Prevalent Complications in Heart Transplantation: A Retrospective Cohort Analysis

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ABSTRACT

Objectives: To identify the prevalent complications after heart transplantation. **Methods:** This is a quantitative retrospective cohort research with post-heart transplant patients from 2010 to 2022 through medical record analysis. **Results:** Forty-nine post-heart transplant patients participated in the study, six of whom died. The leading cause of heart failure before transplantation was idiopathic dilated heart failure (36.7%), followed by chagasic etiology (30.6%), with an average transplant waiting time of 7.4 months (standard deviation [SD] = 9.7). In the post-heart transplantation period, 95.9% of the population presented at least one complication, the most common being acute cellular rejection (81.6%), followed by cytomegalovirus infection (44.9%). **Conclusion:** The study provided relevant data to the literature to identify the prevalent complications in heart transplantation and implement nursing actions such as planning by nurses to improve self-management of care for transplant patients.

Descriptors: Immunosuppression Therapy; Heart Transplantation; Complications Post-Heart Transplantation; Nursing.

Complicações Prevalentes no Transplante Cardíaco: Uma Análise de Coorte Retrospectiva

RESUMO

Objetivos: Identificar as complicações prevalentes no pós-transplante cardíaco (TxC). **Métodos:** Trata-se de pesquisa quantitativa de coorte retrospectiva, com pacientes pós-TxC no período de 2010 a 2022, por meio de análise de prontuário. **Resultados:** Participaram do estudo 49 pacientes pós-TxC, sendo seis óbitos. A principal causa de insuficiência cardíaca prévia ao transplante foi dilatada idiopática (36,7%), seguida de etiologia chagásica (30,6%), com tempo médio de fila de transplante de 7,4 meses [desvio-padrão (DP) = 9,7]. No período pós-TxC, 95,9% da população apresentou ao menos uma complicação, sendo a mais frequente a rejeição celular aguda (81,6%) seguida de infecção por citomegalovírus (44,9%). **Conclusão:** O estudo forneceu dados relevantes para a literatura para de identificar as complicações prevalentes no TxC para implementar ações de enfermagem, como o planejamento realizado pelo enfermeiro para melhorar a autogestão do cuidado ao paciente transplantado.

Descritores: Terapia de Imunossupressão; Transplante de Coração; Complicações Pós-Transplante de Coração; Enfermagem.

INTRODUCTION

Heart transplantation (HTx) is considered a gold standard therapeutic alternative for advanced heart failure (HF) refractory to treatment, as it increases the survival rate and improves quality of life[1]. Pharmacological immunosuppression regimens are usually composed of a combination of different classes of medications to obtain synergism of pharmacological actions and try to reduce the toxicity and adverse events of medications, which may vary throughout the treatment[2].

Therefore, the focus in monitoring these patients is to balance immunosuppression to prevent rejection and infections[3], ensuring graft maintenance and treating possible complications[4]. While some complications are directly related to the characteristics of the graft or its interaction with the recipient's immune system, others depend on the donor's characteristics, the recipient's habits and, mainly, the side effects of immunosuppressive drugs[5]. Acute cellular rejection can occur at any time after HTx, but an incidence of 60% is reported in the first 6 months after transplantation; graft vascular disease occurs in 40% of patients 8 years after HTx[4]. Among those unrelated to the graft, we find infections, reactivation of Chagas disease (CD), renal dysfunction, neoplasia, diabetes mellitus (DM), and systemic arterial hypertension (SAH), among others[5]. Studies show that the association of calcineurin inhibitors is related to the

incidence of hypertension, with cyclosporine being more associated when compared to tacrolimus[6]. Other studies carried out with post-kidney transplant patients state that immunosuppression is a risk factor for the emergence of DM after transplantation, especially corticosteroids and tacrolimus, the latter being more associated with this pathology when compared to cyclosporine[7]. A common infection is cytomegalovirus (CMV), and there are studies with elderly post-kidney transplant patients showing a higher incidence of CMV when using mycophenolate compared to sirolimus[8].

