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ORIGINAL PAPER

Assessment of Clinical Factors in the Evolution of Heart Transplant Patients: A Single-Center Retrospective Cohort Study

Gabriela Vieira de Paula[1,*], Adriele Fogaça Costa[1], Nathalia Alves Viana[1], Claudia Maria Silva Cyrino[1], Marcello Laneza Felicio[1], Flávio de Souza Brito[1], Daniela Ponce[1]

1. Universidade Estadual Paulista – Faculdade de Medicina – Botucatu (SP), Brazil.

*Corresponding author: gvieiradepaula@gmail.com

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ABSTRACT

Introduction: After heart transplantation (HTx), some patients continue to experience disproportionately high mortality. **Objectives**: To investigate which clinical variables are associated with survival after HTx. **Methods:** Retrospective, single-center cohort study with 55 patients undergoing HTx from May 2019 to April 2023. **Results:** Logistic regression identified, as variables associated with death, the increase in creatinine in the immediate postoperative period (POI) (p = 0.0067), pulmonary vascular resistance (RVP) (p = 0.0185) and pulmonary artery systolic pressure (PSAP) before HTx (p = 0.0415). When constructing the ROC curve (receiver operating characteristic curve) with the delta of the increase in creatinine in the first 24 postoperative hours, the cutoff point was 0.35 mg/dL, the sensitivity was 0.76, and the specificity was 0. 90. In the ROC curve for PVR, the cutoff point was 2.23 Woods units (WU), with sensitivity of 0.79 and specificity of 0.72. In the ROC curve for PSAP, the cutoff point was 40.50 mmHg, with a sensitivity of 0.89 and a specificity of 0.86. **Conclusion:** An increase in creatinine to a value greater than or equal to 0.35 mg/dL in the first 24 hours, PSAP with values greater than 40.5 mmHg and an increase in RVP to a value above 2.23 WU are associated with increased rates of hospital mortality after HTx.

Descriptors: Heart Transplantation; Creatinine; Hypertension Pulmonary; Heart Failure; Mortality.

Avaliação de Fatores Clínicos na Evolução de Pacientes Transplantados Cardíacos: Estudo de Coorte Retrospectivo Unicêntrico

RESUMO

Introdução: Após o transplante cardíaco (TxC), alguns pacientes continuam a apresentar mortalidade desproporcionalmente alta. **Objetivos:** Investigar quais variáveis clínicas estão associadas à sobrevida após o TxC. **Métodos:** Estudo do tipo coorte retrospectivo, unicêntrico, com 55 pacientes submetidos a TxC no período de maio de 2019 a abril de 2023. **Resultados:** A regressão logística identificou, como variáveis associadas ao óbito, o aumento da creatinina no pós-operatório imediato (POI) (p = 0,0067), a resistência vascular pulmonar (RVP) (p = 0,0185) e a pressão sistólica da artéria pulmonar (PSAP) prévios ao TxC (p = 0,0415). Ao construir a curva ROC (*receiver operating characteristic curve*) com o delta do aumento da creatinina nas primeiras 24 horas do pós-operatório, o ponto de corte foi de 0.35 mg/dL, a sensibilidade de 0,76 e a especificidade de 0,90. Na curva ROC para a RVP, o ponto de corte foi de 2,23 unidades Woods (WU), com sensibilidade de 0,79 e especificidade de 0,72. Na curva ROC para a PSAP, o ponto de corte foi de 40,50 mmHg, com sensibilidade de 0,89 e especificidade de 0,86. **Conclusão:** Aumento da creatinina para valor maior ou igual a 0,35 mg/dL nas primeiras 24 horas, PSAP com valores superiores a 40,5 mmHg e aumento da RVP para valor acima de 2,23 WU estão associados ao aumento das taxas de mortalidade hospitalar após o TxC.

Descritores: Transplante de Coração; Creatinina; Hipertensão Pulmonar; Insuficiência Cardíaca; Mortalidade.

