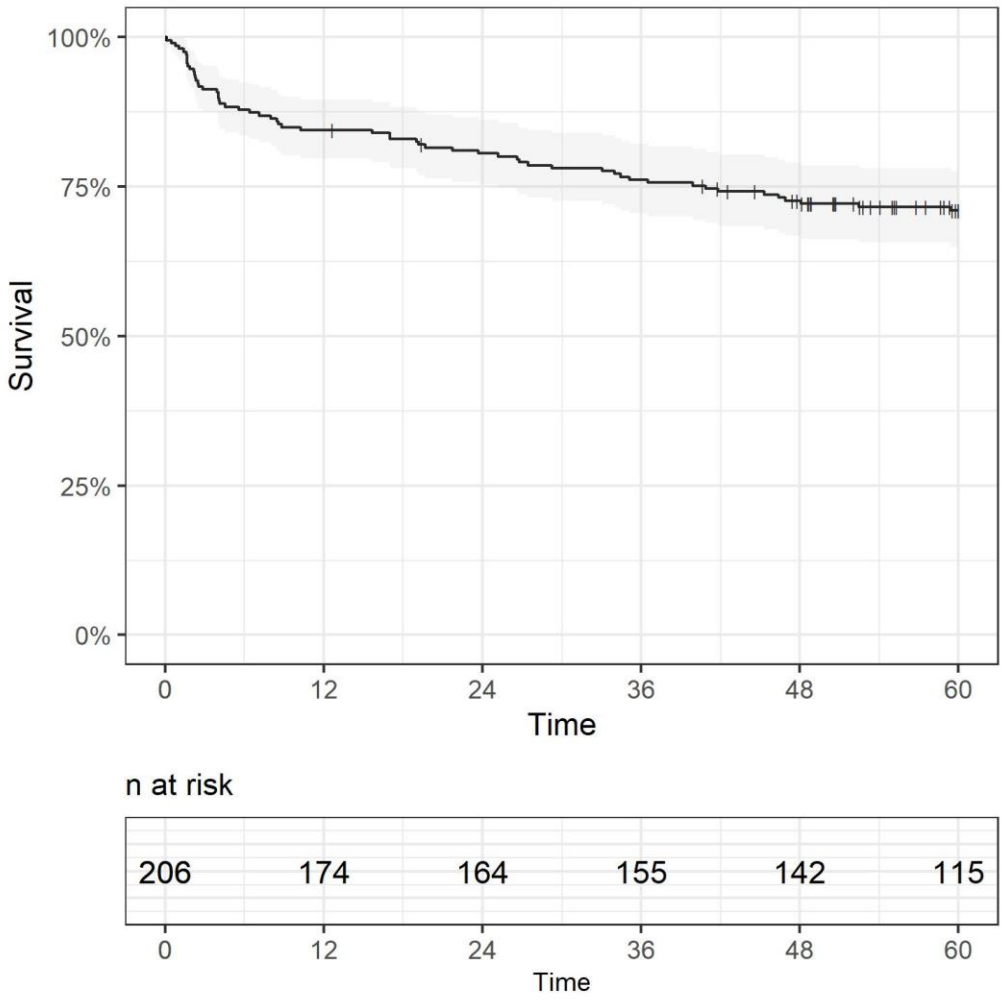

FIGURE 2 – Overall Survival.

Table 1: Demographics, histological features and Liver transplantation data.

