

# ASSESSMENT OF A HEART TRANSPLANTATION COHORT USING A DONOR-RELATED SCORING SYSTEM

## AVALIAÇÃO DE UMA COORTE DE TRANSPLANTE CARDÍACO POR ESCORE RELACIONADO AO DOADOR

### ABSTRACT

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**Introduction:** There are few systems to assess mortality after heart transplantation (CT) that are based on donor-related factors and can predict prognosis. Identifying donor characteristics that impact post-CT survival can contribute to improved outcomes and organ allocation. We applied a US evaluation system to predict mortality after CT in a Brazilian cohort. **Objective:** To evaluate an American score as a predictor of mortality following CT in a Brazilian cohort. **Method:** Database analysis of a Brazilian CT center from 2013 to 2015. Four donor characteristics were evaluated: ischemia time, donor age, donor-recipient race mismatch, and donor renal function. Survival was estimated by the log-rank test in predetermined score ranges. **Results:** There were 110 donors, 89% male and 62% white. The main cause of death was trauma (66.6%). Donors had a mean age of 29.8 years, a mean blood urea nitrogen / creatinine ratio of 18.6, a mean ischemia time of 175 minutes, and race mismatch with the recipient of 42%. There was no difference in survival between the score ranges. **Conclusion:** Although it was a predictor of mortality after cardiac transplantation in an American population, this score was not useful for a Brazilian transplant cohort. Differences, including the high rate of miscegenation, may explain these findings.

**Keywords:** Transplantation; Heart Transplantation; Donors.

### RESUMO

**Introdução:** Existem poucos sistemas de avaliação de mortalidade após transplante cardíaco (TC) que se baseiem em fatores relacionados com o doador e que sejam capazes de prever o prognóstico. Identificar características dos doadores que têm impacto na sobrevida depois do TC pode contribuir para melhorar os resultados e a alocação de órgãos. Aplicamos um sistema de avaliação americano para prever a mortalidade pós-TC em uma coorte brasileira. **Objetivo:** Avaliar um escore americano como preditor de mortalidade depois de TC em uma coorte brasileira. **Métodos:** Análise de uma base de dados de um centro de TC brasileiro de 2013 a 2015. Foram avaliadas quatro características dos doadores: tempo de isquemia, idade do doador, discordância racial doador/receptor e a função renal do doador. A sobrevida foi estimada pelo teste de log-rank em faixas de pontuação pré-determinadas. **Resultados:** Foram 110 doadores, 89% homens e 62% brancos. A principal causa de morte foi trauma (66,6%). Os doadores tinham em média 29,8 anos, 18,6 de relação Nitrogênio da ureia sanguínea / Creatinina, 175 minutos de tempo de isquemia e 42% de discordância racial com o receptor. Não houve diferença de sobrevida entre as faixas de pontuação. **Conclusão:** Apesar de preditor de mortalidade após transplante cardíaco em uma população americana, esse escore não foi útil para uma coorte de transplante brasileira. As diferenças, inclusive a alta taxa de miscigenação pode ser uma explicação para esses achados.

**Descritores:** Transplante; Transplante de Coração; Doadores.

### INTRODUCTION

Heart failure (HF) is a serious and widespread disease, currently affecting more than 23 million people worldwide.<sup>1</sup> In recent decades, thanks to increased life expectancy and

improved treatment of cardiovascular disease it is expected an increasing number of people to develop HF.<sup>2</sup>

Heart transplantation (HT) is the gold standard treatment in the advanced phase of the disease. However, the number

of organs available is still small compared to the number of patients who need the procedure. Data from the Brazilian Association of Organ Transplantation (ABTO) estimate that a 4.34-fold increase in the number of HT in Brazil would be needed to meet demand.<sup>3</sup> Destination ventricular assist devices are emerging options in the treatment of these patients, but they have high costs which often make them inaccessible to most of the Brazilian population. In this scenario, it is essential to establish a rational use of donated organs, allocating them to recipients in which the procedure is most likely to succeed.

To this end, some studies have sought to evaluate recipient characteristics that have prognostic impact after transplantation and this has enabled the creation of receptor evaluation scores.<sup>4,5</sup>

On the other hand, there are few post-heart transplant mortality assessments based on donor-related factors. Thus, developing a score that assesses donor characteristics that are crucial to the success of the procedure can substantially help in organ selection.<sup>5,6</sup>

To this end, an American Heart Donor Assessment Score was created in 2012. This score demonstrated great prognostic power by discriminating, from four donor-related characteristics, the mortality of HT receptors.<sup>7</sup>

In Brazil, the use of these assessment systems is extrapolated, but there are no studies that validate these scores in our population.

The aim of this study is to evaluate the applicability of an American score as a predictor of mortality after HT in a Brazilian cohort.