INTRODUCTION

Cardiovascular diseases are the leading cause of death in Brazil, with emphasis on heart failure (HF), which is the leading cause of hospitalizations. Despite advances in the treatment of this condition, the prognosis remains unfavorable, resulting in high mortality rates[1,2]. Heart transplantation (CTx) is one of the treatments of choice in cases of advanced HF[3].

TxC is a surgical procedure for replacing a sick heart with a healthy heart from a donor, enabling the normalization of the patient's hemodynamics[4-6].

Surgery is a high-risk procedure, and understanding the factors influencing patient survival is extremely important for optimizing the clinical support offered to patients[7].

Even after TxC, the patient may continue to present symptoms related to HF, such as reduced functional capacity, requiring early physiotherapeutic follow-up[8].

Cardiac rehabilitation (CR) is divided into four phases: phase I, which occurs during hospitalization; phase II, carried out on an outpatient basis starting shortly after hospital discharge; and phases III and IV, which aim to maintain the gains obtained in rehabilitation[9]. Phase I begins with gaining physical fitness, emphasizing functional activities, and consists of aerobic and resistance exercises for large muscle groups[9]. CR is an excellent strategy to improve the health recovery of transplant patients, providing greater independence and reducing symptoms of anxiety and depression[3,10,11].

This study aimed to investigate which clinical variables are associated with early mortality, aiming to improve clinical outcomes in this patient population.

METHODS

This article is a retrospective, single-center cohort study based on the analysis of electronic medical records and databases of all patients undergoing TxC surgery at the *Hospital das Clínicas* of the *Faculdade de Medicina de Botucatu* (HCFMB) from May 2019 to April 2023. The TxC service began its activities in May 2019, and this study presents data from the first 55 patients who underwent TxC at this hospital institution.

Epidemiological, clinical and anthropometric data, laboratory tests from the patient's hospitalization after TxC, and information about CR in the ICU were collected.

The Barthel Index (BI) was used to evaluate functional capacity, measuring the level of assistance that a person requires in 10 activities: feeding, personal hygiene, clothing, urine and feces control, bathroom use, bed/chair transfer, mobility and ability to climb stairs. The score ranges from 0 to 100, with higher scores indicating greater functional independence[12,13]. The physiotherapy team applies the BI in an interview format to all patients admitted to the HCFMB intensive care unit (ICU).

Statistical analysis

Categorical variables were represented as absolute and relative frequencies, and continuous variables as mean ± standard deviation (SD). The Kolmogorov-Smirnov (KS) test verified the normality of the distribution. Associations between categorized variables and death were obtained using the chi-square test; for continuous variables with symmetrical distribution, the Student's *t-test* was applied, while for those with asymmetrical distribution, an adjustment was made using gamma distribution. For discrete variables, the comparison was made using Poisson distribution adjustment. A logistic regression model was adjusted, considering the other explanatory variables for the outcome of death during hospitalization.

Subsequently, a receiver operating characteristic curve (ROC) analysis was performed using risk factors as predictors of the outcome of death during hospitalization. Analysis was conducted using Pearson correlations between length of stay after heart transplantation and physiotherapy variables and functionality with survivors after surgery. A $p < 0.05$ was set for statistical significance. The analyses were conducted using SAS 9.4 and SPSS 21 for Windows programs.

Ethic

This study received approval from the Human Research Ethics Committee of Universidade Estadual Paulista (CAAE: 68062123.8.0000.5411).

RESULTS

The clinical characteristics of the 55 patients who underwent TxC from May 2019 to April 2023 are illustrated in Table 1. Of the 55 patients admitted to transplantation, 36 (65.45%) survived the surgery, 26 were male and 10 were female. The average age of the patients was 47 years, with an average body mass index (BMI) of 23 kg/m^2. The average cardiopulmonary bypass (CPB) time was 255 minutes, and 51% of patients preoperatively used an intra-aortic balloon pump (IABP). Only 5% of patients required mechanical ventilation (MV) and ventricular assistance (VA) before transplantation.

