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Metabolic syndrome before liver transplantation: does it have an impact on post-liver transplantation outcome?

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ABSTRACT

Introduction: metabolic syndrome (MS) and cardiovascular risk factors are common in liver transplant (LT) candidates and recipients. Cardiovascular events and *de novo* tumors are increasingly common causes of mortality in liver transplant recipients. The aims of this study were i) to assess the prevalence of MS in LT recipients and its growth over the years, and ii) to determine if the presence of MS pre-LT is associated with a higher risk of post-LT cardiovascular events (CVE), *de novo* tumors, or early and late survival.

Patients and methods: a retrospective study was performed that included LT recipients from January 2012 to December 2017. Baseline features (MS before LT and at 1year post-LT) and outcomes (CVE, *de novo* tumors and survival) were recorded.

Results: a total of 483 recipients were included, MS was present in 20 % of pre-LT subjects with an increasing prevalence over time, from 16 % in 2012 to 34 % in 2017 (p = 0.025). One-year post-LT, an additional 12 % had developed *de novo* MS. At a median of 56 months of follow-up, 13 % developed a CVE and 9 % a *de novo* tumor. One and 5-year survival rates were 91 % and 83 % in those with pre-LT MS, and 93 % and 85 % in those without it (p = 0.94). The presence of MS before LT was independently associated with a higher risk of post-LT CVE (HR: 2.66, 95 % CI: 1.6-4.4, p < 0.001) but

not with *de novo* tumors (p = 0.94) nor early and late survival (p = 0.58 and p = 0.87).

Conclusion: pre-LT MS is increasing among LT candidates and is associated with a higher risk of post-LT morbidity (CVE) yet without affecting mortality.

Keywords: Cardiovascular event. *De novo* tumors. Liver transplantation. Metabolic syndrome. Survival.

INTRODUCTION

The presence of metabolic syndrome (MS) is increasing in the general population together with DM and obesity (1,2). Paralleling these trends, liver transplant (LT) candidate profile is also changing, with MS before and after LT becoming a highly prevalent condition (3). Its association with an increased risk of cardiovascular (CV) disease, malignancies, and all-cause mortality in the adult population is well established (3-5). Moreover, the main causes of medium and long-term morbidity and mortality in LT recipients are CV events (CVE) and malignancies in previous years (6,7).

We hypothesized that the presence of the MS is increasing in LT candidates and that this condition leads to an increased number of CVE post-LT, an increased development of *de novo* malignancies, and lower post-LT survival rates.

The aims of this study were to describe the prevalence of MS before and 1 year after LT, and its course over time in our cohort of LT patients, to determine whether there is an association between pre-LT MS and post-LT CVE, *de novo* malignancies and early/late mortality. Furthermore, whether these outcome measures vary depending on whether MS is present before LT or develops after LT (*de novo* MS) was assessed, and pre-LT baseline features associated with these outcomes were established.

PATIENTS AND METHODS

An observational, retrospective, unicentric cohort study was performed at the Liver Transplant Unit of our center. Adult patients undergoing LT between January 2012 and December 2017 were included and followed up until January 2020. Patients

undergoing liver re-transplantation, or combined heart or lung-liver transplantation were excluded. Data were collected until death or last hospital visit. Pre-LT variables included: recipient demographics (age, gender), etiology of liver disease, presence of hepatocellular carcinoma (HCC), HIV status, tobacco use, model-for-end-stage liver disease (MELD), and Child-Pugh pre-LT. The presence of CV risk factors pre-LT was recorded, including diabetes mellitus (DM), arterial hypertension (AHT), dyslipidemia, renal insufficiency (RI), and obesity (BMI > 30) (8), defined according to the WHO (9). All patients were evaluated by echocardiogram and EKG prior to liver transplantation. MS was defined using the 2001 guidelines from the National Cholesterol Education Program Adult Treatment Panel III and 2004 revision by the American Heart Association and National Heart, Lung and Blood Institute (ATP III). The presence (or treatment) of 3 or more of the following features was considered to be MS: obesity (BMI ≥ 30 kg/m^2 as surrogate for waist circumference), diabetes (plasma glucose > 126 mg/dl), blood pressure (≥ 130/85 mmHg), triglycerides ≥ 150 mg/ml, and high-density lipoprotein < 40 mg/dl in males and < 50 mg/dl in females (10). All the features of MS were considered if they were present at least 6 months before LT.

