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Metabolic syndrome in heart transplantation: impact on survival and renal function

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Summary

The aim of our study was to analyze the early presence of metabolic syndrome (MS) in heart transplant (HTx) patients, and to assess its long-term impact on survival and renal function. From January 2000 to October 2011, 253 consecutive HTx patients who survived more than 90 days were included. MS was diagnosed if patients met revised NCEP-ATP III criteria at HTx or within 3 months post-HTx. The prevalence of MS was 41.9%. Patients with MS had greater overall mortality after a mean follow-up of 1700 ± 979 days (log-rank test, $P = 0.020$). In the multivariate analysis, and subject to a minimum survival of 90 days, the only independent predictor variables of long-term mortality were the presence of MS (OR, odds ratio 2.087, $P = 0.032$), and rejection episodes (OR 1.833, $P = 0.001$). Patients with MS had worse renal function at baseline both in plasma creatinine (1.19 ± 0.44 vs. 1.03 ± 0.29 mg/dl, $P = 0.002$) and glomerular filtration rate estimated by modified diet in renal disease (73.60 ± 26.76 vs. 87.30 ± 43.55 ml/min/1.73m^2, $P = 0.005$), whereas progressive impairment of renal function was of equal magnitude in both groups. The presence of MS prior to transplant or its development within the first 3 months identified a subgroup at greater risk of mortality and long-term renal dysfunction.

Introduction

Metabolic syndrome (MS) is characterized by an increased resistance to insulin action and an alteration in the lipid metabolism. This leads to a proinflammatory and prothrombotic state, with a dysfunction of the vascular endothelium that speeds up cardiovascular arteriosclerotic disease [1–5]. The presence of MS has been associated with a twofold increase in the risk of developing cardiovascular disease, cardiovascular mortality, nonfatal acute myocardial infarction, and stroke. In addition, it has been associated with a 1.5-fold increase in all-cause mortality [6]. On the other hand, obesity plays a key role in pathogenic mechanisms of MS and causes a fourfold increase in the risk of chronic kidney disease (CKD) [7].

The prevalence of MS is increasing to epidemic proportions not only in developed countries but also in developing countries [8]. It affects approximately 25% of adults in the USA [9], and 20–30% of adult population in most countries [10]. In population with solid organ transplantation, a higher prevalence of MS has been reported, which could be because of genetic factors and mainly to the impact of immunosuppressive medication [11–13].

There are few studies in the scientific literature analyzing the impact of MS in heart transplantation (HTx), and most refer to its impact on the development of cardiac allograft vasculopathy (CAV) [14–16]. However, to date, no analysis has been performed on the impact of MS on survival and common post-transplant comorbidities, such as renal dysfunction, rejection episodes, or vascular events.

According to these premises, the study hypothesis was that MS would cause a proinflammatory and prothrombotic condition that would have direct implications on mortality and renal function of HTx patients.

Thus, the aim of the study was to analyze the presence of MS in HTx patients and to assess its long-term impact on survival (primary objective), and on renal function (secondary objective), subject to a minimum survival of 90 days.

Materials and methods

Patients

From January 2000 to October 2011, 344 consecutive HTx patients were included. Patients who survived less than 90 days (81 patients), heart–lung transplants (six patients), retransplants (three patients), and pediatric transplants (one patient) were excluded. The final number of patients included in the study was 253 (Fig. 1).

The study was approved by the Biomedical Research Ethics Committee of our hospital. All patients gave their consent to participate in the study.

Visits and protocol

Patients were assessed before HTx and 1, 2, and 3 months after HTx to determine if they met MS criteria. On each visit, clinical assessment was performed with a complete physical examination, laboratory tests – including a complete blood count, fasting blood glucose, lipid profile, renal and liver function, cytomegalovirus (CMV) viral load, and immunosuppressive drug levels –, echocardiogram exam, and endomyocardial biopsy. Blood pressure was taken with an automatic sphygmomanometer in a sitting position and before taking the medication. According to our protocol, two readings separated by 1–2 min were taken and the higher value was taken as reference value. Venous blood samples were drawn before drug administration and after at least 8 h of fasting.