Also quite recurrent, we may have the reactivation of CD in patients who had chagasic HF in the pre-HTx period; reactivation affects 21 to 45% of recipients in the first year of transplantation and is closely related to aggressive immunosuppression[4]. No studies compare immunosuppressive therapies in these patients, but more reactivations are associated with using mycophenolate. Therefore, the consensus is that these patients receive the lowest possible doses of immunosuppressants as long as there is no rejection[3]. Furthermore, worsening of renal function is common after HTx, occurring in 20% in the 1st year and 40 to 50% in up to 5 years. It may progress to the need for dialysis or even kidney transplantation in 5 to 10% after 10 years. of HTx[4].

Brazil does not have a national database with epidemiological information regarding complications in HTx recipients[9], which is very important for clinical practice. Therefore, this study aimed to identify the prevalent complications after HTx.

METHODS

This is a retrospective cohort study with a quantitative approach. The research was carried out at a prominent public cardiology institute located in the city of São Paulo. The sample was composed of patients who underwent HTx at the institute from 2010 to 2022, selected for the research in a pre-determined period for data collection, from April to September 2023. The convenience sample was used to get as many participants as possible. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[10] checklist was used to design the study better

Patients were invited to participate in the research during outpatient care when the researcher explained the objectives and how the study would be carried out. For patients who agreed to participate, the signature of the Free and Informed Consent Form (FICF) was collected. For those confirmed to have died, a telephone call was made to request acceptance of family participation, at which time the FICF was explained.

The collection was carried out after signing the FICF or accepting the family member's participation, in the case of death, through access to the patient's physical and electronic medical records, using the data collection instrument for sociodemographic characterization (name initials, age, record number in the medical record, gender, education, marital status, employment relationship and origin) and clinical [HF etiology, date of inclusion on the transplant list, date of HTx, comorbidities before and after transplant (SAH, DM, dyslipidemia, chronic kidney disease, smoking), body mass index (BMI), post-transplant conditions and period (graft rejections, infections, neoplasms, right ventricular dysfunction, and graft vascular disease)].

The data was entered into the Research Electronic Data Capture (REDCap) software[11,12], made available by the institute. Continuous variables were described by means and standard deviations (SD) or medians and quartiles; categorical ones were described using absolute and relative frequencies. A significance level of $p < 0.001$ was considered.

A mixed linear model was used to evaluate the change in BMI over time concerning the pre-transplant period, as it depends on the individual (the same patient was assessed over time).

Cardiovascular risk factors were described using pre- and post-transplant frequencies. The McNemar test was used to assess whether changes in the proportions of these diseases were significant over time. Analyzes of the probability of presenting complications up to a particular time were estimated using Kaplan-Meier (KM). The analyses were conducted using the R software, version 4.1.2.

The Research Ethics Council approved the research under opinion number 5,961,527 and CAAE 66809723.7.0000.5462 in 2023.

RESULTS

The study included 49 patients who underwent HTx, of whom 6 died. Men were predominant (73.5%), with a mean age of 54.4 (SD = 14) years, incomplete primary education (22.4%), and marriage (65.3%). The majority came from the state of São Paulo (SP) (36.7%), followed by the state of Minas Gerais (MG) (24.5%).

Of the sample, 38.8% were smokers and 12.2% were alcoholics. Most participants were diagnosed with idiopathic dilated HF (36.7%) followed by chagasic etiology (30.6%). In the pre-transplant period, there were more frequent diseases, such as arrhythmias (45%), hypothyroidism (18.4%), cerebrovascular accident (CVA) (14.3%), pulmonary hypertension (12.2%) and lung disease. coronavirus 2019 (COVID-19) (6.1%).

The waiting time on the transplant queue was, on average, 7.4 months (SD = 9.7).

The most common risk factors [diabetes, hypertension, dyslipidemia and chronic renal failure (CRF)] were described using pre- and post-transplant frequencies. The Mc-Nemmar test was performed on pre- and post-transplant cardiovascular risk factors, with a significant increase in their proportion after transplant, as shown in Table 1.