Table 1. Descriptive analysis of quantitative and qualitative variables of patients who underwent TxC from May 2019 to April 2023 (n = 55).

Variables	Mean/SD
Age (years)	47.13 ± 15.67
Weight (kg)	67.62 ± 14.04
Height (cm)	1.69 ± 0.09
BMI (kg/m2)	23.26 ± 4.25
CPB (min)	255.00 ± 72.19
POI creatinine (mg/dL)	1.29 ± 0.67
Basal creatinine (mg/dL)	1.00 ± 0.42
PASP (mmHg)	42.16 ± 14.90
RVP (WU)	2.70 ± 2.61
Collection distance (km)	279.00 ± 229.00
Total ischemia (minutes)	297.00 ± 58.24
BI	62.09 ± 32.21
Male, n (%)	42 (76.4)
IABP pre-TxC, n (%)	28 (51.0)
MV pre-TxC, n (%)	3 (5.0)
VA pre-TxC, n (%)	3 (5.0)
IABP pre-TxC, n (%)	28 (51.0)
Post-TxC death, n (%)	19 (34.5)

Source: Prepared by the authors.

Regarding the causes of death in this population (Table 2), the main one was vasoplegic shock, followed by graft rejection and acute right ventricular (RV) failure. Other less frequent causes were cardiogenic shock, biventricular systolic dysfunction, blood dyscrasia and septic shock.

Table 2. Descriptive analysis of the causes of death of 19 patients who underwent TxC from May 2019 to April 2023.

Cause of death	n	%
Vasoplegic shock	6/19	31.57
Graft rejection	4/19	21.05
Acute RV failure	3/19	15.78
Cardiogenic shock	2/19	10.52
Biventricular systolic dysfunction	2/19	10.52
Blood dyscrasia	1/19	5.26
Septic shock	1/19	5.26

Source: Prepared by the authors.

Comparisons were made between the clinical and laboratory variables of patients discharged after TxC and those who died. The results showed a statistically significant difference between the groups concerning creatinine in POI ($p = 0.0002$), pulmonary vascular resistance (PVR) ($p = 0.0011$), as well as PSAP ($p < 0.0001$) and the degree of pre-surgical functional capacity measured by BI ($p = 0.0001$) (Table 3).

Table 3. Comparison of clinical and laboratory variables of patients discharged or died during hospitalization.

Variables	High (n = 36) Mean/SD	Death (n = 19) Mean/SD	*p*-value
Age (years)	45.50 ± 16.43	50.20 ± 14.01	0.2820
Weight (kg)	65.00 ± 12.49	71.60 ± 16.06	0.0870
Height (cm)	1.69 ± 0.09	1.69 ± 0.09	0.9360
BMI (kg/m^2)	22.50 ± 3.92	24.60 ± 4.62	0.0810
CPB (min)	246.40 ± 59.10	272.40 ± 91.53	0.1970
POI creatinine (mg/dL)	1.09 ± 0.38	1.68 ± 0.92	**0.0002**
Basal creatinine (mg/dL)	0.97 ± 0.27	1.11 ± 0.64	0.2090
PASP (mmHg)	33.30 ± 8.23	51.50 ± 12.27	**< 0.0001**
RVP (WU)	2.07 ± 1.93	3.77 ± 3.26	**0.0011**
Total ischemia (minutes)	292.00 ± 58.01	302.53 ± 59.73	0.5519
Collection distance (km)	362.00 ± 255.2	313.00 ± 170.20	0.4410
BI	65.00 ± 34.18	56.50 ± 28.14	**0.0001**
Male (%)	75.0	78.0	0.7430
IABP pre-TxC (%)	47.2	57.9	0.4510
MV pre-TxC (%)	5.6	5.3	0.9630
VA pre-TxC (%)	5.6	5.3	0.9630
Pre-TxC hemodialysis (%)	13.9	21.1	0.4940

Source: Prepared by the authors. $p < 0.05$ was established for statistical significance. There was a difference in immediate postoperative creatinine (POI), PASP, RVP and BI between the discharge and death groups.