Variable	n or Median	Min-max or %
Male Gender	158	76.7%
Age	59.50	17.00 - 72.00
>65	51	24.76%
BMI	25.80	17.90 - 43.60
>30	30	14.56%
Cirrhosis Etiology:		
VHC	131	63.59%
Alcohol	58	28.16%
VHB	20	9.7%
MELD score	13	6 - 44
>14	94	45.63%
Child Pugh A	34	16.50%
Child Pugh B	87	42.23%
Child Pugh C	85	41.26%
Pre operative AFP	7.50	1.0 - 1379.0
>200	10	4.85%
Pre LT treatment		
TACE	97	47.09%
RFA	40	19.42%
PEI	12	5.83%
LT variables:		
Donor Age	44	6 - 81
Donor Risk Index	1.52	0.91 ; 2.635
Transfusion	83	40.29%
Retx	23	11.17%
Pathological Features:		
HCC diameter	25.0	0.1 - 71.0
Outside MC	87	42.23%
Edmonson-Steiner Grading I	8	3.88%
Edmonson-Steiner Grading II	49	23.79%
Edmonson-Steiner Grading III	87	42.23%
Edmonson-Steiner Grading IV	11	5.34%
No viable tumor on specimen	39	18.93%
Microvascular invasion	51	24.76%
Macrovascular invasion	11	5.34%
Microsatelite Nodule	29	14.08%
Mixed tumor	7	3.40%

Table 2 – Radiological muscle evaluation

Variable	Female (n = 48)	Male (n = 158)
Partial Psoas Volume		
Mean ± SD	23.91 ± 5.78	30.38 ± 9.31
Median (Q25% ; Q75%)	23.59 (20.09 ; 26.88)	29.90 (24.62 ; 35.63)
Psoas Attenuation		
Mean ± SD	49.04 ± 9.03	47.53 ± 8.43
Median (Q25% ; Q75%)	48.55 (44.20 ; 52.34)	48.50 (43.15 ; 51.60)

Table 3 – Risk factors for HCC recurrence.

Variable	Estimate (95% CI)	p value
Tumoral Macrovascular	**14.72 (3.89 ; 55.7)**	**< 0.001**
>200 AFP	6.36 (1.79 ; 22.58)	**0.004**
HCC size	1.04 (1.01 ; 1.07)	**0.02**
Tumoral Microvascular Invasion	3.5 (1.07 ; 11.46)	**0.039**
Pathologic Outside MC	2.97 (1.02 ; 8.7)	**0.047**
Edmondson-Steiner Grading	1.56 (0.95 ; 2.58)	0.081
TACE	2.42 (0.83 ; 7.09)	0.106
Gender	4.41 (0.58 ; 33.52)	0.152
Presence of Microsatelites nodules	2.28 (0.72 ; 7.15)	0.159
VHC	2.25 (0.63 ; 7.97)	0.209
Active vs. Necrotic tumor	3.4 (0.45 ; 25.86)	0.237
Child-Pugh B	3.35 (0.42 ; 26.81)	0.254
Donor's Age	0.98 (0.96 ; 1.01)	0.271
>14 MELD score	1.76 (0.63 ; 4.93)	0.285
Child-Pugh A	2.54 (0.31 ; 21.08)	0.389
Recipient Age	0.58 (0.13 ; 2.59)	0.479
VHB	0.58 (0.08 ; 4.45)	0.604
RFA	0.73 (0.17 ; 3.27)	0.686
Donor Risk Index	1 (0.95 ; 1.05)	0.888
Obese recipient	0.94 (0.21 ; 4.18)	0.938
Retx	1.07 (0.14 ; 8.14)	0.948
Alcohol	0.97 (0.31 ; 3.05)	0.96
Intraoperative Transfusion	1.01 (0.29 ; 3.51)	0.982
Mixed tumor	0 (0 ; Inf)	0.998
Sarcopenia Evaluation		
Pat <50	4.55 (1.3 ; 16.67)	**0.009**
PV <50	1.24 (0.44 ; 3.49)	0.681

Pat: psoas attuation; PV: Partial psoas volume.

Table 4 – Multivariable analysis for HCC recurrence

Variable	Estimate (95% CI)	p value
Preoperative AFP >200	4.97 (0.83 ; 29.63)	0.097
HCC size	1.37 (0.65 ; 2.91)	0.401
Microvascular invasion	3.55 (0.71 ; 17.8)	0.169
Macrovascular invasion	4.63 (0.43 ; 49.95)	0.169
Pathological Outside MC	1.03 (0.27 ; 3.97)	0.963
Edmondson grading	3.16 (0.34 ; 29.85)	0.283
Pat <50	5.88 (1.52 ; 25)	0.005

The median PV was 23.91 ± 5.78 for females and 30.98± 9.31 for males. Sarcopenia had no impact in the overall survival (p<0.68) or in disease free survival (p<0.679) in this cohort. Uni and multivariate analysis identified only reTX as an independent risk factor for survival (HH: 6.28, IC95% of 2.79 - 14.14, and p<0.001).