Table 1. Analysis of pre-and post-HTx cardiovascular risk factors, São Paulo, SP, Brasil, 2023.

Illnesses	Pre-HTx	Post-HTx	P-value
DM	5/49 (10,2%)	19/49 (38,8%)	< 0,001
Dyslipidemia	23/49 (46,9%)	37/49 (75,5%)	< 0,001
SAH	23/49 (46,9%)	35/49 (71,4%)	< 0,001
CRF	5/49 (10,2%)	13/49 (26,5%)	0,008

Source: Elaborated by the authors.

In the post-transplant period, there were more frequent illnesses, such as acute diarrhea (7.9%), acute renal failure (ARF) (7.8%), chronic diarrhea and arthropathy (5.3%). Table 2 represents the main complications found after performing HTx.

Table 2. Main post-HTx complications, São Paulo, SP, Brasil, 2023.

Variables	Total
Number of complications, mean ± SD	2.5 ± 1.0
At least one post-HTx complication	47/49 (95,9%)
Acute cell rejection	40/49 (81,6%)
Acute humoral rejection	15/49 (30,6%)
CMV infection	22/49 (44,9%)
CD reactivation	7/19 (36,8%)
Right ventricular dysfunction	2/49 (4,1%)
Vascular graft disease	1/49 (2,0%)
Neoplasia	2/49 (4,1%)
Other infections	34/49 (69,.4%)

Source: Elaborated by the authors.

The population presented an average of 2.5 (SD = 1) complications, and 95.9% presented at least one complication after HTx. The most common complication was acute cellular rejection (81.6%), and the least frequent was vascular disease of the graft (2%). Regarding the complications mentioned above, KM estimated the probabilities of presenting them up to a specific time so that, as time passed, the likelihood of presenting the complication increased.

Table 3 shows the median time, in days, in which half of the patients experienced a given complication. It was observed that 50% of the population presented acute humoral rejection in 11 days and acute cellular rejection in 13 days. CD reactivation occurred in 54 days in 50% of the population.

Table3. Median times of complications, São Paulo, SP, Brasil, 2023.

Complications	Median time in days
Acute cell rejection	13
CMV infection	39
CD reactivation	54
Acute humoral rejection	11

Source: Elaborated by the authors.

Table 4 shows an average of four rejections per participant, the most common being grade 1 rejection.

Table 4. Grading of acute cellular rejection, São Paulo, SP, Brasil, 2023.

Variables	Descriptive
Number of rejections per participant	
Mean ± SD	4.0 ± 3.3
Median (1st quartile; 3rd quartile)	3.0 [1.0; 7.0]
Number of grade 1 rejections	
Mean ± SD	3.4 ± 3.2
Median (1st quartile; 3rd quartile)	3.0 [0.0; 6.0]
Number of grade 2 rejections	
Mean ± SD	0.6 ± 0.8
Median (1st quartile; 3rd quartile)	0.0 [0.0; 1.0]
Number of grade 3 rejections	
Mean ± SD	0.1 ± 0.2
Median (1st quartile; 3rd quartile)	0.0 [0.0; 0.0]

Source: Elaborated by the authors.

The descriptive analysis of BMI over time showed that the increase in patients' BMI after 5 and 10 years compared to the BMI in the pre-transplant period was relevant, with a tendency for BMI to increase.