Post-LT variables recorded 12 months after LT included: presence of CVRF, laboratory results, clinical outcomes including death (early death < 6 months and late death > 6 months), CVE, and *de novo* tumors.

The CVE included in this study were acute coronary syndrome, ischemic/hemorrhagic stroke, heart failure, sudden death, peripheral artery disease, arrhythmias such as atrial fibrillation (AF)/flutter, and thromboembolic phenomena. CVE occurring in the setting of sepsis, hemorrhage or during surgery were excluded. The tumors recorded were non-melanoma skin tumors, gastrointestinal, lung, gynecological, ENT, and hematological.

This study was approved by our institutional ethics committee at the Institute and conducted according to the Declaration of Helsinki. All the variables were collected under the signature of the data protection document. This manuscript adheres to the STROBE statement guidelines for reporting observational studies.

Statistical analysis

Data were expressed as median or mean according to their distribution, and interquartile range (Q1-Q3) or range as measures of their dispersion, respectively. Categorical variables were presented as percentages. The chi-square test was used for categorical variables and Student's t-test for continuous variables to analyze statistically significant differences between patients with MS and patients without MS. Cox adjusted regression models with age, NASH, sex, alcohol, and tobacco as possible confounders were used to evaluate the differences in risk of CVE and tumors between patients with and without MS. To evaluate the risk of mortality between groups, a Cox regression model and multivariate analysis was adjusted by MELD, age, renal failure, echocardiography features, and sex as confounding factors. The results were represented by Kaplan-Meier curves fitted to the Cox regression, together with the hazard ratio (HR) and their 95 % confidence intervals. The level of statistical significance was $p < 0.05$. The statistical analysis was performed by SPSS Statistic 18, release 18.0.0 (July 30, 2009).

RESULTS

From January 2012 to December 2017, 483 patients were included in the study. The main pre-LT characteristics including CV risk factors are summarized in table 1. The majority were males (76 %) with a median age of 57 years (IQR, 51-68). The main etiology for LT was HCV-related cirrhosis (31 %) followed by alcohol (26 %). NASH cirrhosis accounted for 7 %. CV risk factors before and 12 months after LT are summarized in figure 1A. Thirty-three patients (7 %) had a pre-transplant cardiovascular event and, of these, 9 had atrial fibrillation (27 %). Clinical characteristics associated with the presence of MS before LT are shown in table 2. Patients were older in the MS group (p = 0.02), NASH etiology and HCC were more frequent in those with MS vs those without MS (17 % vs 4 %, p < 0.001 and 58 % vs 44 %, p = 0.016), respectively. Diastolic dysfunction was more frequent in the MS group (p = 0.006). Pre-LT MS was present in 20 % (n = 97) of the entire cohort with an increase over time (16 % in 2012 vs 34 % in 2017; p = 0.025) (Fig. 1B). From 426 patients alive at one year, 120 (25 %) had MS, of which 50 developed it *de novo* (12 %).

Impact of pre-LT metabolic syndrome on post-LT outcomes

Survival

During the follow-up of 56 (25-97) months, 116 patients (24 %) died. Twenty-four patients had MS pre-LT (20 %). Infections, HCC recurrence and *de novo* malignancies accounted for most deaths. Early death post-LT occurred in 42 patients (9 %). Infections, graft failure and post-surgery problems were the most frequent causes. Patient survival at 1, 3 and 5 years after LT was similar between patients with and without MS (p = 0.94) (Fig. 2A). Patient survival at 3 and 6 months (early death) was 95 % and 92 % in patients with MS, and 96 % and 94 % in patients without MS, respectively (p = 0.87).