## METHODS

A database of 110 heart donors from a Brazilian HT center from 2013 to 2015 was analyzed. These donors were scored according to an American assessment score consisting of four variables that were strongly associated with receptor mortality: ischemia time, donor age, donor/recipient racial disagreement, and donor renal function represented by BUN (blood urea nitrogen)/creatinine. Ischemia time, defined in minutes, involved the moment of clamping of the aorta in the donor until reperfusion of the heart in the recipient after implantation. The donor age was defined in years, according to the information generated by the OPO responsible for the donor offer. Regarding the races, they were defined as x, y, z with mismatch when there was no compatibility. The BUN/Creatinine ratio was established from urea and creatinine (in mg/dL) on the day of explantation, converted to BUN after division by 2.14. The relationship was considered altered when  $> 30$ , because in the American study, this group of patients had a one-year increase in mortality when compared to those with  $< 30$ . Each result of these variables generated a score that together defined the final donor score. According to this value, the donor was allocated to one of the scoring ranges (Table 1). Recipient survival after transplantation was estimated for each of these ranges using the long-rank test.<sup>7</sup>

## RESULTS

We analyzed 110 donors from the heart hospital database (INCOR) from 2013 to 2015, of which 89% were men and 62% were white. The main cause of brain death was trauma (66.6%)

Table 1. Heart donor score.

Variable	Score			
Ischemia time				
< 2 hours	1			
2 – 3.9 hours	2			
4 – 5.9 hours	3			
6 – 7.9 hours	4			
8 hours or more	5			
Donor age				
Less than 40 years	0			
40-49 years	3			
50 years or more	5			
Race mismatch between donor and recipient	2			
BUN/creatinine ratio > or = 30	3			
Score ranges	0-2	3-5	6-8	9-15

followed by subarachnoid hemorrhage and hemorrhagic stroke (23%), which does not differ from most causes found in the literature. Donors were on average 29.8 years old, therefore considered young donors. In our findings, only one donor was 50 years old, which makes it difficult to compare this variable as a factor of poor prognosis.

The measurement of urea concentration in whole blood, serum or plasma is known as blood urea nitrogen or BUN (Blood Urea Nitrogen). In our study we used the BUN/creatinine ratio where the BUN was calculated by dividing the urea value by the constant 2.14 and defining as altered BUN/creatinine ratio values greater than 30. The average ratio found was 18.6 or it was not related to higher mortality, since the literature reinforces that only ratios greater than 30 are predictors of increased mortality. Our highest BUN/creatinine ratio was 71 in a 22-year-old donor.

The average ischemia time was 175 minutes. There is a strong correlation between ischemia time and one-year survival. Ischemia times longer than 480 minutes are associated with a 16.6% increase in mortality compared to shorter times of up to 120 minutes.<sup>7</sup> The ischemia time of the Brazilian cohort was shorter than the American, but this difference had no impact in survival.

Racial disagreement was an important variable found in the US cohort where discordant donors had a mortality of 15.8% compared with 14.1% for paired patients ( $p 0.004$ ).<sup>7</sup> In our study 42% of donors had racial disagreement with recipient, showing that Brazil is a country of high miscegenation.

The prevalence according to score grading ranges was 30.6% to 0-2 points, 53.15% to 3-5 points, 14.4% to 6-8 points and 0.9% to 9-15 points. There was no difference in survival between ranges (0-2 points: 669 days, 3-5 points: 634 days, 6-8 points: 527 days and 9-15 points: 662 days;  $p 0.78$ ). (Figure 1)

However, the items that scored the highest in the American score and, therefore, had the highest correlation with mortality (BUN/creatinine ratio greater than 30; donor age greater than 50 years and ischemia time greater than 480 minutes) were not evidenced in our cohort. Most of our patients scored between 3-5 points. The reality of Brazilian donors is different from American donors. In Brazil, the vast majority are young, previously

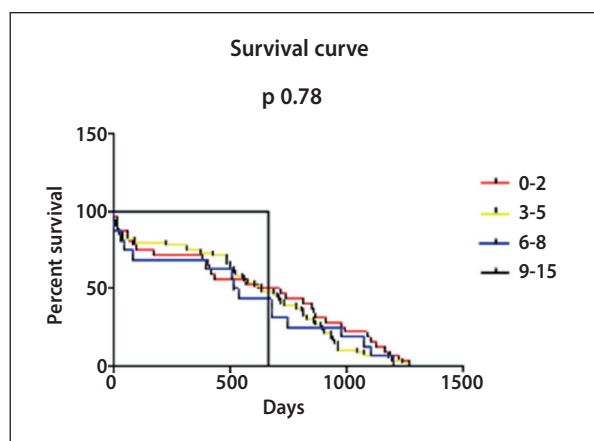


Figure 1. Recipient survival according to donor score.

healthy, with good renal function, and we do not have long ischemia times because distant harvestings are few. The highest ischemia time found was 306 minutes. These findings corroborate the need to develop a score focused on the Brazilian reality.

