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

Julia Herreras López[1,3], Lorena Puchades[1,3,5], Tommaso Di Maira[1,3,5], Antonio José Cañada[4], Javier Maupoey[2,3], Rafael López-Andújar[2,3], Martín Prieto Castillo[1,3], Marina Berenguer Haym[1,3,5,6], Victoria Aguilera [1,3,5]

1) Hepatology and liver transplantation Unit. La Fe University and Polytechnic Hospital, Valencia.
2) Hepatobiliary pancreatic surgery unit, La Fe University and Polytechnic Hospital, Valencia.
3) Instituto de Investigación Sanitaria La Fe, Group of Hepatology and Liver Transplantation. La Fe University and Polytechnic Hospital, Valencia
4) Data science Health Research Institute La Fe, Valencia.
5) Center for Biomedical Research Network on Liver and Digestive Diseases (CIBERehd), Instituto de investigación Carlos III, Madrid.
6) University of Valencia, Department of Medicine, Valencia.

Corresponding author:
Julia Herreras. Instituto de Investigación Sanitaria La Fe, Grupo de Hepatología, Cirugía Hepatobiliopancreatica y Trasplante Hepático.
Avenida de Fernando Abril Martorell, 106, 46026, Valencia, España. Secretaría Aparato Digestivo. 5ª Planta, Torre F.
Correo electrónico: herreras.julia8@gmail.com

Authorship

JH: Study design and concept, performance of the research, data analysis, drafting the manuscript
LP: critical review of the manuscript

TD: Study design and concept, critical review of the manuscript

AC: study design and concept, data analysis,

JM: critical review of the manuscript

RL: critical review of the manuscript

MP: critical review of the manuscript

MB: Study design and concept, critical review of the manuscript

VA: study design and concept, performance of the research, drafting of the manuscript and critical review of the manuscript.

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Key words: Cardiovascular event. *De novo* tumours. Liver transplantation. Metabolic syndrome. Survival.

ABSTRACT

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

Patients and methods: Retrospective study 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* tumours and survival) were recorded.

Results: 483 recipients were included, MS was present pre-LT in 20% with an increasing prevalence over time, from16% 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

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follow-up, 13% developed a CVE and 9% a *de novo* tumour. One and 5-yr survival rates were91% and 83 % in those with pre-LT MS and 93% and 85 % in those without (p=0.94).The presence of MS before LT was independently associated with a higher risk of post-LT CVE (HR: 2.66 IC (95%): 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.

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INTRODUCTION

The presence of metabolic syndrome (MS) is increasing in the general population together with DM and obesity (1,2). Paralleling these trends, the liver transplant (LT) candidates' 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 (3,4,5). Moreover, the main causes of medium and long-term morbimortality in LT recipients are CV events (CVE) and malignancies in last 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 in our cohort of LT patients, the prevalence of MS before and 1 year after LT and its course over time, to determine whether there is an association between pre-LT MS and post-LT CVE, *de novo* malignancies and early/late mortality, whether these outcome measures vary whether the MS is present before LT or develops after LT (*de novo* MS) and establish pre-LT baseline features associated with these outcomes.

PATIENTS AND METHODS

We conducted an observational, retrospective, unicentric cohort study at the Liver Transplant Unit of our centre. We included adult patients undergoing LT between January 2012 and December 2017. They were 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), aetiology of liver disease, presence of hepatocellular carcinoma (HCC), HIV status, tobacco use, model-for-end-stage liver disease (MELD), and Child-Pugh pre-LT. We recorded the presence of CV risk factors pre-LT that included diabetes mellitus (DM), arterial hypertension (AHT), dyslipidemia,

obesity and renal insufficiency (RI) and obesity (BMI>30) (8), defined according to the WHO (9). All patients were evaluated by echocardiogram and EKG pre 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: 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 men and < 50 mg/dl in women (10). All the features of the 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 moths), CVE and *de novo* tumours.

The CVE included in this study were acute coronary syndrome, ischemic/ haemorrhagic 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, haemorrhage or during the surgery were excluded. The tumours recorded were no melanoma skin, gastrointestinal, lung, gynaecological, otolaryngology and haematological.

This study was approved by our institutional ethics committee of the Investigation Institute, and conducted according to the declaration of Helsinki. All the variables have been 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, while interquartile range (Q1-Q3) or range as measures of their dispersion, respectively. Categorical variables were presented by percentages. The chi-square test for categorical variables and student t test for continuous variables were performed to analyzed statically significant differences between patients with MS and patients

without MS. To evaluate the differences in the risk of CVE and tumours between patients with and without MS, regression models were Cox adjusted by age, NASH, sex, alcohol and tobacco as possible confounders. To evaluate the risk of mortality between groups, a Cox regression model and multivariable 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 has been considered $P < 0.05$. Statistical analysis was performed by SPSS Statistic 18, release 18.0.0 (July 30, 2009).