For myosteatosis, the median PA was 49.04± 9.03 for females and 47.53± 8.43 for males. The continuous value of PA was negatively associated with HCC recurrence risk (p=0.017).

Discussion

Our study demonstrates that muscle mass quality or myosteatosis measured by PA is a predictor for HCC recurrence in DDLT. The overall recurrence rate was 7.76% over time and there is a trend toward a high risk of recurrence in sarcopenic recipients with lower PA.

Sarcopenia and myosteatosis make up the frailty complex present in cirrhotic patients, characterized by a decrease in reserve and resistance to stressors, which results in a cumulative decline in the physiology of the various organ systems and a predisposition to poor outcomes[12]. Nevertheless, such alterations in body composition have gained attention in the last decade, in view of their modifiable character, whose recognition and periodic evaluation can be beneficial due to their association with morbidity, mortality and quality of life[13-15].

In the context of liver cirrhosis, sarcopenia is a multifactorial process whose mechanisms are still not completely understood, but involve malabsorption, hyperammonemia, a hypermetabolic state characterized by catabolism and amino acid deficiency, as well as hormonal defects[16]. Hyperammonemia can be explained by decreased elimination due to pathological changes in liver architecture, resulting in inactivation of protein synthesis, which leads to sarcopenia. Another related factor is inadequate diet, which can be aggravated by nausea and early satiety secondary to ascites, delayed gastric emptying, impaired gut motility, and small intestinal bacterial overgrowth[17,18].

In our study, sarcopenia did not prove to be a significant risk factor for HCC recurrence. This finding is similar to a recent study by Grat et al with 77 patients undergoing DDLT, with sarcopenia defined as psoas muscle area (PMA) and total skeletal muscle area (TSMA)[19]. D`Arcangelo et al[20] used as parameter the skeletal muscle index (the total cross-sectional muscle area (CSMA) at level of the 3rd lumbar vertebra divided per patient's height), showed that in patients with HCC beyond Milan criteria, rate of recurrence was slightly higher in patients with sarcopenia compared to patients without sarcopenia, but the difference was not statistically significant. Similar result was observed by Beumer et al[21], in a study with patients submitted to LT beyond the Milan Criteria, in which sarcopenia was significantly associated with post-transplant survival on univariable and multivariable analyses, but there was no significant increase in the risk of recurrence in sarcopenic patients.

In a recent Chinese study[22] sarcopenia was significantly associated with recurrence of HCC in univariate analysis, but it was not evidenced as an independent risk factor for recurrence in multivariate analysis. Contrary to the above, the study by Kim et al[9] with 92 patients showed an incidence of 78% sarcopenic and recurrence risk was greater in sarcopenic patients in univariable (hazard ratio [HR]=8.06 [1.06–16.70], p =0.044) and multivariable analysis (HR=9.49 [1.18–76.32], p=0.034). The most common cause of death in sarcopenic recipients was post-transplant HCC recurrence. Similarly, in patients undergoing hepatectomy due to HCC, several studies have also shown a significant risk of recurrence in sarcopenic patients[5,23-25].

The mechanisms that explain the association between sarcopenia and HCC recurrence are still unclear. The factors involved probably include inflammation, cytokines and immunity generated by the tumor microenvironment, especially intraoperatively and early post-transplant, a period of greater vulnerability to metastases due to surgery-induced stress, immunosuppression, platelet activation and transfusion[26,27].

