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Donor and recipient risk assessment and its influence on clinical outcome in heart transplantation at a reference center in Brazil

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BACKGROUND: Heart transplantation is the gold standard treatment for end-stage heart failure patients. However, the shortage of donor hearts limits its applicability. This study aims to evaluate the risk factors associated with survival within 1-year after heart transplantation.

METHODS: A single-center retrospective cohort study evaluated 299 adult patients who underwent transplantation at the Heart Institute (Incor) between January 2013 and December 2019. Univariate and multivariate Cox regression analyses were conducted to identify independent predictors of 1-year survival among well-established prognostic clinical characteristics described in the literature. Patients were followed until death or the last observation on October 12, 2022. A Simple Risk Index was created based on the hazard ratio of each factor.

RESULTS: Chagas disease was the most common cause of cardiomyopathy (36%). Most patients were male (65%) with a median age of 50 (39-58) years. Four variables observed during the last clinical assessment in the intensive care unit before surgery were found to be statistically significant: maximum Sequential Organ Failure Assessment (SOFA) score, creatinine clearance in 3 quartile categories, C-reactive protein in 3 categories, and white blood cell count in 3 categories. The model demonstrated good discrimination (C-index = 0.74) and calibration. The group at high risk (>20 points) exhibited significantly higher mortality rates at 1 year ($p < 0.001$).

CONCLUSIONS: The study introduces a risk prediction score for 1-year post-transplant mortality in a reference center in Brazil. The score is based on four variables: maximum SOFA score, creatinine clearance, C-reactive protein, and white blood cell count.

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Background

Heart failure represents a significant public health challenge, with high mortality rates and frequent hospital readmissions, particularly among patients with advanced disease. It is estimated that 1% to 2% of the population in developed countries is affected by heart failure, with projections indicating an increase in prevalence as the population ages.[1] Heart transplantation (HT) remains the recommended treatment for patients with end-stage heart failure.[2] However, the total number of transplants that can be performed is ultimately limited by the availability of suitable donors.[3] Despite recent initiatives to expand the donor pool, the current supply remains insufficient to meet demand.[4] To address the needs of patients with end-stage heart failure, Brazil's organ sharing and heart allocation policy incorporates a four-tiered system designed to enhance access to HT for the sickest patients, thereby reducing wait-list mortality. Consequently, the majority of heart transplants in Brazil are performed on patients who are hospitalized and in cardiogenic shock, with priority status on the waiting list.[5]

Since the initial publication of the risk stratification paradigm for patients with acute myocardial infarction by Killip and Kimball, risk prediction models have become an increasingly important tool in the cardiac intensive care unit (ICU). The Sequential Organ Failure Assessment (SOFA) score is an example of a risk stratification model that evaluates organ failure in patients with sepsis. It has since been extensively validated for use in critically ill patients with conditions other than sepsis, and it has been established as a reliable tool for predicting ICU mortality and adverse outcomes.[6]

The International Society of Heart and Lung Transplantation (ISHLT) has provided a comprehensive description of risk factors for heart transplant patients.[7] However, most of the information in the ISHLT database is derived from the United States, Europe, and Asia, and the applicability of these results to Latin American cohorts may be limited. Further insight into the factors that influence post-transplant survival in this population could facilitate the optimal use of available grafts and health care resources.

The aim of this study was to evaluate prognostic factors associated with 1-year mortality after HT in a Brazilian heart transplant reference center and to develop a risk index for post-transplant mortality.

Methods

Study design

This is a retrospective cohort study conducted at a single center, which included 384 adult patients (over 18 years old) who were listed for emergency HT at Incor HC-FMUSP between January 2013 and December 2019. The analysis excluded 74 patients who died before transplantation, 1 patient who received multiple organs, and 10 patients with missing follow-up data (Figure 1). The study data were collected and managed using REDCap electronic data capture tools hosted by HC-FMUSP. The files consist of patient-level records containing information on both recipients and donors. A team of heart transplant specialists conducted a retrospective review of the electronic medical records of transplant patients and entered selected data into the RedCap platform. The study collected a variety of data points, including patient demographics, donor information, length of hospital stays, lab data, imaging studies, and clinical status, 24 hours before surgery, as well as the use of immunosuppressive medications in induction therapy. These variables were selected based on clinical criteria and previous research indicating their potential impact on prognosis following HT.