Cardiovascular events

During a median follow-up of 45 (28-69) months, 66 patients (13 %) developed a CVE (29 patients of those with MS pre-LT and 37 of the non-MS pre-LT (p < 0.001)). Atrial fibrillation occurred in 16 patients (25 %), and 12 patients had a heart myocardial injury (18 %). Thirteen patients (20 %) suffered a stroke, hemorrhagic in 4 cases and ischemic in 9. Of those with an ischemic cause, two were cardioembolic and seven were atherothrombotic. Other causes of CVE included: 2 atrial flutter arrhythmias, 10 thromboembolic events, 5 peripheral arterial disease cases, 5 cardiogenic shocks, and 3 sudden deaths. A total of 16 (4 %) CVE occurred within the first 6 months after LT. Eight percent of patients died from CV events. The cumulative risk of CVE at 1, 3 and 5 years was 11 %, 23 %, and 36 % in those with pre-LT MS, and 4 %, 8 %, and 10 % in those without MS before LT (p < 0.001) (Fig. 2B).

De novo tumors

Nine percent (n = 43) developed a *de novo* malignancy (8 patients in the MS pre-LT group and 35 in the non-MS pre-LT (p = 0.214)). Lung and gastrointestinal tumors were the most frequent tumors. The median time between LT and the development of a *de novo* tumor was 24 (12-43) months. Fourteen percent of patients died from *de novo* tumors. The cumulative risk of *de novo* tumors at 1, 3 and 5 years was 1 %, 7 % and 12 % in those with pre-LT MS, and 2 %, 4 % and 8 % in those without pre-LT MS (p =

0.486).

Differential effect of MS according to whether it was present before or occurred *de novo* early after LT

There were no statistically significant differences in survival and *de novo* tumors between patients with pre-LT MS, *de novo* early MS, or without MS before and after LT. Patient survival according to pre-LT MS, *de novo* MS, and without MS at 1, 3 and 5 years was 91 %, 86 % and 83 %; 100 %, 86 % and 78 %; and 87 %, 80 % and 75 %, respectively (p = 0.211). In contrast, patients with MS before LT had a greater risk of developing CVE post-LT than patients without MS or those with *de novo* MS early post-LT (HR, 2.1; 95 % CI, 1.1-3.9; p < 0.001). The cumulative risk of developing CVE post-LT at 1, 3 and 5 years was higher in those with MS before LT as opposed to those without MS or those with *de novo* MS (p < 0.001) (Fig. 3).

Pre-LT baseline features associated with the outcomes

In the multivariate analysis, patients with pre-LT MS had a significantly independent higher risk of developing post-LT CVE (p < 0.001); male gender, age and obesity also showed an association. There was no association between pre-LT MS and survival (p = 0.94), nor was there any with *de novo* tumors (p = 0.58). Baseline features associated with late survival included renal dysfunction and HCC. Renal dysfunction was also associated with early death (HR, 1.67 (1.04-2.45), p = 0.043). Echocardiography results (left atrial dilatation, HR: 0.85 (0.38-1.92); p = 0.69; left ventricular hypertrophy, HR: 1.28 (0.5-3.25); p = 0.60; and diastolic dysfunction, HR: 0.41 (0.006-2.95); p = 0.37) before LT showed no association with CVE or survival. No baseline features associated with the development of *de novo* tumors were found (Table 3).

DISCUSSION

The association of the MS with higher CV risk, poor survival, and increased incidence of tumors is well established in the general population (3,4,11). In the LT setting, data on the effects of MS after LT, particularly the higher rates of CVE (but not poorer survival), are well established (12). However, data on the effects of MS already present before

LT are lacking.

The main results of our study can be summarized as follows: the presence of MS among LT candidates increases gradually over time; pre-LT MS is associated with the development of CVE after LT, and this association is higher in those patients who develop the MS after LT; pre-LT MS is not associated with the development of *de novo* tumors, nor with early and late mortality after LT; and renal dysfunction is the most important condition that is associated with early and late survival.