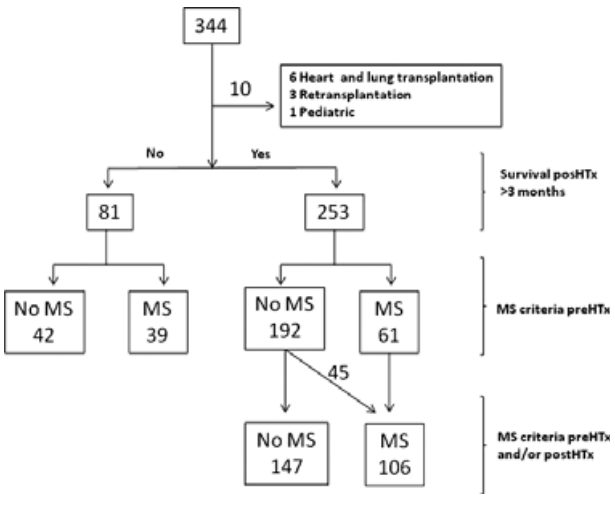

Figure 1 Flowchart of the patients according to metabolic syndrome (MS) criteria.

Immunosuppression and CMV prophylaxis

Until February 2002, induction therapy was performed with OKT3, and after that date with anti-CD25 monoclonal antibody therapy. In both cases, a triple combination maintenance therapy (calcineurin inhibitor + mycophenolate mofetil + steroids) was used. The steroid used in our hospital is deflazacort, with an initial dose of 1.2 mg/kg, in progressive descending doses if no incidences are found in protocol biopsies. The goal is to maintain a minimal dose of corticosteroid at 1 year post-HTx (3–6 mg/day).

Cytomegalovirus prophylaxis was given during 3 months in cases where the donor was CMVIgG-positive and the recipient CMVIgG-negative. Treatment was performed with either ganciclovir or valganciclovir, adjusted to renal function.

Rejections and infections

Rejection was considered as any episode requiring a significant increase in the immunosuppression regimen (episodes of acute cellular rejection grade 2R and/or nonpre-existing acute deterioration of left ventricular function, without taking into account the result of endomyocardial biopsy, and after ruling out any other cause for this dysfunction).

Infectious conditions requiring hospital admission were also taken into account. CMV infection was considered when a significant increase in CMV antigenemia or plasma viral load was observed – compared to previous assessments –, in which case pre-emptive therapy was administered (ganciclovir IV 5 mg/kg twice daily or valganciclovir 900 mg twice daily for 3 weeks or until viral load was negative in two consecutive analysis). In cases of CMV disease (viremia with fever, malaise, and involvement of a specific organ), treatment was given with valganciclovir 900 mg orally twice daily or ganciclovir intravenously 5 mg/kg twice daily until viral eradication was achieved. Antiviral treatment was always adjusted to renal function.

Diagnosis of MS and related treatments

The presence of MS was assessed before HTx and 1, 2, and 3 months after HTx. Patients who met MS criteria on at least one of these four follow-up assessments were analyzed in the MS group. Patients who did not meet MS criteria at any of these four time points were included in the non-MS group.

According to modified, revised NCEP-ATP III (Third Report of the National Cholesterol Education Program) criteria [17], diagnosis of MS was made when the

patient met at least three of the following criteria: triglyceride levels ≥150 mg/dl (1.7 mmol/l) or drug treatment for hypertriglyceridemia; high-density lipoprotein (HDL)-C < 40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.3 mmol/l) in women or drug treatment to raise HDL-C levels; diabetes mellitus and treatment for elevated glucose or fasting glucose levels ≥100 mg/dl; blood pressure ≥130/85 mm Hg or on antihypertensive drug treatment, and, waist circumference over 102 cm in men and over 88 cm in women. This latter parameter was substituted for body mass index (BMI) > 30 as the cutoff point for obesity.