In addition to sarcopenia, myosteatosis has also been associated with worse clinical outcomes in different pathological conditions. It can be defined as qualitative changes in the structural composition of muscle with excessive ectopic accumulation of fat in the intermuscular and intramuscular compartments, significantly decreasing muscle quality and functional status[28]. To this date, our study is the first one in the literature that has analyzed the association between myosteatosis and HCC recurrence in patients undergoing DDLT, which proved to be a significant risk factor for recurrence.

In recent literature, myosteatosis has already been presented as a risk factor for poorer outcomes in cancer patients[29]. Czigany et al[30] showed that patients with myosteatosis had significantly higher all-cause mortality. In a British meta-analysis of patients with gastrointestinal cancer, myosteatosis had significantly poorer cancer-specific survival and recurrence-free survival[30].

Recent study by Masetti et al[31], the first in the literature to assess the correlation between myosteatosis in patients with HCC undergoing locoregional treatment (transarterial embolization), 76% of the patients had myosteatosis, however it was not associated with a different HCC burden, length of hospitalization, complication rate, and readmission in the first 30 days after discharge. Overall survival was not influenced by the presence of myosteatosis.

On the other hand, Bannangkoon et al[32] using the same methods to define myosteatosis, showed that the presence of myosteatosis was significantly associated with poor TACE response and reduced survival. Such recent studies, showing a new emerging concept and divergent results in the context of muscle composition in patients with hepatocellular carcinoma, highlight the need for further studies with sarcopenia and myosteatosis to assist in the perioperative preparation of patients with hepatocellular carcinoma, in terms of body composition and nutritional profile for the search for better outcomes.

Pancreatic steatosis (PS) is an emerging and poorly understood clinical entity strongly associated with obesity, type 2 diabetes mellitus, nonalcoholic fatty liver disease and metabolic syndrome. Measurement of pancreatic neck is an attempt to introduce a PS as a predictor factor in liver transplantation. Our study shows a trend toward an increased risk of mortality in patients with thinner PN in the multivariate analysis (p<0,073).

There are several limitations in our study. First, due to the retrospective design, a direct cause and effect relationship between sarcopenia and HCC recurrence remains unknown. Secondly, the small patient sample reduced the ability to construct stronger statistical models using more covariates for the analysis. However, a rigorous statistical approach was adopted with the intent to select the best covariates to be used.

Another limitation refers to the way of measuring sarcopenia used in our study. Several studies advocate the use of SMI as a sarcopenia marker, being more complete, efficient and robust than isolated markers such as the psoas muscle area (PMA). Patients who fit as non-sarcopenic using PMA, when classified by the SMI are classified as sarcopenic, therefore, this index is more comprehensive and reliable with the outcomes in these patients[33]. Nevertheless, the heterogeneity of the literature in terms of different indices (including several other indices based on muscle area, volume and thickness) and cutoff values for different muscle compartments limits the comparability of our findings with some other reports. Due to its retrospective nature, this study did not include any functional analysis of patient frailty, fitness and muscle strength, which should also be noted as a significant limitation.

Conclusion

The mechanisms linking sarcopenia and HCC recurrence are not yet fully understood, likely involving inflammation, cytokines, and immunity within the tumor microenvironment. Myosteatosis has also been linked to poorer clinical outcomes in various pathological conditions and, in our study, emerged as a significant risk factor for HCC recurrence.

Based on our study, we can conclude that myosteatosis, measured by PA, is a significant predictor for HCC recurrence in patients undergoing DDLT. Sarcopenia and myosteatosis, which constitute the frailty complex in cirrhotic patients, contribute to decreased reserve and resistance to stressors, leading to poorer outcomes. Our study did not find sarcopenia to be a significant risk factor for HCC recurrence, probably due the limited muscle evaluation employed to define sarcopenia.

Further research must evaluate the roles of sarcopenia and myosteatosis in the perioperative preparation of HCC patients aiming to improve outcomes by addressing body composition and nutritional profiles. Despite the study's limitations it underscores the importance of recognizing and evaluating these factors in the management of cirrhotic patients undergoing liver transplantation.

Conflict of Interest:

None of the authors have any kind of personal conflicts of interest.

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