In our study, MS was present in 20 % of our LT candidates, which is similar to reports in the general population and other series with rates ranging from 6 % to 22 % (12,13). In addition, we found that MS was more frequent in the older population, and in those with alcohol or NASH etiologies, as described in other studies (14). Importantly, the increasing prevalence with time, as previously described by Fussner et al. (15), is concerning, with only 16 % of candidates having this condition in 2012 compared to a third in 2017.

Post-LT MS prevalence was lower than described in the literature (25 % in our series vs 45-50 % in the USA literature) but higher than in the general population (16,17). Geographic disparities and the time of evaluation, which was one year after transplantation, may explain these differences.

We found a positive association between pre-LT MS and post-LT CVE. In different series, the incidence of CVE after LT ranges between 10 %-20 % at 3-5 years (14,18), with an impact on short and long-term survival. In fact, it is considered the 3rd cause of late mortality. In our center, factors that have been previously reported to be associated with increased CVE post-LT include pre-LT DM, AHT, Framingham score risk before LT, renal dysfunction and age (19). We can now add the presence of the MS before LT as an independent factor associated with the development of CVE post-LT.

The relationship between post-LT MS and increased risk of post-transplant CVE and short-term survival has been described in several series (12,20,21). Albeldawi et al. showed that patients with MS post-LT had significantly more CVE than those without it ((18 % vs 7 %) $p < 0.001$), speculating that MS alone could predict up to 25 % of all cases of new-onset CV disease (22). Mari-Laryea et al showed that the cumulative incidence of major CVE was statistically more frequent in the post-MS group (MS: 8 %,

24 %, 29 % at 1, 2 and 5 years of follow-up vs 3 %, 6 %, 10 % in non-MS cases) (p = 0.003) (20). A meta-analysis showed that developing MS post-LT increased the risk of having a CVE by approximately 4 times compared to those without MS post-LT, without affecting all-cause mortality (3,23).

In our study, factors associated with the development of CV in addition to MS were male gender, advanced age, and obesity pre-LT, which have already been reported in the literature (24,25). Although diastolic disfunction and myocardial hypertrophy before LT have been associated with CVE in the post-LT setting, we observed a greater prevalence of these two conditions before LT, but they were not associated with the development of CVE or survival after LT in our study (26).

Obesity and diabetes are often involved in the development of tumors and these associations are based on the state of chronic inflammation with MS (27,28). Moreover, in the LT setting, *de novo* tumors are increasing and currently represent the second cause of death (29,30). In line with other studies and despite the effect of the MS on CVE, we did not find an association with post-LT early and late survival or malignancies (6,12,25,31). A large multicenter study with long-term follow-up examined the additive impact of pre-transplant metabolic factors on survival post-liver transplantation. They found that diabetes was associated with reduced patient and graft survival post-liver transplant. However, pre-LT diagnosis of MS had no impact on overall survival (32), which is in line with our results. The MS is a cluster of modifiable factors where early interventions can potentially prevent more deleterious consequences, especially CVE in LT recipients with MS, which should be considered as a high CV risk population independently of the cause of the liver disease.

While our study has some strengths such as the large sample size, the homogeneity of patient monitoring and the long duration of follow-up, it also has some limitations. In particular, the retrospective nature of the study means that some baseline variables were not included. More specifically, the abdominal perimeter was not included, which has previously been calculated based on the BMI and ascites, although this was performed in prior studies.

In conclusion, MS before LT is associated with the development of CVE after LT. This risk is higher than in patient who develop MS early after LT and significantly higher

than that observed in patients without MS before and after LT. We recommend the identification of patients with MS before LT to establish preventive measures, both while on the waiting list and after LT.