According to Fig. 1, of the total of 96 patients, it was possible to analyze the median survival of 42.3 months; in up to 42.3 months, 50% of the population survived. As time passes, the probability of survival reduces. Of the deaths assessed, the leading cause was cardiogenic shock (33.3%).
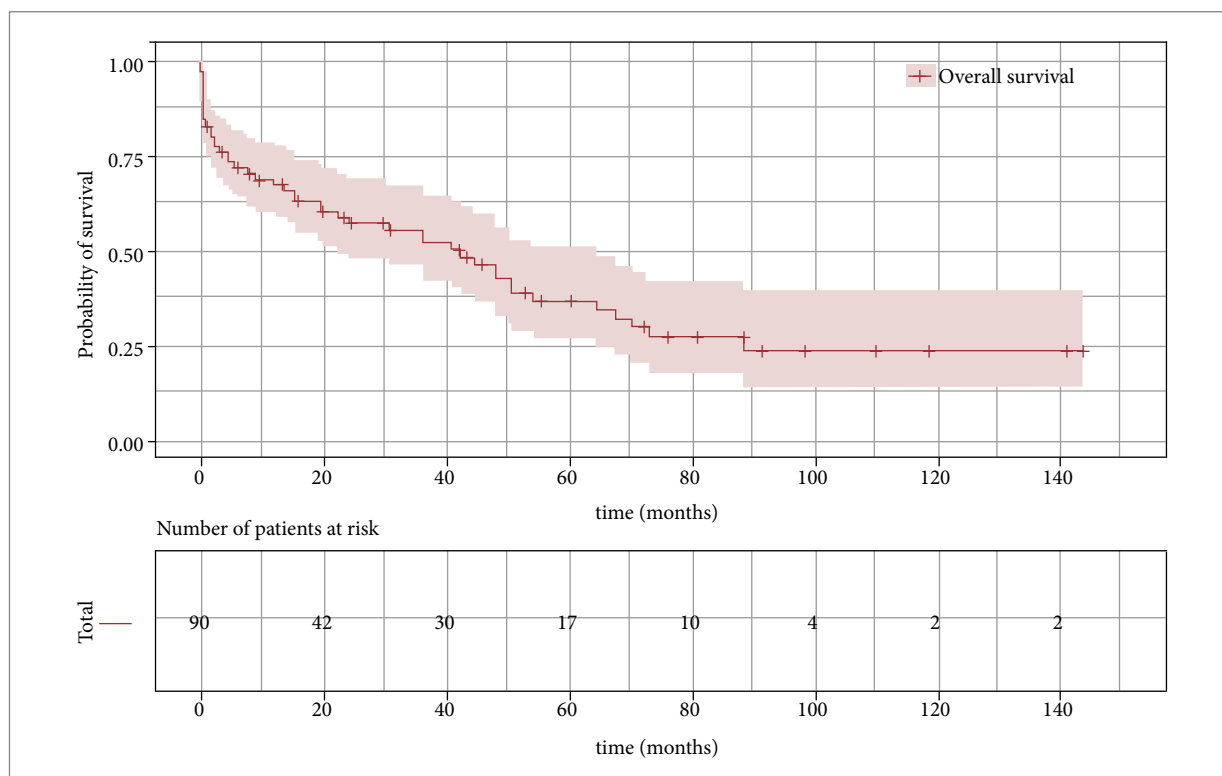
Source: Elaborated by the authors.

Figure 1. Survival curve using the KM method, São Paulo, SP, Brazil, 2023—reliability index (95%CI) 22.4-64.3 months; median survival: 42.3 months.

DISCUSSION

HTx remains the treatment choice for patients with advanced and refractory HF. In the post-HTx period, balanced immunosuppression is essential to prevent rejection and infections, ensure graft maintenance, and treat complications that arise. The study showed significance when evaluating the pre- and post-transplant comorbidities of the sample, with a significant increase in the presence of DM, hypertension and dyslipidemia. Furthermore, it showed that 95.9% of the sample had at least one complication post-HTx period, highlighting rejections, CMV infection and CD reactivation[1,4,5].

Regarding sociodemographic data, we can assess that the study showed data similar to those in the literature. A study carried out with 302 patients undergoing HTx in a Brazilian university hospital from 2006 to 2018 also showed the majority were male, median age was 47 years, married, and the majority suffered from chagasic heart disease[13]. In this study, the majority were male and married, with an average age of 54.4 years; however, the most common cause was idiopathic dilated HF, followed by chagasic etiology. It is also worth highlighting that the study mentioned above was conducted in MG – a state considered one of the most prevalent in CD in Brazil[14]. Meanwhile, most of this sample came from SP, followed by MG.