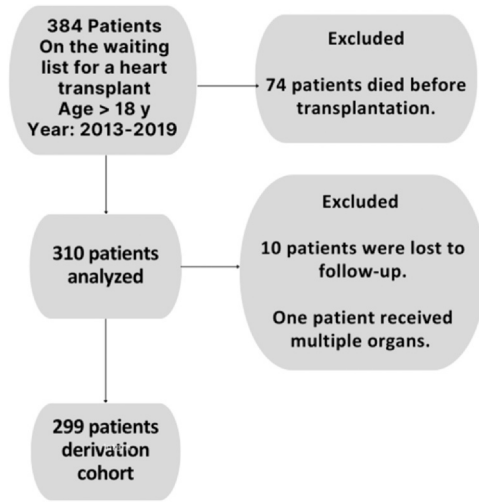

Figure 1 Flowchart of the study. This flow diagram depicts selection of the study cohort from Heart Institute—Brazil Heart Transplant patients.

This retrospective study was approved by the Institution Ethics Committee, with a waiver of informed consent. It adheres to the highest standards of ethical conduct, as outlined in the ISHLT ethics statement.

Study outcomes

The primary outcome of this analysis was death within 1 year after the HT procedure. Outcome events were identified by cardiologists through a review of medical charts.

Statistical analysis

The baseline characteristics of the recipients and donors were summarized in Table 1. Quantitative variables were presented as either means and standard deviations (SD) or medians and interquartile range (IQR), while qualitative variables were presented as absolute and relative frequencies. To evaluate factors associated with survival and create a prognostic risk score based on estimated values of the hazard ratios (HR), univariate and multivariate Cox regression models were fitted. To ensure easy interpretation of the risk score, numerical variables were categorized into

Table 1 Baseline Characteristics of Recipients and Donors

	Overall	Alive at 1 year	Deceased at 1 year	
Clinical characteristics	N = 299[a]	N = 216[a]	N = 83[a]	*p*-value[b]
Recipient characteristic				
Female sex	106 (35%)	76 (35%)	30 (36%)	0.9
Age (years)	50 (39-58)	47.5 (37-57)	55 (42-61)	< 0.001
BMI (kg/m^2)	22.9 (20.3-24.8)	22.7 (20.2-24.8)	22.9 (20.5-24.7)	0.9
Race				
Caucasian	204 (68%)	142 (66%)	62 (75%)	0.291
Black	41 (14%)	33 (15%)	8 (9.6%)	
Multiracial	54 (17.7%)	41 (19%)	13 (15.4%)	
Heart failure diagnosis				
Dilated	106 (35%)	85 (39%)	21 (25%)	0.2
Chagasic	108 (36%)	74 (34%)	34 (41%)	
Ischemic	48 (16%)	32 (15%)	16 (19%)	
Other	37 (12%)	25 (12%)	12 (14%)	
Blood type				
A	111 (37.1%)	77 (35.6%)	34 (41%)	0.659
AB	15 (5%)	12 (5.6%)	3 (3.6%)	
B	41 (13.7%)	32 (14.8%)	9 (10.8%)	
O	132 (44.1%)	95 (44%)	37 (44.6%)	
LVEF (%)	24.5 (20-29)	24 (20-28)	25 (20-30)	0.5
Diabetes before HT	44 (15%)	30 (14%)	14 (17%)	0.5
Estimated GFR < 50 (ml/min/1.73 m^2) before HT	119 (40%)	77 (36%)	42 (51%)	0.018
Most recent class I PRA (%)	0 (0-12)	0 (0-0)	0 (0-12)	0.044
Heart failure MAGGIC score at admission	24 (22-26)	24 (21-26)	24 (22-27)	0.4
Donor characteristic				
Female sex	54 (18%)	40 (19%)	14 (17%)	0.7
Age (years)	30 (22-37)	29 (22-36.2)	32 (22-39)	0.3
BMI (kg/m^2)	25.5 (23.5-27.7)	25.5 (23.4-27.7)	25.7 (23.8-27.9)	0.6
Ischemic time (hour)	3.6 (2.5-3.8)	3.3 (2.5-3.8)	3.2 (2.4-3.9)	0.962
Prior hypertension	21 (7.0%)	12 (5.6%)	9 (11%)	0.11
Creatinine (mg/dl)	1.1 (0.8-1.5)	1.1 (0.8-1.5)	1.1 (0.8-1.8)	0.2
Gender mismatch				
No	205 (68.6%)	148 (68.5%)	57 (68.7%)	0.905
Female recipient/male donor	73 (24.4%)	52 (24.1%)	21 (25.3%)	
Male recipient/female donor	21 (7%)	16 (7.4%)	5 (6%)	

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate before heart transplant; HT, heart transplant; IQR, interquartile range; LVEF (%), left ventricular ejection fraction (%); MAGGIC, meta-analysis global group in chronic heart failure risk score; PRA, panel reactive antibodies; SD, standard deviations.