A logistic regression model was developed to analyze the outcome of death during hospitalization, considering the other predictor variables. Initially, a stepwise regression model was fitted and influential variables were gradually added to identify associated risk factors.

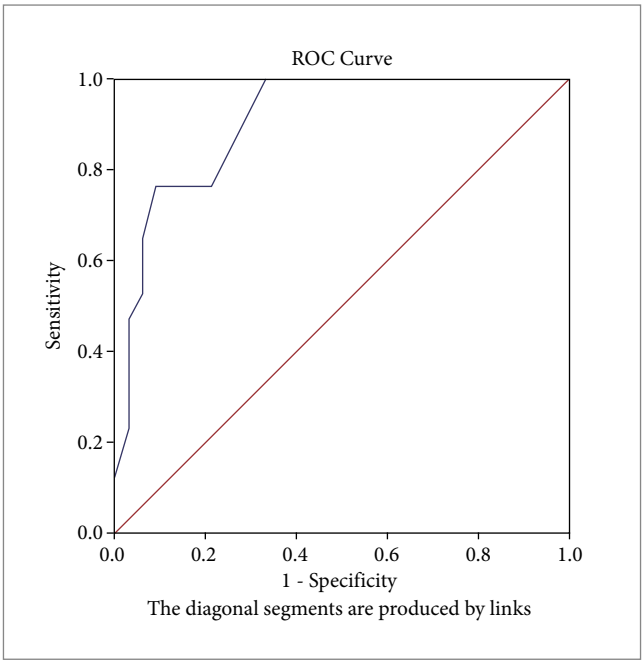
The increase in creatinine in the first 24 postoperative hours was identified as a significant risk factor for mortality during hospitalization ($p = 0.0067$). Likewise, RVP ($p = 0.0185$) and pulmonary artery systolic pressure (PASP) ($p = 0.0415$) showed a significant association (Table 4).

Table 4. Model using the maximum likelihood estimation method with stepwise logistic regression, taking into account influencing variables to determine the risk factors associated with the outcome of death during the hospitalization of patients after TxC.

Variables	Estimate	SE	Wald χ^2	OR	IC95%	*p*-value
Creatinine POI	2.181	0.801	7.406	8.860	1.841-42.632	**0.0067**
RVP	0.362	0.153	5.549	1.437	1.063-1.942	**0.018**5
PSAP	0.052	0.025	4.154	1.054	1.002-1.109	**0.0415**
Sex	-0.607	0.451	1.813	0.297	0.051-1.739	0.5242
Pre-TxC hemodialysis	-0.318	0.499	0.405	0.529	0.075-3.746	0.5242
BMI	0.122	0.092	1.767	1.130	0.943-1.355	0.1837
Age	0.001	0.025	0.005	1.002	0.952-1.054	0.9412

Source: Prepared by the authors. $p < 0.05$ was established for statistical significance. SE = Standard error; CI 95% = Confidence Interval 95%; OR = *odds ratio*.

When constructing the ROC curve with the delta increase in creatinine in the first postoperative period compared to the baseline value, the cutoff point of 0.35 mg/dL was identified (Fig. 1). At this point, sensitivity is 0.76 and specificity is 0.90 (area under the curve: 0.908).