Regarding the main comorbidities before transplantation, we had 46.9% with hypertension and dyslipidemia and 10.2% with CRF and DM. Similar data were evidenced in a study carried out in the state of Pernambuco (PE) with 96 post-HTx patients, showing the previous presence of SAH (45.4%), DM (8.3%) and CRF (5.2%), not detecting dyslipidemia[15]. In the same pre-HTx period, this study also identified other pathologies, such as arrhythmias (45%), hypothyroidism (18.4%), stroke (14.3%), pulmonary hypertension (12.2%) and COVID-19 (6.1%). It is interesting to highlight that in the study carried out in MG[13], There was also the presence of arrhythmias, more specifically atrial fibrillation (30.8%), dyslipidemia in a smaller percentage (10.6%) and hypothyroidism (17.9%).

Regarding lifestyle habits before HTx, the EP study showed that 45.8% were smokers and 41.7% were alcoholics[15], while in this sample, we had 38.8% smokers and 12.2% alcoholics.

Regarding the waiting time in the HTx queue, a period of 227.9 days (± 292) was found, corresponding to 7.4 months (± 9.7), while in the MG study, a period of 83,5 was found, highlighting that the majority of its patients (65.2%) were waiting for HTx in urgent status[13]. In another study carried out in MG, the percentage of deaths was 40.4%[14] from 2006 to 2016, while in this sample, it was 38.61% from 2010 to 2022. It is essential to highlight that the severe acute respiratory syndrome coronavirus (SARS-CoV- 2, COVID-19) pandemic occurred in this sample period.

Regarding the post-HTx period, the study carried out in PE showed the development of DM in 23.8% of the sample in its follow-up period[15]. The literature varies regarding the prevalence of DM in patients undergoing HTx, showing rates of 20-30%[15] or 20-40%,[16] while our sample presented a rate of 38.8% in this period. It is essential to highlight that there was a significant increase (p < 0.001) in DM (from 10.2 to 38.8%), dyslipidemia (46.9 to 75.5%) and hypertension (from 46.9 to 71.4%). When comparing the pre-and post-HTx periods of this sample. Furthermore, the presence of "other diseases" during this period was assessed, the most common being acute diarrhea (7.9%), ARF (7.8%), chronic diarrhea and arthropathy (5.3%).

Regarding weight, a pre-transplant BMI greater than 30 kg/m^2 is associated with worse results in the post-HTx period[14]. Notably, in this study, the average BMI in the pre-HTx period was 23.68 kg/m2 (SD = 3.95). Furthermore, it was observed that there was a significant increase in BMI in patients after 5 and 10 years compared to the pre-HTx period, showing a tendency for increase.

The literature shows that acute cellular rejection can occur at any time post-transplant. Still, the probability is more significant from the 1st to the 3rd month, with the risk being low after one year[4]. Up to 60% experience one or more rejections in the first 6 months[4]. This study did not evaluate according to time but showed that 81.6% of the sample presented acute cellular rejection at some point. Furthermore, of the patients who developed rejection, it was possible to analyze that the most frequent grade was 1R, with an average of four rejections per participant. Acute cellular rejection is characterized by an inflammatory response mediated mainly by T lymphocytes. It can occur at any time after transplantation, with a greater risk in the first 6 months of immunosuppression. The primary diagnostic method for rejection is endomyocardial biopsy, histopathologically classified into 3 grades (0R, 1R, 2R and 3R, with 3R being the most advanced rejection). Generally, in grade 1R, there is spontaneous resolution, but it is necessary to evaluate the immunosuppression regimen and serum levels of immunosuppressants. From grade 2R onwards, drug treatment is indicated, such as oral corticosteroids or even pulse therapy, depending on medical evaluation[4]. Acute humoral rejection, in more recent studies, was present in approximately 34% of biopsies; in this study, at 30.6%, a similar rate[4]. No studies performed the same type of statistical analysis for better comparison.