[a]*n* (%), mean (SD), or median (IQR).

[b]Pearson's chi-square test or Welch 2 sample *t*-test.

quartiles: (1) less than or equal to the first quartile, (2) greater than the first quartile and less than the third quartile, and (3) greater than or equal to the third quartile. The presence of multicollinearity was examined using the Variance Inflation Factor (VIF). The multivariate Cox regression used the Backward Stepwise selection method.

The study evaluated the model's ability to classify death occurrences within 30 days, 6 months, and 1 year after HT (discrimination ability) using the Harrell C-index and its bias-corrected estimate through 2,000 times bootstrap validation with a sample size equal to 25 for 3 time points: 30, 60, and 365 days and adjustment for optimism. Values close to 1 indicate a perfect ability of the model to predict death. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate the model calibration. A nonstatistically significant test ($p > 0.05$) indicates that the model has an adequate fit.[8,9]

To create the prognostic risk score, weights were assigned to each feature of the final model based on the estimated values of HR. Receiver operating characteristic curve (ROC) analysis was used to determine the optimal threshold for dividing the score into 2 groups to predict the occurrence of death within 30 days, 6 months, and 1 year after HT. Sensitivity, specificity, and accuracy were calculated. Kaplan-Meier curves were used to examine overall survival stratified by risk grouping. The Log-Rank test was used to test for differences between risk groupings. A significance level of 0.05 was consistently considered throughout the study. The data were analyzed using SPSS v25 and R v4.3.1 software.[10,11]

Results

Patient demographics

Table 1 provides an overview of the baseline characteristics of the recipients and donors. Among the 299 patients (recipients), the majority were male ($n = 193$; 65%), with a median body mass index (BMI) of 22.9 (20.3-24.8) kg/m^2. Sixty-eight percent were identified as Caucasian ($n = 204$). The median age at the time of transplantation was 50 years old, with a range of 39 to 58 years. A history of diabetes before HT was reported in 44 patients (15%) and prior renal insufficiency, as indicated by a glomerular filtration rate (GFR) of less than 50 ml/min, was present in 119 patients (40%). The most prevalent underlying cause of heart failure in this cohort was Chagas cardiomyopathy, affecting 36% of patients ($n = 108$). Additionally, 106 patients (35%) exhibited dilated cardiomyopathy, while 48 patients (16%) demonstrated ischemic cardiomyopathy. The analysis of pulmonary artery pressures yielded the following results: a mean pulmonary artery pressure of 30.2 mm Hg (SD 8.4) and a median pulmonary vascular resistance of 2 (2-3) Wood units. The median left ventricular ejection fraction was 24.5% (20-29) based on the results of the transthoracic echocardiogram conducted at the time of admission. The results of the systemic hemodynamics analysis indicated a median cardiac index of 2.5 (1.9-3) liter/min/m^2 and a mean systemic arterial blood pressure of 70.2 (11.8) mm Hg.

Table 2 presents the laboratory and clinical conditions of the recipients at the time of HT. A total of 168 recipients (56.2%) were in hemodynamic support with an intra-aortic balloon pump at the time of transplantation, while 23