## DISCUSSION

Data from the Brazilian Association of Organ Transplantation show that in 2017, 380 HT were performed in Brazil, well below the estimated need for 1,649 transplants. In this scenario, establishing a rational use of grafts with allocation criteria that ensures a greater chance of success is essential. In addition, only 11.1% of the organs offered are accepted, which shows a low level of achievement.<sup>3</sup> Improvements in donor maintenance conditions and the establishment of which factors actually impact recipient survival could contribute to increased utilization of these organs and the number of transplants. Several studies have been developed to identify prognostic factors after heart transplantation related to donor, recipient, or both variables.<sup>4,5,7</sup>

In 2012 a score called the Heart Transplant Risk Donor Index (RDI) was published which through four variables (donor age, ischemia time, renal function and race mismatch) assesses the impact on recipient survival after transplantation. This score was developed and tested in an American cohort and showed good discriminatory power between the score score (donor risk range) and recipient survival and is therefore useful in the process of organ acceptance and distribution. Each increase of one point in the score corresponded to a 9% and 13% increase in the recipient's one-year mortality risk at shunt cutoff and score validation, respectively. Increased score scores were also related to poor survival at five-year follow-up.<sup>7</sup>

Our work tested this same score in a Brazilian cohort. When evaluated in relation to the four variables, most patients in both cohorts were classified in the same score range between 3-5 points, however, in our results the score was not able to discriminate the survival of the recipient.

The first variable analyzed was the age of the donor. The importance of this variable is consistent with the results of several studies that showed that the older the donor, the worse the transplant outcome and the greater the chance of developing graft vascular disease.<sup>5,8</sup>

The second variable was ischemia time, also well established in the literature as an important prognostic factor. There is evidence to suggest that ischemia time is of greater importance in older recipients, where increased ischemia time leads to worse outcomes than younger recipients.<sup>8,9</sup>

The average age of donors and the average ischemia time of the American cohort was 31.3 years and 186 minutes, respectively, slightly higher than the 29.8 years and 175 minutes of the Brazilian cohort donors, which we believe is not sufficient to explain the difference in results.

The third item assesses the donor BUN/creatinine ratio which seems much less likely to reflect the quality of the donor heart than, for example, donor heart echocardiographic variables (ventricular function, wall thickness).<sup>8</sup> As in our study, most patients in the American cohort had a BUN/creatinine ratio <30.<sup>7</sup>

Finally, the last item considered concerns race mismatch between donor and recipient, and was more frequent in the Brazilian cohort. Racial classification in countries of significant miscegenation, where there is a great genetic heterogeneity such as Brazil is complex. Studies show a low correlation between physical (morphological characteristics) and genetic appearance. In a group of self-styled white Brazilian men from different regions of the country, the patriarch lineage analyzed by the Y chromosome showed a predominantly European origin. The evaluation of the matriarch lineage by mitochondrial DNA showed indigenous influence in 33% and African in 28%, reflecting the country's colonization history.<sup>10</sup> Thus, it is difficult to allocate such a mixed population into defined race categories (white, brown, or black). We believe that this variable may have significantly influenced the loss of discriminatory power of this score in the Brazilian population.

Other studies draw attention to the importance of gender mismatch (female donor and male recipient), hemorrhagic stroke death, history of cancer, donor/recipient size disproportion, vasoactive drug doses, and type of cardioplegia.<sup>6,9</sup>

In 2016, the United Network for Organ Sharing (UNOS) developed a mixed score based on donor and recipient characteristics that showed an association with survival after 30 days, one year and five years after transplantation. The association of low risk donor and recipient has an estimated survival of 83% at five years. In the combination of high risk donors and recipients, the estimated survival drops to 49% in five years. In the risk spectrum, the association of high-risk donor and low-risk recipient had better survival rates than the opposite combination,<sup>5</sup> demonstrating that the recipient's health seems to have more influence than the donor's on the outcome of the procedure.<sup>5,11,12</sup>

The donor evaluation process is currently being reviewed. A recent publication has shown that the use of organs considered to be at risk may have better results than keeping the transplanted patient in line, especially in priority recipients. In this context, according to the recipient's health status, the use of donor grafts with a history of hypertension, diabetes, drug use, immunological window for hepatitis C, after cardiocirculatory arrest and ventricular dysfunction probably caused by inherent changes to brain death can be considered.<sup>8,13</sup>

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## CONCLUSION

Despite being a strong predictor of mortality after heart transplantation in an American population, this score was not useful for a Brazilian transplantation cohort. Differences including the difficulty in characterizing racial mismatch by the high rate of miscegenation may have contributed to these findings and point to the need to develop new evaluation systems focused on the Brazilian reality.

In addition, the literature has shown that recipient health seems to be more important for transplant success than donor

health.<sup>5,11,12</sup> Therefore, new reflections should be performed to determine which criteria should really be used to evaluate the donor's heart, thus optimizing organ utilization and increasing the number of HTs.

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## CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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**AUTHORS' CONTRIBUTIONS:** MGB, LLEM and MHLT were the main contributors to bibliographic research and manuscript elaboration. LFBCS, MSA, FGMB, IWC gathered clinical data related to receptors. FB, AMPCD, AP, JM collected data on donors. SM and FB analyzed the data of the statistical analysis, oriented the work and revised the manuscript. each author contributed individually and significantly to the development of the manuscript.

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