Right ventricular dysfunction is a postoperative complication and one of the leading causes of transplant failure, occurring in 20 to 50% of cases[4]. In the population of this study, the occurrence was 4.1%. Furthermore, CMV infection is one of the most common opportunistic infections in these patients. A study carried out in China, with 308 post-pulmonary HTx patients, detected CMV in 52.3% of the sample[17], while this study showed 44.9% and a median time of 39 days, that is, 50% of the population presented CMV within 39 days post-HTx.

Patients with chagasic HF before HTx are at risk of experiencing CD reactivation with immunosuppression. A study in the city of São Paulo, with a population of 107 patients, showed a reactivation rate of 40.2%. In contrast, in the United States of America, in a sample of 31 patients, 61% presented reactivation[3]. In this sample, disease reactivation was 36.8%, with a median time of 54 days. Diagnosis is made by evaluating clinical signs and symptoms and/or the presence of Trypanosoma cruzi in the blood, bone marrow, cerebrospinal fluid or other tissues. After detection, drug treatment is carried out with a recommended antiparasitic (benznidazole)[4].

Regarding the main late complications, we have neoplasia, in which the literature shows us that post-HTx patients are three times more likely to develop them than those with other types of transplants[18]. In the population of this study, we had a rate of 4.1% of neoplasms. Furthermore, external ventricular drain (EVD) is another common complication during this period. In a study of MG[14], in which 81 patients underwent coronary angiography, 18.5% were diagnosed with EVD, while in this sample, only 2% did. Ischemic cardiomyopathy is associated with the progression of coronary plaque after transplantation. Still, only 14.3% of the sample in this study had it, which may be one of the reasons why they had a low rate of EVD.

It was found that, as time passes, there is a greater chance of developing a complication. This means there was no distinction in the statistical analysis between early and late complications. The literature is emphatic in stating that the presence of early complications such as infections and rejection is more common in the first months of immunosuppression due to the dosage. In contrast, complications such as neoplasms and EVD tend to occur later. This can be observed when analyzing Table 3, with the median times of complications, which show us that the first complications to arise were acute humoral and acute cellular rejections, with times of 11 and 13 days, respectively.

Regarding survival, a study carried out in a Brazilian university hospital shows that 65.4% of patients who underwent transplantation died, 43% in the first 30 days after surgery. Our data analysis shows a median survival of 42.3 months since, until

this period, 50% of participants were alive. Furthermore, it shows that, over time, the probability of survival reduces, as already described in the literature[4,13].

CONCLUSION

The present study presented relevant data to the literature, as, in addition to sociodemographic data, it showed a significant increase in cardiovascular risk factors after transplantation, such as hypertension, DM and dyslipidemia, and which prevalent complications these patients presented. Many complications will be inherent to immunosuppression, but knowing the profile of these patients, the nurse has a more excellent scientific basis for implementing nursing actions. In addition, the nurse will monitor patients and provide routine guidance on treatment essential for graft survival and a better quality of life for the patient. These guidelines include healthy eating habits, taking medications correctly, and having healthy lifestyle habits, such as performing physical activity and not smoking. The nurse-patient and family relationship must be trustworthy, as this professional aims to qualify the self-management of care for the transplant patient, promoting a better understanding of their health condition so that they become agents in their health-disease process and clarifying doubts from family members. By adhering to the guidelines given by the team, the patient's quality of life tends to improve due to the probability of increased graft survival, in addition to reducing expenses with recurrent hospital admissions[19,20].

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Borzani GR, Poltronieri NVG, Simonetti SH; **Conception and design: Concepção e desenho:** Borzani GR, Poltronieri NVG, Simonetti SH, Damiani BB; **Data analysis and interpretation:** Borzani GR, Poltronieri NVG, Simonetti SH; Damiani BB; **Article writing:** Borzani GR; **Critical revision:** Borzani GR, Poltronieri NVG, Simonetti SH; **Final approval:** Borzani GR, Poltronieri NVG, Simonetti SH.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

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