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Table 1. Baseline characteristics pre-LT

Characteristics	**n = 483**
Men (%)	367 (76 %)
Age (median/ IQR)	57 (51-68)
Etiology (%)	
- HCV	151 (31 %)
- Alcohol	125 (26 %)
- NASH	33 (7 %)
- HCV + alcohol	52 (11 %)
- NASH + alcohol	24 (5 %)
- Others	98 (20 %)
HCC (%)	226 (47 %)
MELD (median/IQR)	16 (10-20)
History cardiovascular disease (%)	33 (7 %)

Table 2. Variables associated with pre-LT metabolic syndrome

	Metabolic syndrome (n = 97, 20 %)	**No metabolic syndrome (n = 386, 80 %)**	**p-value**
Men (%)	78 (80 %)	289 (74 %)	0.154
Age (median, IQR) yrs	61 (57-64)	56 (50-62)	0.02
MELD (median, IQR)	14 (9-18)	10 (10-21)	0.214
Etiology (%)			
- HCV	21 (23 %)	130 (33 %)	0.65
- Alcohol	27 (28 %)	98 (25 %)	0.175
- NASH	17 (17 %)	16 (4 %)	< 0.001
- Alcohol + NASH	17 (17 %)	7 (2 %)	< 0.001
- HCV + alcohol	10 (10 %)	42 (11 %)	0.15
- Others	5 (5 %)	93 (25 %)	
- HCC	56 (58 %)	170 (44 %)	0.016
Echocardiography			
- Left auricula dilatation	28 (29 %)	63 (16 %)	0.005
- Left ventricle hypertrophy	14 (14 %)	33 (8 %)	0.084
- Diastolic dysfunction	86 (88 %)	16 (4 %)	0.006
Smoking	21 (21 %)	62 (13 %)	0.06
AHT	76 (78 %)	67 (17 %)	< 0.001
DM	76 (78 %)	70 (18 %)	< 0.001
Dyslipidemia	44 (45 %)	29 (7 %)	< 0.001
Obesity	66 (68 %)	59 (15 %)	< 0.001
Renal dysfunction	22 (23 %)	62 (16 %)	0.06

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Table 3. Cox regression analysis of factors associated with outcomes: CVE, late survival and *de novo* tumors

Variable	HR (95 % CI)	p-value
CVE post-LT		
- MS before- LT	2.66 (1.62-4.45)	0.001
- Men	2.4 (1.14 -5.58)	0.02
- Age	1.1 (1.06-1.17)	0.001
- Obesity	3.3 (1.82-5.9)	0.001
Late survival		
- Renal dysfunction	2.09 (1.19-3.60)	0.01
- HCC pre-LT	1.77 (1.07-2.90)	0.02

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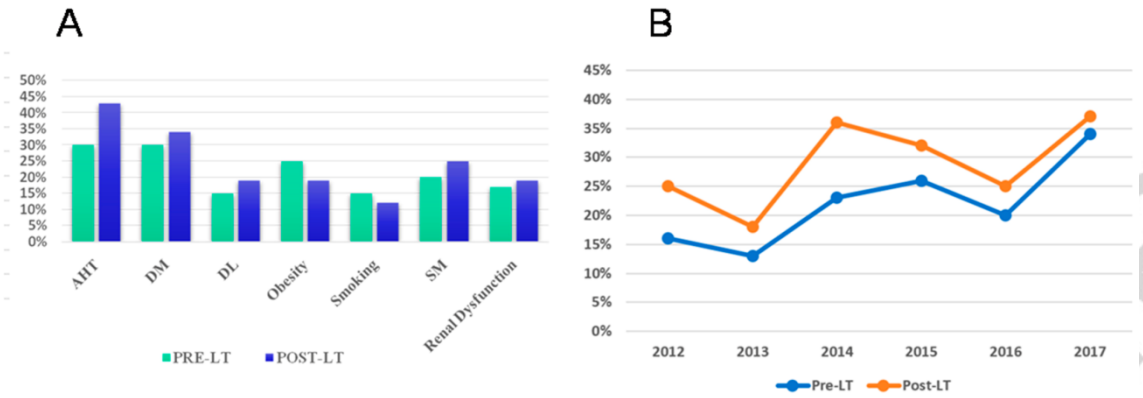

Fig. 1. A. Cardiovascular risk factors and MS pre-LT and 1-year post-LT. B. Prevalence of the metabolic syndrome over time (p = 0.025).