The diagnostic criteria used for MS in our study have been used in various studies associating MS with cardiovascular disease in the general population and also in HTx recipients. Furthermore, BMI > 30 is part of the definition of MS according to the criteria of the World Health Organization (1999) [18] and the American Association of Clinical Endocrinologists (2003) [19], and it has also been used and associated with the development of CAV and graft failure in other studies on MS in HTx [14,20].

All patients received treatment with statins after the 3rd month post-HTx with a total cholesterol objective of <200 mg/dl. Patients with triglyceride levels persistently higher than 250 mg/dl despite diet measures were treated with a fibrate. In patients with diabetes mellitus, diet and pharmacological treatments were optimized with a HbA1c objective of 7%. Patients with persistent hypertension (BP > 140/90 mmHg) despite hygienic-dietetic measures were treated preferably with ramipril, adding amlodipine as a second drug if blood pressure was uncontrolled.

Statistical analysis

Qualitative variables were expressed as percentages and quantitative variables as mean ± standard deviation. Comparisons of continuous variables were made with Student's *t*-test for independent samples or the Mann–Whitney *U* test if the variables did not fit a normal distribution. Differences between percentages were compared using Pearson's chi-squared test with Fisher's correction when the number of expected values was less than five.

Multivariate analysis was performed using the Cox proportional hazards method (Enter method), in which the dependent variable was the occurrence of death during the follow-up. The independent variables were those present 3 months after HTx and those shown in other studies to be associated with mortality during follow-up.

A difference was considered statistically significant if $P < 0.05$. The statistical program used was SPSS® version 15 for Windows (SPSS Inc., IL, USA).

Results

Baseline patient characteristics

According to modified, revised NCEP-ATP III criteria, the prevalence of early MS (pre-HTx or in the first 3 months post-HTx) in our HTx patients was 41.9% (106 of a total of 253 finally included). Among patients with MS, 61 (57.5%) met criteria before HT, and 45 (42.5%) after HT (Fig. 1). This distribution remained homogeneous at 1 year post-HTx. Thus, 95.2% ($n = 101$) of patients in Group 1 maintained MS criteria at 1 year post-HTx, and 98.7% ($n = 145$) in Group 2 remained free of MS criteria.

The only significant differences in the baseline characteristics of both groups (Table 1) were in recipient age at transplantation (MS 54 ± 9 vs. non-MS 50 ± 11 years; $P = 0.005$), and baseline plasma creatinine level (MS 1.19 ± 0.44 vs. non-MS 1.03 ± 0.29 mg/dl; $P = 0.002$).

Among those patients excluded because they did not reach 3 months of survival (81 patients), 42 patients did not suffer from MS before HTx and 39 did. There were no significant differences between both groups according to basal characteristics.

Table 2 shows the values of the diagnostic parameters for MS at baseline (pre-HTx) and 3 months post-HTx in both groups, with significant differences in all values defining the presence of MS.

There were no significant differences in the incidence of rejection episodes, infections, CAV or tumors during the follow-up of both groups. The only difference found was a higher incidence of CMV infections in the MS group (1.28 ± 0.64 vs. 1.13 ± 0.46, $P = 0.046$).

Univariate analysis

Patients in our series who met MS criteria at baseline had greater overall mortality after a mean follow-up of 1700 ± 979 days (33% vs. 20.4%, $P = 0.024$). Higher mortality in the MS group was primarily caused by chronic rejection/sudden death (40% vs. 30%) and other cardiovascular events (14.3% vs. 3.3%) (Table 3). When analyzing survival curves, significantly higher long-term survival was found in patients from the non-MS group (log-rank test, $P = 0.02$), with divergent curves from the start until stabilization at about 7 years of follow-up (Fig. 2).

Patients from the MS group had worse renal function from baseline, both in plasma creatinine and glomerular filtration rate, estimated by modified diet in renal disease (MDRD; 73.60 ± 26.76 vs. 87.30 ± 43.55 ml/min/1.73 m^2, $P = 0.005$). As shown in the table, a progressive decline in renal function of very similar magnitude can be observed in both groups, but only 5 years after HTx did

Table 1. Baseline characteristics of patients according to the presence of metabolic syndrome (MS).