Table 2 Clinical Status on the Day of Heart Transplantation

	Overall	Alive at 1 year	Deceased at 1 year	
Clinical status	N = 299[a]	N = 216[a]	N = 83[a]	*p*-value[b]
INTERMACS				
I	22 (7.4%)	10 (4.6%)	12 (14%)	0.012
II	150 (50%)	109 (50%)	41 (49%)	
III	112 (37%)	88 (41%)	24 (29%)	
IV	15 (5.0%)	9 (4.2%)	6 (7.2%)	
In ventricular assist device support	23 (7.7%)	11 (5.1%)	12 (14.5%)	0.006
In intra-aortic balloon support	168 (56.2%)	119 (55.1%)	49 (59%)	0.538
Renal replacement therapy at HT	20 (6.7%)	12 (5.6%)	8 (9.6%)	0.2
*Cardiac index (liter/min/m^2)	2.5 (1.9-3)	2.5 (2-3)	2.4 (1.9-2.7)	0.2306
*Mean systemic blood pressure (mm Hg)	70.2 (11.8)	70.5 (12.9)	69.5 (8.1)	0.2405
*Pulmonary capillary pressure (mm Hg)	19.8 (7.3)	19.8 (7.8)	19.9 (5.8)	0.8973
*Mean pulmonary artery pressure (mm Hg)	30.2 (8.4)	30.2 (8.7)	30.4 (7.8)	0.80448
*Pulmonary artery systolic pressure (mm Hg)	45 (35-52)	45 (35-53)	43 (37-51)	> 0.9
*Pulmonary vascular resistance, Woods	2 (2-3)	2 (2-3)	2 (2-3)	> 0.9
Estimated GFR (ml/min/1.73 m^2)	60.8 (42-84.1)	65.7 (46.4-87)	48.2 (35.1-69.9)	< 0.001
Leukocytes (/mm3)	7,120 (5,595-9,030)	6,890 (5,475-8,572.5)	7,900 (5,880-10,375)	0.001
C-reactive protein (mg/dl)	14.9 (6.1-33)	12.9 (5.1-24.8)	24.1 (9.2-51.3)	0.007
SOFA score	4 (3-5)	4 (3-5)	5 (3.5-6)	< 0.001
Hemoglobin (g/dl)	9.6 (8.6-11.2)	9.9 (8.8-11.4)	9.1 (8.1-10.4)	0.00255
*Albumin (g/dl)	3.1 (0.6)	3.2 (0.6)	2.9 (0.6)	< 0.001
*BNP (pg/ml)	610 (287-1,281)	538 (245-1,275)	742.5 (401.8-1397.5)	0.236
Urea (mg/dl)	54.7 (29.4)	52.1 (29.2)	61.5 (29.1)	0.013
*Arterial lactate (mg/dl)	12.5 (10-16)	12 (10-16)	13 (10-15)	0.778
*MELD-XI score	14 (11-18)	14 (11,17)	16 (13-20)	< 0.001
Receiving amiodarone (> 400 mg/d)	91 (48%)	65 (46%)	26 (53%)	0.4
Received induction immunosuppressive therapy	40 (13%)	25 (12%)	15 (18%)	0.14
Positive virtual cross-match				0.2
Negative	273 (93%)	199 (94%)	74 (90%)	
Positive	20 (6.8%)	12 (5.7%)	8 (9.8%)	
Days on priority list for HT	33 (13-64)	33.5 (14-62)	25 (9-67)	> 0.9

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; GFR, glomerular filtration rate; HT, heart transplantation; INTERMACS, interagency registry for mechanically assisted circulatory support; IQR, interquartile range; LVEF (%), left ventricular ejection fraction (%); MELD-XI, Model for End-Stage Liver Disease excluding international normalized ratio; SD, standard deviations; SOFA, Sequential Organ Failure Assessment.

[a] *n* (%), mean (SD), or median (IQR).

[b] Pearson's chi-square test or Welch 2 sample *t*-test.

* Variables with missing values.

recipients (7.7%) were receiving mechanical circulatory support (Supplementary Material Table 1A). The median duration of intra-aortic balloon support (IABP) was 16 days. Among patients who were receiving mechanical circulatory support, 16 (70%) were in extracorporeal membrane oxygenation (ECMO) with a median time in hemodynamic support to HT of 7.5 days. The median SOFA score at the time of transplantation was 4 (3-5) points. The median most recent class I panel reactive antibody was 0 (0-12), and a virtual cross-match was positive in 20 patients (6.8%).

HT was performed on patients classified as INTERMACS I (interagency registry for mechanically assisted circulatory support I) in 22 cases (7.4%), and on patients classified as INTERMACS II in 50% of cases (150 patients). Additionally, 112 patients (37%) classified as INTERMACS III underwent HT. Twenty patients (6.7%) were undergoing renal replacement therapy, and 3 patients (1%) were on mechanical ventilation at the time of transplantation. Furthermore, 91 patients (48%) were taking amiodarone at doses exceeding 400 mg per day. The median time spent on the heart transplant waiting list was 33 (13-64) days, with a median ischemic time of 3.6 (2.5-3.8) hours. Induction immunosuppressive therapy was administered to 40 patients (13%).

The characteristics of the donors are presented in Table 1. A gender mismatch, specifically a female donor to a male recipient, was observed in 21 cases (7%). The majority of donors were male (82%, 245 cases), with a median BMI of 25.5 (23.5-27.7) kg/m^2. Prior hypertension was observed in 7% of donors (21 cases). The median donor creatinine was 1.1 (0.8-1.5) by the time of HT. Infection was identified as the primary cause of 1-year mortality following HT during the specified interval, accounting for 32 cases (38.5%). The second most common cause of mortality was primary graft dysfunction (16 cases, 19.2%), followed by central nervous system bleeding (8 cases, 9.6%), as documented in the patient records. Rejection was the cause of death in 7 patients (8.4%), with antibody-mediated rejection being notably associated with the poorest outcomes. The occurrence of Chagas disease reactivation did not correlate with 1-year mortality (Supplemental Material Tables 2A and 3A).