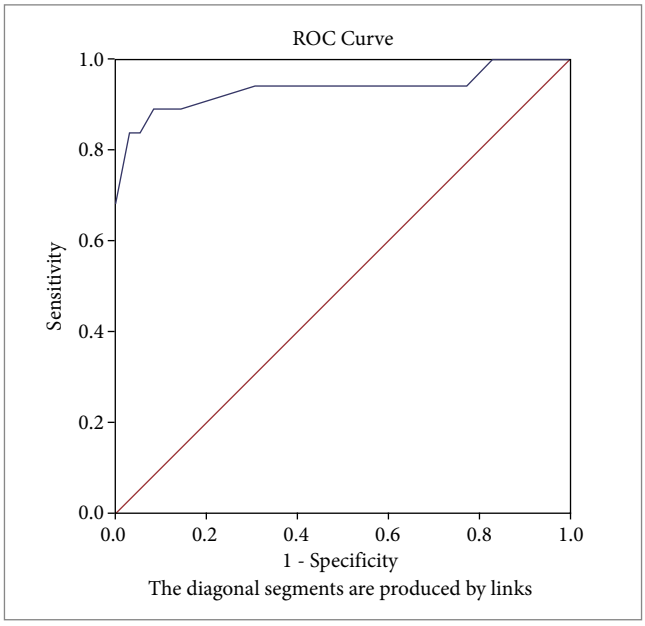
Source: Prepared by the authors.

Figure 1. ROC curve considering creatinine delta of patients who underwent TxC from May 2019 to April 2023.

When analyzing the ROC curve for PSAP, we found a cutoff point 40.5 (Fig. 2). At this point, sensitivity is 0.89, and specificity is 0.86 (area under the curve: 0.940).

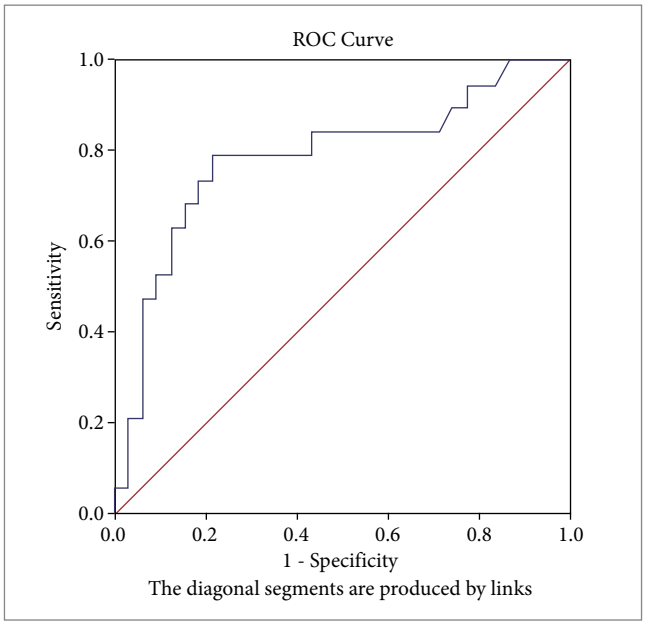
For PVR, the ROC curve's analysis revealed a cutoff point of 2.23 Woods units (WU) (Fig. 3). At this point, sensitivity is 0.79, and specificity is 0.72 (area under the curve: 0.783).

Table 5 shows the descriptive analysis of survivors, considering the phase I CR Variables. Of the 36 patients who underwent CR, the average number of days of hospitalization after surgery was 27. On average, they started CR on the 5th day after surgery. -operative and performed their first sitting and ambulation on the 6th and 13th days, respectively.



Source: Prepared by the authors.

Figure 2. ROC curve considering the PSAP value of patients who underwent TxC from May 2019 to April 2023.



Source: Prepared by the authors.

Figure 3. ROC curve considering the PVR (WU) value of patients who underwent TxC from May 2019 to April 2023.

Table 5. Descriptive analysis of quantitative variables of 36 patients who underwent CR after TxC from May 2019 to April 2023.