	MS (n = 106)	Non-MS (n = 147)	P
Recipient age (years)	54 ± 9	50 ± 11	0.005
Sex (male, %)	86.8	79.6	0.136
Ischemia time (min)	156.76 ± 45.88	163.85 ± 49.26	0.256
Etiology of heart failure			
Ischemic	52.8	40.8	
Idiopathic dilated cardiomyopathy	39.6	40.8	0.051
Valvular	4.7	8.2	
Other	2.8	10.2	
Previous cardiac surgery (%)	14.2	15.6	0.743
Creatinine before HTx (mg/dl)	1.19 ± 0.44	1.03 ± 0.29	0.002
Smoking (%)			
Yes	41.5	31.7	0.054
No	29.2	24.1	
Former	29.3	44.2	
CMV serology			
R+/D+	64.2	68	0.702
R+/D−	17.9	14.3	
R−/D+	14.2	15.6	
R−/D−	3.8	2	
Donor age (years)	37 ± 11	35 ± 11	0.201
Emergency HTx (%)	25.5	30.6	0.371
Bicaval technique (%)	78.3	81.5	0.561
Primary graft failure (%)	20.8	21.8	0.846
Rejection during first year	1.09 ± 1.03	1.16 ± 1.09	0.607
Rejection during follow-up	1.40 ± 1.36	1.26 ± 1.24	0.399
≥1 episode of rejection (%)	68.6	71	0.675
CMV infections during follow-up	1.28 ± 0.64	1.13 ± 0.46	0.046
Infection during first year	0.79 ± 1.03	0.63 ± 0.90	0.214
Infection during follow-up	1.22 ± 1.48	1.02 ± 1.41	0.281
Tumors during follow-up	1.30 ± 0.86	1.38 ± 0.95	0.517
Cardiac allograft vasculopathy (%)	46.7	35.5	0.131
Maintenance immunosuppression (%)			
Cyclosporine	73.6	76.9	0.549
Tacrolimus	26.4	23.1	
Steroids	100	100	
Other treatments at 1 year pos-HTX (%)			
ACEI	67.3	34	<0.0001
Statins	100	100	

Values expressed as percentages and mean ± standard deviation.

CMV, cytomegalovirus; R/D, recipient/donor; ACEI, angiotensin-converting enzyme inhibitor; HTx, heart transplantation.

mean glomerular filtration rate reach a pathological range (less than 60 ml/min/1.73 m^2) and only in the MS group (Table 4, Fig. 3).

Multivariate analysis

In the multivariate analysis, the only independent predictor variables of long-term mortality in patients surviving a minimum of 90 days were presence of MS [odds ratio (OR) 2.087, 95% confidence interval (CI) 1.066–4.083, P = 0.032], and rejection episodes (OR 1.833, 95% CI 1.406–2.389, P = 0.001) (Table 5).

None of the MS criteria by itself reached the statistical significance related to survival. Only the combination of them (metabolic syndrome) was relevant.

Discussion

Metabolic syndrome (MS) arose 30 years ago to define a noncoincidental clustering of metabolic factors (abdominal obesity, dyslipidemia, high blood glucose, and high blood pressure), frequently observed in clinical practice [21], and related to an increased risk of cardiovascular arteriosclerotic disease.

Table 2. Metabolic syndrome (MS) criteria.

	MS (n = 106)	Non-MS (n = 147)	P
Arterial hypertension before HTx (%)	57.1	16.3	0.001
BMI before HTx (kg/m^2)	29.45 ± 13.74	24.53 ± 3.55	0.001
HDL before HTx (mg/dl)	32.27 ± 8.72	35.94 ± 12.50	0.017
Triglycerides before HTx (mg/dl)	147.05 ± 76.53	104.61 ± 40.26	0.001
Glucose before HTx (mg/dl)	124.68 ± 49.08	98.62 ± 30.65	0.001
Arterial hypertension 3 months after HTx (%)	61.1	31.5	0.001
BMI 3 months after HTx (kg/m^2)	29.47 ± 13.78	24.50 ± 3.55	0.001
HDL 3 months after HTx (mg/dl)	45.09 ± 13.91	56.13 ± 12.22	0.001
Triglycerides 3 months after HTx (mg/dl)	174.79 ± 70.86	136.13 ± 46.66	0.001
Glucose 3 months after HTx (mg/dl)	119.42 ± 53.61	100.62 ± 46.45	0.017