Outcome and predictors

The study revealed that the 1-year survival rate was 72.25%, with 83 deaths occurring within the first year following HT. In the univariate analysis (Table 4A and 5A in Supplementary Material), 12 recipient factors were statistically significant ($p < 0.05$) and selected for multivariate analysis. These factors included the need for ventricular assist device support, SOFA score, serum hemoglobin, creatinine clearance, serum albumin, the Model for End-Stage Liver Disease excluding international normalized ratio score, serum C-reactive protein (CRP), age at transplantation (in years), brain natriuretic peptide, serum leukocytes, serum urea, and central venous lactate. The VIF values ranged from 1.125 to 1.913, indicating the absence of multicollinearity between the selected variables. After applying the backward stepwise selection method, we identified 4 variables that were statistically significant in predicting 1-year survival after HT (Table 3). These variables were observed at the time of the last clinical evaluation in the intensive care unit, within 24 hours before surgery. The variables include maximum SOFA score (< 5 and ≥5), creatinine clearance (GFR) (ml/min/1.73 m^2) in 3 quartile categories (≥84; between 42 and 84; and ≤42), CRP (mg/dl) in 3 categories (≤6; between 6 and 33; and ≥33), and white blood cell count (leukocytes/mm^3) in 3 categories (≤5,590; between 5,590 and 9,237; and ≥9237). The statistical model showed a significant likelihood ratio test ($p < 0.001$) and a strong ability to discriminate outcomes (C-index equal to 0.748 and equal to 0.742 by internal validation using 2,000-fold bootstrap resampling and adjustment for optimism). The Hosmer-Lemeshow test demonstrated a nonsignificant result, indicating a good calibration of the final model (Table 4). It is noteworthy that in the model lacking creatinine clearance, the VIF values ranged from 1.09 to 2.54, indicating a low degree of autocorrelation between the variables in the model. The risk score values were centered on a mean of 19.5 points with a SD of 11.6 points and a range between 0 and 49 (Figure 2). The ROC analysis indicated that a score of 20 points was the optimal cut-off for discriminating death within 30 days, 6 months, and 1 year after HT. Figure 3 shows the

Table 3 Variables Associated With Survival 1-Year After Heart Transplant

Variable	Category	Score	HR	CI (95%)		p
SOFA	< 5	0				
	≥5	8	1.828	1.131	2.955	0.014
Creatinine clearance(ml/min/1.73 m^2)	≥83.8	0				
	> 41.9 e < 83.8	5	1.553	0.800	3.015	0.194
	≤41,91	19	2.880	1.468	5.652	0.002
C-reactive protein(mg/dl)	≤6	0				
	> 6 e < 33.3	5	1.476	0.763	2.855	0.248
	≥33.3	11	2.136	1.063	4.291	0.033
Leukocytes(Leukocytes/mm^3)	≤5,590	0				
	> 5,590 e < 9,237.5	3	1.259	0.687	2.309	0.456
	≥9,237.5	11	2.073	1.088	3.952	0.027

Abbreviations: CI, confidence interval; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment.

Table 4 Discrimination and Calibration Results of the Risk Score Based on the Final Model

Statistic	30 days	6 months	1 year
Accuracy	65.22% [59.52%; 70.61%]	65.89% [60.21%; 71.25%]	66.89% [61.24%; 72.20%]
Sensitivity	84.09% [69.93%; 93.36%]	71.05% [59.51%; 80.89%]	71.08% [60.09%; 80.52%]
Specificity	61.96% [55.69%; 67.95%]	64.13% [57.45%; 70.42%]	65.28% [58.52%; 71.61%]
PPV	27.61% [20.24%; 36.00%]	40.30% [31.92%; 49.11%]	44.03% [38.50%; 49.72%]
NPV	95.76% [91.45%; 98.28%]	86.67% [80.51%; 91.45%]	85.45% [80.53%; 89.30%]
H-L	$p = 0.268$	$p = 0.1014$	$p = 0.1938$

Abbreviations: H-L, Hosmer-Lemeshow test; NPV, negative predictive value; PPV, positive predictive value.