Variables	Mean/SD	Minimum value	Maximum value	Median
Pre-TxC hospitalization days	78.05 ± 83.3	0	330	51.5
MV days post-TxC	1.61 ± 3.0	0	12	0.0
MP start day	4.92 ± 5.4	0	27	3.0
Day 1st Sedestation	6.82 ± 5.2	2	27	5.0
Day 1st Ambulation	13.75 ± 12.2	5	59	10.0
BI	65.00 ± 34.1	0	100	55.0
Days of hospitalization post-pre-TxC	27.42 ± 16.0	9	65	20.0

Source: Prepared by the authors. MP = motor physiotherapy.

Analysis was conducted using Pearson's correlations between length of stay after TxC and physiotherapy variables and functionality with the 36 survivors after surgery. There was a positive correlation between the start of physiotherapy and the duration of hospitalization after TxC; that is, there was a significant association between the late start of physiotherapy and the patient's more extended period of hospitalization, with a statistically significant difference ($p = 0.013$).

Furthermore, a negative correlation was identified between the patient's functionality and length of stay, indicating that the lower the patient's functional capacity, the longer the length of stay, and this relationship was also statistically significant ($p = 0.007$) (Table 6).

Table 6. Pearson correlation analysis between length of stay after TxC, functional capacity and physiotherapy variables of the 36 patients who underwent TxC and RC from May 2019 to April 2023.

Intersection	DF	Estimated parameter	ER	value of *t*	*p*-value
BI	1	-0.1496	0.05195	-2.88	**0.007**
MP Start	1	2.29008	0.86791	2.64	**0.013**
Sedestation	1	0.93929	1.16193	0.81	0.425
Ambulation	1	0.41245	0.36974	1.12	0.273

Source: Prepared by the authors. DF = degrees of freedom.

DISCUSSION

An increase in creatinine to a value greater than or equal to 0.35 mg/dL in the first 24 hours, PSAP with values greater than 40.5 mmHg and PVR to a value above 2.23 WU are associated with increased hospital mortality rates after TxC.

Acute kidney injury (AKI) is characterized by abrupt loss of kidney function. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, stage I is characterized by an increase in serum creatinine more significant than or equal to 0.3 mg/dL in 48 hours, an increase in serum creatinine ≥ 1.5-fold the baseline value in the last 7 days and urinary volume < 0.5 mL/kg/h for 6 hours[14].

AKI is a frequent complication after TxC and is linked to a higher risk of early mortality[15]. García-Gigorro et al.[16] found that patients with AKI, especially those requiring renal replacement therapy (RRT), had higher in-hospital mortality than those without AKI. However, after hospital discharge, AKI was not associated with poor long-term outcomes[16].

According to the results of this study, the increase in creatinine in the first 24 hours was shown to be a risk factor for mortality. In this context, the importance of implementing strategies to prevent or limit progression to AKI is emphasized, which, consequently, can improve the survival of these patients.

Pulmonary hypertension (PH) is known to be a poor prognostic factor after TxC[17]. In patients who are candidates for TxC, PSAP, PVR and other hemodynamic parameters are obtained by right heart catheterization. This invasive exam is considered the gold standard for diagnosing and classifying PH and is recommended for evaluating candidates for TxC[18]. Furthermore, PH is monitored non-invasively using indirect transthoracic echocardiogram measurements.

PVR must be calculated individually for each patient using the formula PVR = (mean pulmonary arterial pressure – pulmonary capillary occlusion pressure)/cardiac output. According to the 2022 European Society of Cardiology (ESC) Guideline, typical PVR values are between 0.3 and 2.0 WU[18].

Matkovic et al.[19] conducted an observational study with 44 patients to investigate the impact of preoperative PH on survival after HTx. They concluded that PH is a risk factor associated with a higher mortality rate within 30 days after HTx.