Values expressed as percentages and mean ± standard deviation.
BMI, body mass index; HDL, high-density lipoprotein; MS, metabolic syndrome; HTx, heart transplantation.

Table 3. Overall mortality and etiology.

	MS (n = 106)	Non-MS (n = 147)	P
Overall mortality	35 (33%)	30 (20.4%)	0.024
Acute rejection (%)	8.6	26.7	
Chronic rejection + cardiac arrest (%)	40	30	
Infection (%)	11.4	13.3	0.266
Other cardiovascular (%)	14.3	3.3	
Cancer (%)	11.4	6.7	
Others (%)	14.3	20	

MS, metabolic syndrome.

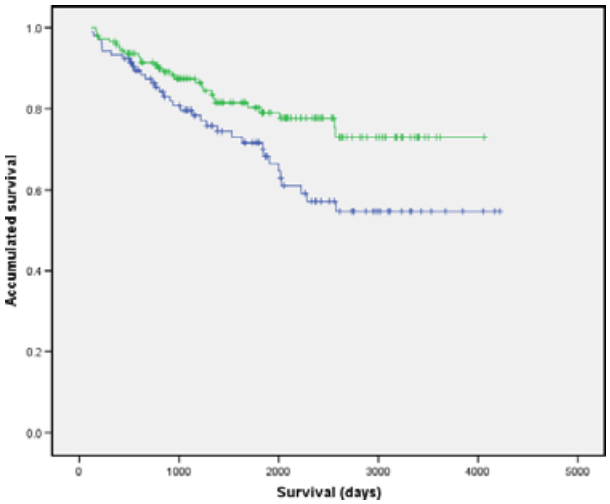

Figure 2 Long-term survival in MS and non-MS groups. Significantly higher long-term survival was found in patients from the non-MS group (log-rank test, P = 0.02), with divergent curves from the start until stabilization at about 7 years of follow-up.

The presence of MS has been associated in the general population with a significant increase in the risk of cardiovascular morbility and mortality, and overall mortality

Table 4. Renal function.

	MS (n = 106)	Non-MS (n = 147)	P
Creatinine before HTx	1.19 ± 0.44	1.03 ± 0.29	0.002
Creatinine at first year HTx	1.39 ± 0.86	1.20 ± 0.38	0.023
Creatinine at 5 years HTx	1.54 ± 0.78	1.26 ± 0.51	0.025
MDRD before HTx	73.60 ± 26.76	87.30 ± 43.55	0.005
MDRD at first year HTx	63.45 ± 20.32	70.58 ± 21.83	0.012
MDRD at 5 years HTx	56.50 ± 20.73	67.25 ± 19.41	0.006

HTx, heart transplantation; MDRD, modified diet in renal disease in ml/min/1.73 m^2.
Creatinine in mg/dl.

[4–6]. There are few studies to date which assess MS impact in HTx.

The study hypothesis was that MS would cause a proinflammatory and prothrombotic state that would have direct implications on mortality and renal function in HTx patients. Thus, the aim of the study was to analyze the early presence of MS in HTx patients, and to assess its long-term impact on survival (primary objective) and renal function (secondary objective).

It was found that MS presence has prognostic implications and that renal dysfunction is more frequent in these patients.

The prevalence of early MS (pre-HTx or in the first 3 months post-HTx) in our series of patients who were alive 3 months after transplant was 41.9%. This percentage coincides with previous series, which reflects a higher prevalence of MS in transplant population, ranging from 28.6% to 63% [11–13]. Thus, a prevalence of MS of 42.3% was found in a series of 111 HTx patients, although they were patients with a mean of 7 years since HTx and, therefore, with greater exposure time to immunosuppressive medication [22].