RESULTS

From January 2012 to December 2017, we included 483 patients. The main pre-LT characteristics including CV risk factors are summarized in table 1. The majority were men (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-tree patients (7%) had a pre-transplant cardiovascular event, of those, 9 was 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 aetiology and HCC were more frequent in those with MS vs those without (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 all cohort with an increased overtime (16% in 2012 vs 34% in 2017; p=0.025) (Fig. 1B)**.** From 426 patients alive at one year, 120 (25%) had MS. Of these, 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 with 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 both MS and those without it (p=0.94) (Fig. 2A). Patients' survival at 3 and 6 moths (early death) was 95% and 92 % in patients with MS and 96% and 94% in patients with SM 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%); Twelve patient had a heart myocardial injury (18%). Thirteen patients (20%), suffered a stroke, of those, 4 were haemorrhagic and 9, ischemic. Of those with ischemic cause, two were cardioembolic and seven were atherothrombotic. Other causes of CVE included: 2 atrial flutter arrhythmia, 10 thromboembolic events, 5 peripheral arterial disease, 5 cardiogenic shock y 3 sudden deaths. A total of 16 (4%) CVE occurred within the first 6 months after LT. Eight percent of patients died from CV event. The cumulative risk of CVE at 1,3, and 5 years was 11 %, 23%,36%in those with pre-LT MS and 4%, 8%, 10 %in those without MS before LT (p<0.001) (Fig.2B).

De novo tumours: 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 tumours were the most frequent tumours. The median time between LT and the development of *de novo* tumour was 24 (12-43) months. Fourteen percent of patients died from *de novo* tumours. Cumulative risk of de novo tumours at 1,3, and 5 years was 1 %, 7%, 12%, in those with pre-LT MS and 2%, 4%, 8%in those without pre-LT MS (p =0.486).

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

We did not observe statistical differences in survival and *de novo* tumors between patients with pre-LT MS, *de novo* early MS or those 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 %, 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 did patients without MS or those with *de novo* MS early post-LT(HR 2.1 IC 95% 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 multivariable analysis, patients with pre-LT MS had a significantly independent higher risk of developing post-LT CVE (p< 0.001) as well as male gender, age and obesity. We did not observe an association between pre-LT MS and survival (p=0.94) nor 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 auricula dilatation HR 0.85 (0.38-1,92) p=0.69, Left ventricle 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 nor 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 arena, data on the effects of the MS after LT, particularly the higher rates of CVE (but not poorer survival) are well established (12); yet the data on the effects of the MS present before LT are lacking.

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

condition which is associated with early and late survival.

In our study, the MS was present in 20% of our LT candidates, a rate similar to that described in the general population and other series with percentages that range from 6% to 22% (12,13). In addition, we found that the 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, 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, one year after transplantation, may explain these differences.

We indeed found a positive association between pre-LT MS and post-LT CVE. In different series, the incidence of CVE after LT has ranged between 10%-20% at 3-5 years (14,18), with an impact on short and long-term survival; indeed, it is considered the 3rd cause of late mortality. In our centre, 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 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 [(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 follow-up vs 3%, 6 %, 10 % in non-MS) (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, factors already 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 those two conditions before LT but they were not associated with the development of CVE nor survival after LT in our study (26).

Obesity and diabetes are often involved in the development of tumours and reasons to explain these associations are based on the state of chronic inflammation with MS (27,28). Moreover, in the LT setting, *de novo* tumours are increasing and represent currently the second cause of death (29,30). In line with other studies, 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) 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 should be considered as a high CV risk population independently of the cause of the liver disease.

While our study has some strength such as the large sample size, the homogeneity in patient monitoring and the long duration of follow-up, it has also limitations. In particular, the retrospective nature of the study few baseline variables were missed. More specifically, we did not include the abdominal perimeter which has been previously calculated based on the BMI and ascites, jet, although done in prior studies.

In conclusion, MS before LT is associated with the development of CVE after LT; this risk is higher than in those who develop MS early after LT and significantly higher than that observed in those without MS before and after LT. We recommend identification of patients with MS before LT to establish preventive measures both while in the waiting list and after LT.

Acknowledgements

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Table1. 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
Echocardiograpy			
- 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* tumours.