Another study[20] involving 102 patients after TxC investigated the relationship between the presence of PH and survival. Patients were divided into two groups: without PH (< 25 mmHg) and with PH (> 25 mmHg). Furthermore, the PH group was subdivided into mild (25 to 34 mmHg), moderate (35 to 44 mmHg) and severe (> 44 mmHg). Of the 102 patients evaluated, 61 (59.8%) had PH before TxC, with 25 classified as mild, 34 as moderate and two as severe. It is concluded that the presence of preoperative PH did not have a significant impact on survival after HTx. However, it is essential to highlight that only two patients were classified in the severe PH group, which may explain the lack of differences between the groups[20].

Comparing our sample with the study by Cantero et al.[20], we observed significantly higher levels of PH. The mean PSAP of survivors was 33.3 mmHg, while in the death group, it was 51.5 mmHg. This discrepancy justifies our sample's lower survival rate (65.45%) compared to the 79.9% survival reported by Cantero et al.[20].

It was found that there was a significant association between the implementation of CR phase I and the length of hospital stay after TxC. Specifically, the earlier the patient started CR, the shorter the length of stay observed in this sample. These data are essential, as they show the dynamics between the early implementation of phase I CR and a reduced period of hospitalization after TxC.

This suggests that rehabilitation can play a fundamental role in post-surgical recovery, allowing patients to recover more quickly, avoiding complications related to prolonged hospitalization and facilitating the transition to hospital discharge. These results highlight the importance of including rehabilitation as an integral part of post-TxC care. In this context, conducting randomized clinical trials and more studies on phase 1 CR become essential, aiming to deepen our understanding of the specific benefits of this intervention in improving the prognosis and quality of life of patients undergoing heart transplants.

Rosenbaum et al.[21] conducted a retrospective study in which 201 patients who underwent CR after TxC were analyzed. Early CR was found to be associated with long-term survival after HTx.

Another relevant finding in this study was the negative correlation between the patient's functionality, measured through the BI, and the length of stay. This observation means that the lower the patient's functional capacity, the longer the hospitalization period. Although we cannot infer a cause-and-effect relationship due to the methodology used, the results highlight the importance of functionality in the duration of post-TxC hospitalization. This association highlights the need to consider patients' functional capacity as a crucial aspect of postoperative management, although more research is needed to understand this relationship fully.

CR is beneficial in patients with HF, especially those awaiting transplantation, and is recommended as a class 1 indication (level of evidence A) in HF practice guidelines[22]. Several systematic reviews indicate that patients with HF who undergo CR experience a reduction in mortality and hospitalization rates, in addition to an improvement in quality of life[23,24].

Unfortunately, despite the clear benefits in the literature, CR in the pre-TxC period remains underused[25].

These findings emphasize the need to institute measures to preserve the patient's functional capacity during hospitalization or outpatient care while waiting on the transplant waiting list through pre-TxC rehabilitation. Furthermore, it is vital to emphasize phase I CR for better outcomes after surgery.

The inherent limitation is that this is a single-center retrospective study with limited patients. As the implementation of TxC in this service is in its initial phase, we must consider some essential points: the impact of the team's experience, the lack of availability of resources and infrastructure inherent to new services and the lack of longitudinal data on patients, which can limit analyzes and correlations with late complications.

CONCLUSION

An increase in creatinine to a value greater than or equal to 0.35 mg/dL in the first 24 hours, PSAP with values greater than 40.5 mmHg and PVR to a value above 2.23 WU are associated with increased hospital mortality rates after TxC.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Paula GV, Costa AF, Viana NA, Cyrino CMS, Felicio ML, Brito FS, Ponce D; **Conception and design:** Paula GV, Costa AF, Felicio ML, Brito FS, Ponce D; **Data analysis and interpretation:** Brito FS, Ponce D; **Article writing:** Paula GV, Costa AF, Viana NA, Cyrino CMS, Felicio ML, Brito FS, Ponce D; **Critical revision:** Cyrino CMS, Felicio ML, Brito FS, Ponce D; **Final approval:** Paula GV, Costa AF, Viana NA, Cyrino CMS, Felicio ML, Brito FS, Ponce D.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

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