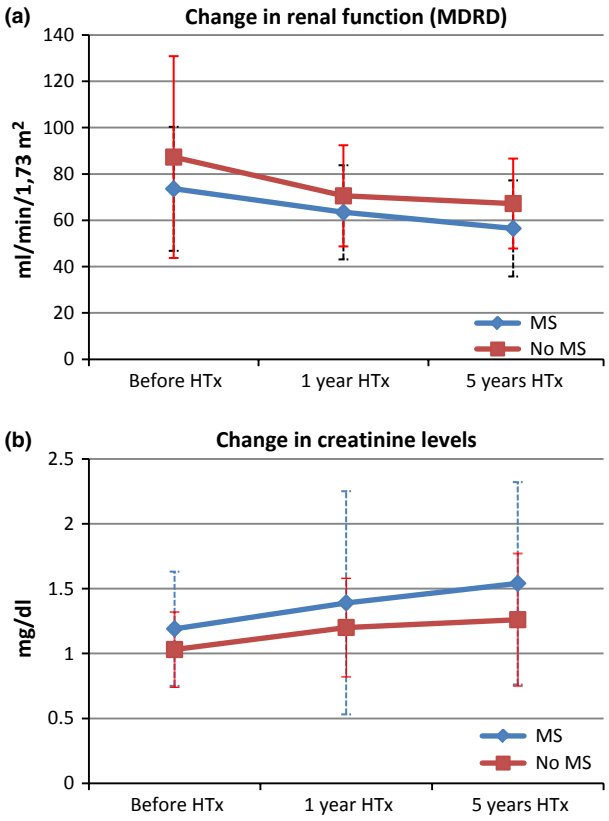

Figure 3 Evolution of renal function in MS and non-MS groups. Patients from the MS group had worse renal function from baseline, both in plasma creatinine and glomerular filtration rate, estimated by MDRD. A progressive decline in renal function of very similar magnitude can be observed in both groups, but only 5 years after HTx did mean glomerular filtration rate reach a pathological range (less than 60 ml/min/1.73m^2) and only in the MS group.

Table 5. Mortality logistic regression.

	OR	95% CI	*P*
MS	2.087	1.066–4.083	0.032
Renal function (MDRD) before HTx	1.002	0.993–1.010	0.676
Ischemic time	1.004	0.997–1.011	0.285
Age	1.022	0.985–1.061	0.242
Sex	1.323	0.525–3.332	0.552
PGF	1.117	0.513–2.435	0.780
Rejection episodes	1.833	1.406–2.389	0.001
Infections	1.054	0.843–1.318	0.645

OR, odds ratio; CI, confidence interval; MS, metabolic syndrome; MDRD, modified diet in renal disease; HTx, heart transplantation; PGF, primary graft failure.

The chronological development of MS is a relevant concern regarding its prognostic value. We considered important to compare the prognostic impact of MS before and immediately after HTx. All patients with MS criteria before HTx maintained these criteria during the first 3 months post-HTx. On the other hand, MS development right after HTx probably identifies patients who met some of the MS criteria and with certain predisposition to insulin resistance and hypertension, triggered by the use of higher doses of immunosuppressants in the first period after HTx. With this distribution, samples have remained relatively homogeneous 1 year post-HTx. Thus, 95.2% (n = 101) of patients in Group 1 maintained MS criteria 1 year post-HTx, and 98.7% (n = 145) in Group 2 remained without criteria of MS 1 year post-HTx.

When baseline characteristics of the patients were analyzed, significant differences were found in recipients' age, which was higher in patients from the MS group. Ischemic heart disease –as the main cause of HTx–, and smoking were more prevalent in the MS group, without reaching statistical significance. A higher prevalence of MS is expected in patients with ischemic heart disease, despite the fact that in many cases its chronicity and progression to advanced heart failure may result in the disappearance of previous parameters, such as hypertension and abdominal obesity.