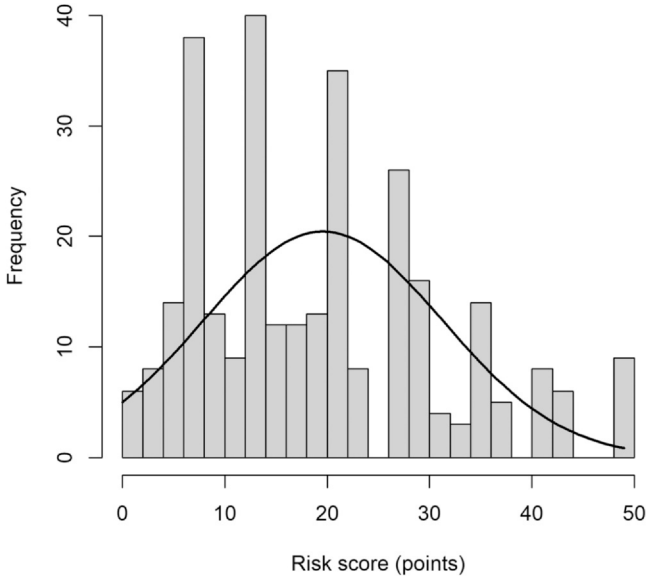

Figure 2 Frequency distribution of the risk score, in points.

Kaplan-Meier curves by risk score group. The high-risk group (> 20 points) had significantly higher 30-day and 1-year mortality rates than the low-risk group (≤20 points), with rates of 27.6% and 44% versus 7.9% and 14.6%, respectively (HR = 3.82; CI (95%) = [2.374, 6.142]; $p < 0.001$).

We conducted an additional multivariate analysis to examine the relationship between clinical variables at listing or presentation and 1-year mortality after HT. The results are presented in the Supplementary Appendix.

Discussion

The severity of advanced heart failure in patients receiving only optimized clinical management can be assessed by the mortality of this group, which can be as high as 75% within 1 year, with a 2-year survival rate of only 8%.[12] Although HT remains the definitive treatment for these patients, long-term left ventricular assist devices (LVADs) are an option for patients with end-stage HF. However, durable LVADs are not widely available in all regions of the world, and the number of heart transplants is limited by donor availability. Therefore, one of the most pressing challenges in HT remains the optimal use of donor hearts and health care resources to minimize mortality from advanced heart failure on the waiting list while maintaining favorable outcomes following HT.[13] In our cohort of heart transplant recipients

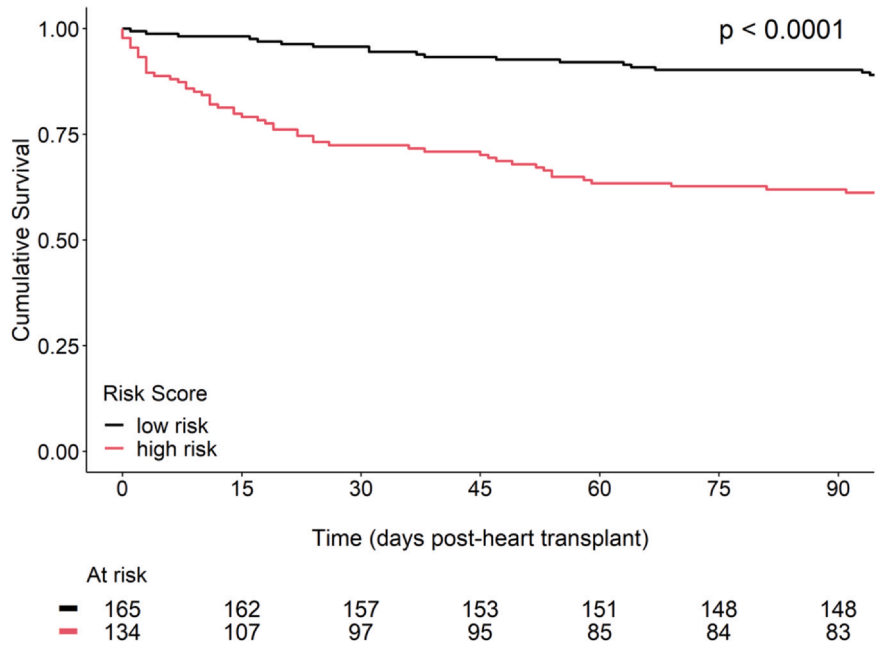

Figure 3 Overall survival curves stratified by score-based risk groups.

at a cardiology reference center in Brazil, we examined the relationship between clinical and laboratory factors of heart transplant recipients and donors and post-transplant survival within a 1-year period. Our aim was to better understand the factors associated with 1-year survival after HT in our population. After multivariable adjustment, 4 variables observed at the last clinical assessment within 24 hours before HT were statistically significant in predicting 1-year mortality ($p < 0.05$): maximum SOFA score, creatinine clearance, CRP, and white blood cell count.