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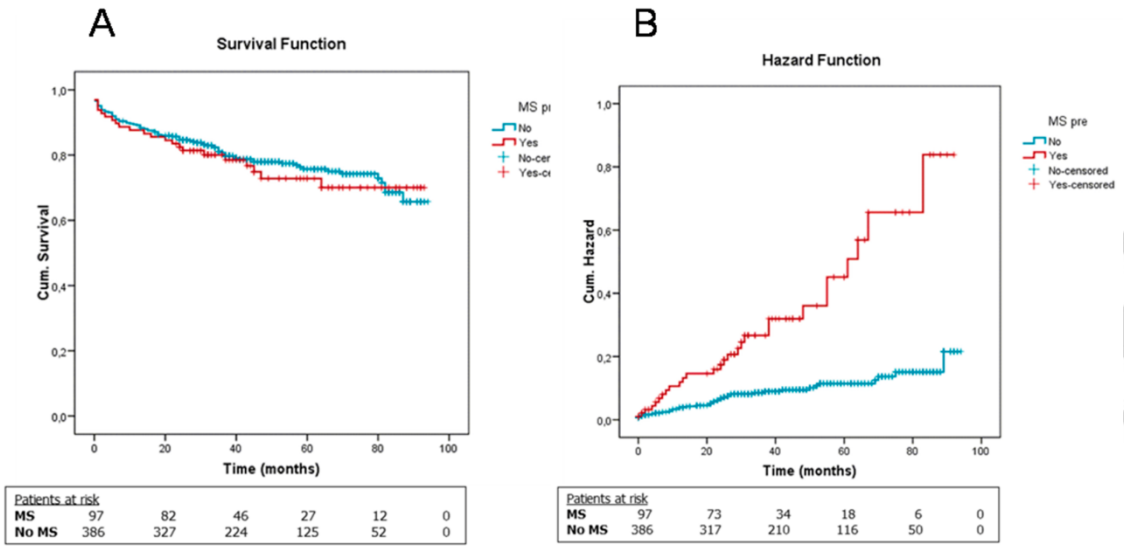

Fig. 2. A. Cox regression survival-SM ($p = 0.94$). B. Cumulative risk of cardiovascular events post-LT ($p < 0.001$).

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The Spanish Journal of Gastroenterology

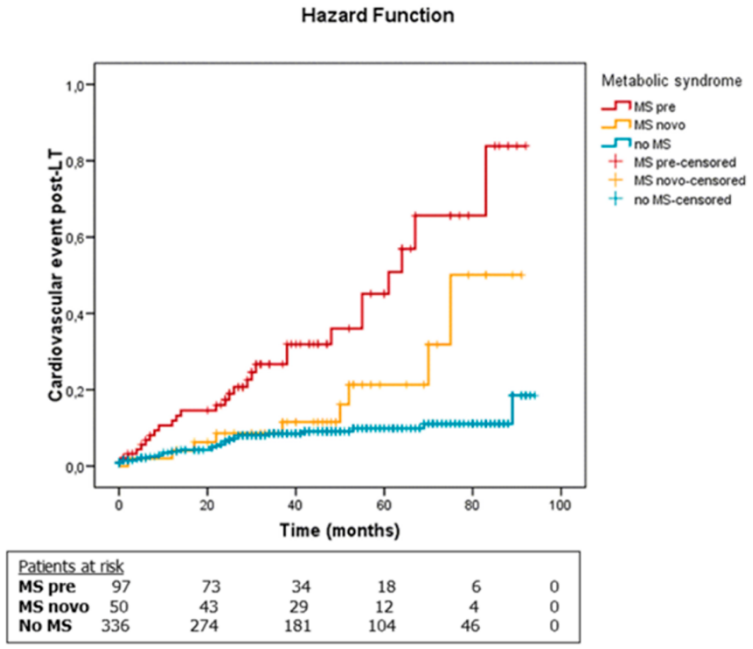

Fig. 3. Cumulative risk of CVE after LT in patients with MS before LT, *de novo* MS and patients without MS pre or post-LT ($p < 0.001$).