When each of the parameters involved in the definition of MS was analyzed, we observed a proportional increase in blood pressure levels, BMI, triglycerides, plasma HDL, and blood glucose 3 months after HTx when compared to baseline values in both the MS and non-MS groups. These findings are probably directly related to immunosuppressive therapy, particularly intense in this early phase. Different studies have shown a predisposition to the development of hypertension, dyslipidemia, and altered carbohydrate metabolism in transplant population [23–25].

We did not find differences in variables such as donor age, ischemia time of graft, prior cardiac surgery, percentage of HTx performed on an emergency basis, or primary graft failure. These variables are traditionally associated with decreased survival after HTx. Despite the fact that our study excluded patients who died in the first 90 days, the lack of differences in these variables between both groups confers more reliability on the assessment of the impact of MS on survival and long-term renal function.

Among the follow-up variables, no significant differences were found in immunosuppressive maintenance treatment, number of rejections, or number of infections either in the first year or during the follow-up. The only difference was a higher incidence of CMV infections in the MS group. Previous studies have observed an association between MS and opportunistic infections, including CMV, both in general and liver transplant population [26,27].

No significant differences in CAV prevalence were found between both groups during the follow-up. This finding may be explained by the fact that a systematic search was not carried out for the presence of CAV in the medium–long term. Instead, CAV was diagnosed by coronary

angiography and/or intravascular ultrasound (IVUS) after clinical changes, findings suggestive of ischemia, or graft dysfunction. Differences in the development of tumors between both groups were not observed either.

Patients in our series who met early MS criteria had greater long-term mortality. In a recent meta-analysis [6] of 87 studies including over 950 000 patients outside of the context of HTx, the presence of MS was associated with an increase of 2.40 in the relative risk of cardiovascular death, and of 1.58 in mortality from all causes. In this regard, we published our preliminary experience on the impact of MS on survival in a smaller population of patients undergoing HTx with survival greater than 1 year. We observed a higher mortality trend in the MS group, without reaching statistical significance [28].

Higher mortality in the MS group was primarily because of chronic rejection/sudden death and other cardiovascular events. Among solid organ transplant patients, metabolic abnormalities that lead to the development of insulin resistance have proven to be related to a higher number of major vascular events and impaired graft function [11–13]. Specifically in HTx patients, different metabolic abnormalities have been associated with the development of CAV or chronic rejection [14,15], which is one of the main causes of graft failure and death during the first year after HTx [29]. In this regard, our group recently published the first study directly relating the presence of MS – based on international criteria–, with development of CAV 1 year after transplant – diagnosed using IVUS [16]. In this series, coronary angiography and IVUS were performed systematically at baseline and $t = 1$ after HTx. When assessing the presence of CAV in the medium–long term, no protocolized serial coronariographic study was performed in the follow-up. It was performed only to detect clinical findings of ischemia or graft dysfunction. This explains why we did not find a significantly different proportion of CAV in the follow-up between both groups.

In the multivariate analysis, the only independent predictor variables of long-term mortality in patients surviving a minimum of 90 days were the presence of MS and rejection episodes. None of the MS criteria by itself reached the statistical significance related to survival. Only the combination of them (metabolic syndrome) was relevant. Recipient history of diabetes has been identified in the latest report of the International Society for Heart and Lung Transplantation (ISHLT) registry as an independent risk factor for mortality after 5 and 10 years. On the other hand, recipient weight, as a continuous factor, was an independent risk factor for mortality after 10 and 15 years [29]. In our study, none of these variables reached the statistical significance in the context of a mean 6-year follow-up, and conditional on survival to 90 days. The number of rejections in the first year has been identified in the latest report of the ISHLT registry as an independent risk factor for mortality after 5-years in patients who have survived the first post-transplant year [29]. On the other hand, serum creatinine at time of transplant, as continuous factor, has been shown as independent risk factor for 1, 5 and 10-year mortality post-HTx, even in 1-year conditional survival [29]. In our work, this factor has not been shown as independent predictor variable of long-term mortality in patients surviving a minimum of 90 days. However, no other study that specifically assesses the impact of MS on survival in HTx patients is available to date.