The SOFA score is a widely used tool in critical care settings to measure the severity of end-organ dysfunction and predict mortality during ICU stays. The scoring system includes factors related to cardiovascular, respiratory, hepatic, renal, coagulation, and neurological function.[14,15] Interest in risk stratification models previously validated in other critically ill ICU patients, such as the SOFA score, has arisen in the context of advanced cardiovascular disease. This is based on the clinical similarities between these patients and general ICU patients with multisystem dysfunction. Jentzer et al recently evaluated the predictive value of the SOFA score for mortality in a contemporary cardiac ICU population of 9,961 patients. The patients' mean age was 67.5 years, and the incidence of all-cause hospital mortality was 9.0%. The day 1 SOFA score predicted hospital mortality with good discriminative ability (area under the ROC curve of 0.83). The mean and maximum SOFA scores over multiple ICU days had even greater discriminative ability. The study showed that higher short-term mortality was associated with progressive organ dysfunction, as indicated by increasing SOFA scores between day 1 and day 2 in the ICU. Additionally, mortality was higher for patients with a SOFA score greater than or equal to 4.[16,17] In our report, we found that patients on the heart transplant waiting list had a mean SOFA score of 4.2 on the day of HT, reflecting the severity of multiorgan dysfunction despite maximal cardiovascular support. Additionally, we discovered that SOFA score greater than 5 was a major risk factor for poor postoperative prognosis after HT.

Renal dysfunction represents a significant risk factor for mortality following cardiac surgery. A recent meta-analysis of heart transplant recipients revealed that changes in creatinine levels were significantly associated with increased 1-year mortality (HR 1.11 per 1 mg/dl increase, 95% CI 1.06-1.16, high quality).[18] Furthermore, the ISHLT registry observed a higher 1-year mortality in patients with a GFR of less than 30 ml/min/1.73 m^2. In our analysis, a creatinine clearance of less than 42 ml/min/1.73 m^2 at the time of HT was an independent predictor of reduced survival.

Several classes of inflammatory markers have been described: cytokines/chemokines, acute phase proteins (CRP and serum amyloid A), reactive oxygen species, among others. Recently, Qu et al showed that CRP > 6.2 mg/dl at the time of ICU admission was associated with a higher likelihood of ICU mortality, regardless of whether the patient was septic or not.[19] This may reflect the lack of specificity of CRP in septic and nonseptic patients, suggesting that inflammation may be associated with higher ICU mortality. Our analysis found that higher levels of inflammatory markers, CRP, and white blood cell counts on the day of HT were associated with increased postoperative mortality.

Mortality rates following HT vary globally. These differences may be attributed to donor selection and/or recipient urgency. To reduce waiting list mortality, expanding the donor pool could be considered; however, this strategy may impact survival after transplantation.[20] Trivedi et al analyzed donor prognostic factors, including donor age over 50 years, ischemia time over 4 hours, gender mismatch, and diagnosed diabetes, to study heart transplant survival. Although the literature has established that an increase in donor risk factors is associated with adverse survival after HT, the impact of donor variables on post-HT mortality seems to be less significant than the clinical condition of the recipient.[21,22] After analyzing the donor-recipient relationship in this cohort of patients, we found no independent association between the clinical condition of the donor and a negative prognosis after HT. This finding may be related to donor characteristics being more frequently closer to low risk, as established in the literature, and our heart transplant team's use of strict evidence-based low-risk donor selection criteria (Table 6A in Supplementary Material). The organ sharing and heart allocation policy may also have an impact on wait-list mortality and HT outcomes.[23] To address this objective, the Heart Allocation System in Brazil has been designed to prioritize the allocation of hearts to sicker patients, thereby reducing waiting list mortality. A 4-tier categorization system is used to rank candidates based on disease severity, in accordance with federal regulations. In priority status 1, patients receive short- to intermediate-term circulatory support with ECMO as a bridge to transplantation. Patients with cardiogenic shock receiving hemodynamic support with IABP are included in priority status 2. Patients requiring inotropes for cardiogenic shock, including those with hypertrophic cardiomyopathy, restrictive cardiomyopathy, and patients with complications associated with long-term circulatory support devices, are included in priority status 3. All other active candidates are included in condition 4, which is a nonpriority status with organ allocation based on waiting time. In addition, exceptions approved by the Technical Committee are included in priority status 3. Inotrope-dependent patients on the transplant waiting list with priority status 3 for more than 6 months will be upgraded to priority status 2. Objective evidence of clinical deterioration with cardiogenic shock based on hemodynamic or clinical criteria is required for the majority of candidates to be considered for priority status (status 1-3).[5] Most patients listed for HT in Brazil are hospitalized patients in priority status 2 or 3. Compared to the US population in the Scientific Registry of Transplant Recipients,[24] the Brazilian cohort is younger, with a median age of 50 (39-58) years versus 56 (46-63) years in the United States, and a lower BMI of 23 (20-25) versus 28 (24-31) kg/m^2. The incidence of diabetes among recipients was lower in the Brazilian cohort (15% vs 27% in the United States). Median estimated GFR (ml/min/m^2) was similar: 60.8 (42-84.1) versus 63 (48-79). Chagas cardiomyopathy (36%) followed by dilated cardiomyopathy (35%) was the most common etiology of advanced heart