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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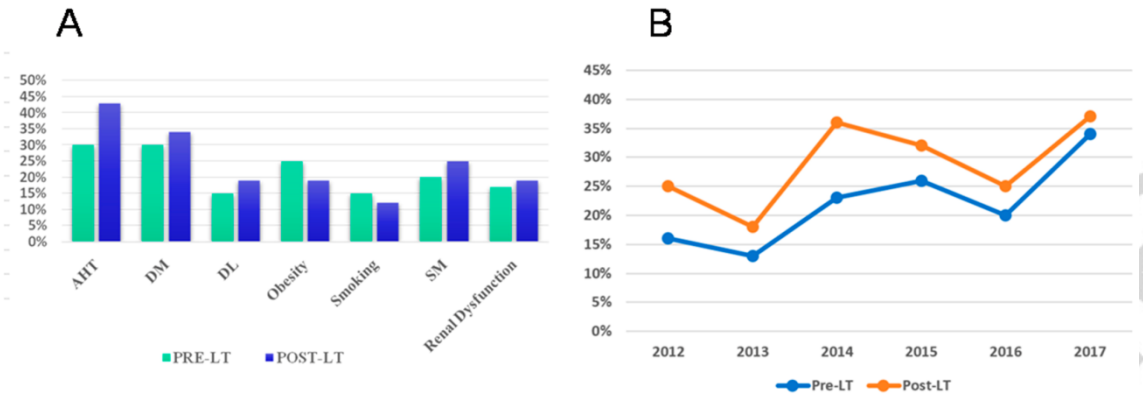

Figure 1. (A) Cardiovascular risk factors and MS pre-LT and 1-year post-LT. (B) Prevalence of the Metabolic Syndrome overtime. (p=0.025).

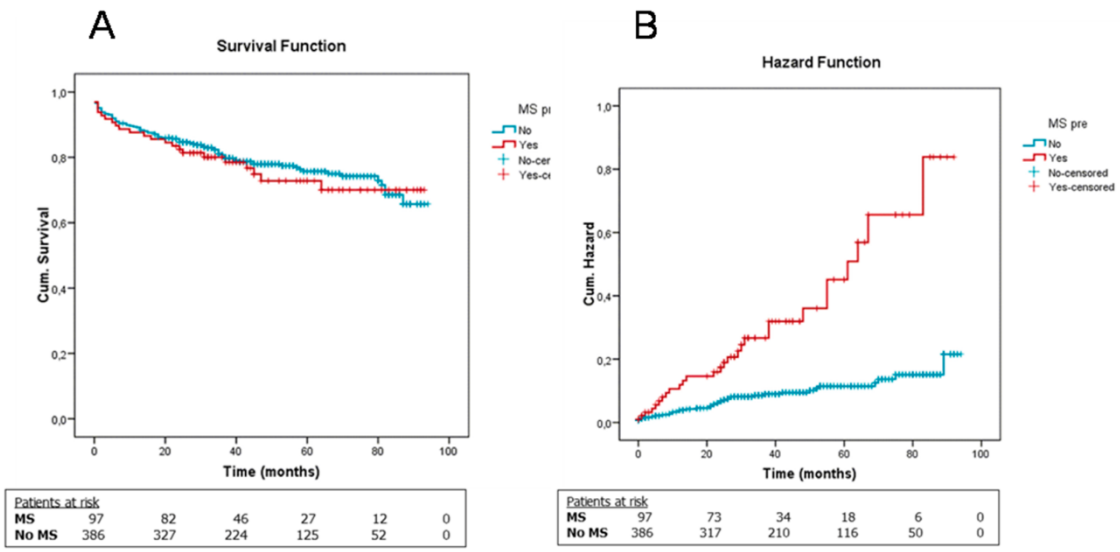

Figure 2. (A) Cox regression survival-SM (p=0.94). (B) Cumulative risk of cardiovascular events post-LT (p<0.001).

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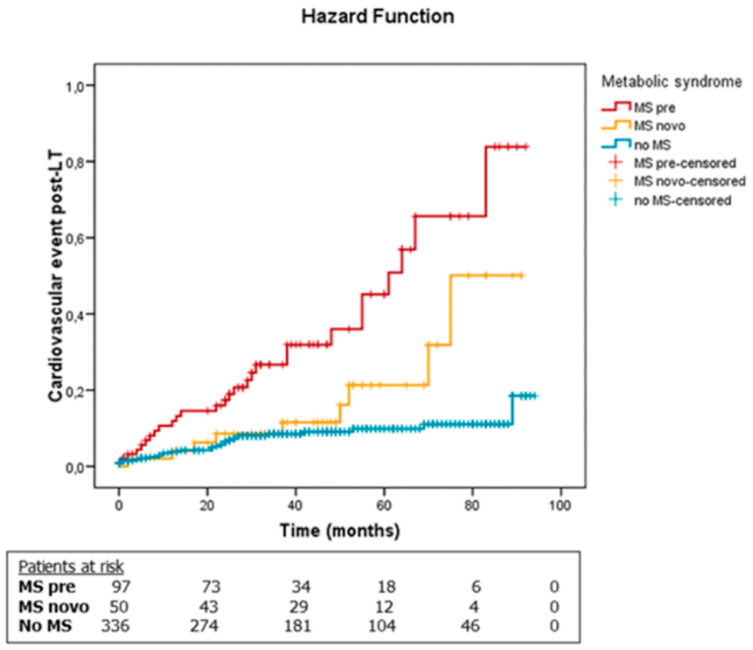

Figure 3. Cumulative risk of CVE after LT in patients with MS before LT, de novo MS and patients without MS pre or post-LT ($p < 0.001$).