Patients from the MS group had worse renal function from both in plasma creatinine and glomerular filtration rate estimated by MDRD, but we cannot confirm that this fact was because of the presence of MS or just because of the cumulative effects of MS components, as this was not the objective of this study. Analysis of long-term course shows a similar progressive decline in renal function in both groups, but mean glomerular filtration rate reached a pathological range only 5 years after HTx did (less than 60 ml/min/1.73 m^2), and only in the MS group. In studies with general population, MS has shown to be an important predictive factor of early renal dysfunction. It was observed that the odds ratio of CKD and microalbuminuria increase in proportion to the number of MS components [30,31]. In the context of kidney transplantation, MS has shown to be an independent risk factor for the development of chronic graft dysfunciton [32,33]. It is considered to require special surveillance to achieve an early diagnosis, aggressive control of its components, and a favorable immunosuppression strategy [34]. In the setting of HTx, different studies have proven the influence of classic cardiovascular risk factors (especially hypertension, diabetes and dyslipidemia) on the development of early and late renal dysfunction post-HTx [35,36]. Furthermore, in the latest ISHLT registry report, recipient's weight and systolic blood pressure were identified as independent risk factors for the development of renal dysfunction 1 year post-HTx in patients surviving the early post-transplant period [29]. However, there is no specific reference to the impact of MS on renal function in HTx. The slight development impact of the early presence of MS on renal function parameters at 5 years post-HTx in our population is striking, and probably related to a stronger control of MS components (e.g., MS group was more likely to be on angiotensin-converting enzyme inhibitors in the context of higher prevalence of hypertension), and to a more nephroprotective immunosuppression profile (mainly, lower plasmatic levels of calcineurin inhibitors).

Thus, when searching for early noninvasive markers which can clearly identify those patients at greater risk of developing CAV, the diagnostic procedure for MS seems to be justified. The early presence of MS after HTx identified in our study a subgroup of patients with lower long-term

survival and worse renal function. In these subjects, it would probably be preferable to use individualized diagnostic and treatment strategies, including an aggressive approach to control risk factors, with a greater degree of nephroprotection. Our results show a worse prognosis and poorer renal function in those patients who had MS before HTx or right after it. The shortage of organs makes that this data must be taken into account when selecting patients to receive a HTx, but we also think that the sole presence of MS should not justify the rejection of a HTx candidate. Moreover, these patients probably should be followed closer as they are more prone to develop cardiovascular events. Long-term prospective studies are required to show the benefit of these strategies in the transplant population.

This is the first study to analyze and determine the impact of MS – defined by international criteria–, on long-term survival and renal function in patients undergoing HTx. However, this study has some limitations. On one hand, the relatively limited number of patients in comparison to studies that analyze MS in the general population. Nevertheless, this is a single-center consecutive study in the context of HTx, with the consequent advantages in terms of homogeneity in the selection, diagnostic, and therapeutic management of the patients. The period of the first 3 months after HTx which is considered for the diagnosis of MS may seem short to assess its impact on long-term follow-up. However, it corresponds to the period in which immunosuppression is most intense and, therefore, is most likely to induce metabolic abnormalities. Moreover, it is the period in which the transplant patient achieves a relative clinical stability after the surgical procedure.

Transplant patients with earlier mortality were excluded from the study, although it should be taken into account that this event is usually directly related to patient severity parameters, graft preservation, and immediate surgical complications. In addition, this strategy facilitates analyzing the development of MS in the first months, as well assessing its expected impact on medium–long-term follow-up.

Conclusions

The early presence of MS in our series of HTx patients is an independent predictor of long-term mortality and causes worse renal function at baseline, which is maintained during the follow-up.

Authorship

LM-D: conceived and designed the study, and wrote this article. IJS-L: analyzed and interpreted the data. He reviewed and approved the manuscript. LA-B, MP, MR, AS, JAM: critically reviewed and approved the article.

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