failure in patients undergoing HT in Brazil. In the US cohort, dilated cardiomyopathy (44%) and ischemic cardiomyopathy were the most common etiologies. Also, in Brazil, most HT procedures are sponsored by the federal government through the United Health System (90%). Recent analyses of the HT cohorts have suggested an increase in the number of high-risk individuals placed on the heart transplant waiting list, despite a marked improvement in mortality in this setting. This improvement has been attributed, at least in part, to the advent of long-term mechanical circulatory support (LVAD) as a bridge to transplant (BTT) therapy.[25] In a recent survival analysis by Moonsamy et al, wait-list mortality was significantly higher for patients on ECMO or temporary mechanical circulatory support (TCS-VAD) than for patients awaiting HT with long-term LVADs. In addition, patients with a permanent LVAD as BTT therapy have shown similar post-transplant survival to primary heart transplant recipients who do not receive hemodynamic support at the time of HT. In this analysis, covariate-adjusted post-transplant survival was significantly improved for patients bridged with all temporary circulatory support- ventricular assist device (TCS-VAD) types compared to ECMO and was similar compared to LVAD.[26] In Brazil, LVADs are not available as BTT strategy in the Single Health System (SUS). Circulatory support in this setting is mainly represented by ECMO and IABP, which are available in the SUS and represent 61.5% of support in HT patients (IABP 56.2%, ECMO 5.3%) at the time of HT. It is important to note that in the US cohort, compared to the Brazilian cohort, approximately 60% of heart transplant patients do not require pretransplant hemodynamic support and LVADs are used in the remaining 20% to 30% of patients. In the US cohort, ECMO was the treatment of choice for BTT in 0.1% to 1.4% of patients, depending on geographic variation.[26]

Our analysis of 299 heart transplant patients (SUS) showed that the low-risk group had a 92.1% probability of survival at 3 months and an 85.4% probability of survival at 1 year, which is comparable to the survival rates reported by the ISHLT registry. However, a decreased survival rate after HT was documented, which may be due to the severity of the recipients, resulting from a higher degree of multiorgan dysfunction at the time of HT. Another possible explanation for this finding is the limited experience with long-term mechanical circulatory support as a bridge to HT due to financial constraints. Prolonged waiting times for high-risk patients on hemodynamic support with IABP or ECMO may result in device-related complications, clinical deterioration, and end-organ dysfunction, which could lead to worse post-transplant outcomes and increased wait-list mortality.

Chagas disease is a significant cause of advanced heart failure in Brazil.[27] Despite the initial concern of Chagas disease recurrence with immunosuppression, heart transplants have been a successful treatment for these patients in Latin America.[28-30] In our study, we did not observe a significant impact on 1-year survival when comparing different etiologies of heart failure. In a recent analysis, Furquim et al[31] found no difference in the survival of Chagasic patients regardless of the antiproliferative regimen used in the immunosuppressive protocol after HT. This suggests that, although Chagas reactivation requires prophylactic vigilance, it responds well to adequate therapy and does not significantly affect 1-year post-transplant survival.

Study limitations

The analysis was conducted at a single center in Brazil, resulting in a small sample size compared to similar studies. Additionally, it is important to validate this model in an external and independent sample, which is currently underway. This model also does not consider the risks associated with remaining on the HT waiting list. However, it may be useful to evaluate the next step in a patient's therapy for advanced heart failure given our available resources.

Conclusions

This analysis identified 4 independent predictors of survival 1 year after HT in our population: maximum SOFA score, creatinine clearance, CRP level, and absolute leukocyte count. The study also presents new observations and raises questions regarding the prognostic potential and characteristics of patients with Chagasic heart failure on the waiting list for HT. Further evaluations are necessary to better understand the metrics of the model in external populations.

Ethical approval

This study was approved by the Institution Ethics Committee, with a waiver of informed consent. It adheres to the highest standards of ethical conduct, as outlined in the ISHLT ethics statement.

Author contributions

All authors have been directly involved in the planning, execution, or analysis of this study and all authors agree with the content of the article.

Disclosure statement

All other authors have nothing to disclose.
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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100154.

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