High Survival and Mortality Characteristics in Heart Transplant Patients at a National Institute

Christian Rojas,¹ Gabriel De la Cruz-Ku,²,³ Bryan Valcarcel-Valdivia²,³

Abstract

Objectives: The identification of variables related to the survival of heart transplant patients is vital for a good medical practice. Few studies have examined this issue in a Latin American population. Therefore, the aim of this study was to analyze, retrospectively, the survival and mortality characteristics of patients after heart transplant.

Materials and Methods: Information on patients was obtained through review of medical records; we collected information on all patients who underwent this procedure from 2010 to 2015. Sociodemographic, clinical, and surgical characteristics associated with posttransplant mortality were analyzed. Survival over 5 years was determined with the Kaplan-Meier method.

Results: The overall survival rate of the 35 patients who underwent heart transplant was 85%. Those with low total cholesterol values (< 160 mg/dL) had a lower survival at 5 years than patients with higher values (74% vs 100%; P = .044). The overall mortality was 14.3%, and the main cause of death was acute graft rejection (40%). Lower total cholesterol level (< 160 mg/dL; P = .036), presence of chronic kidney disease stage 1 (P = .049), intraoperative bleeding (> 600 mL; P = .013), and number of sepsis incidents (P = .03) were more frequent in patients who died.

Conclusions: The survival in our institute at 5 years is higher than shown in the reported literature, and the mortality is lower. In addition, a low total cholesterol value negatively affects survival of heart transplant patients at 5 years.

Key words: Cardiac surgery, Cholesterol, Graft rejection, Sepsis

Introduction

Compared with past decades, the International Society for Heart and Lung Transplantation and other institutions have recorded improved survival after heart transplant at 1, 5, and 10 years.¹,² This is relevant because this surgical procedure remains the treatment of choice in patients with severe heart failure from different causes.³ Data have also demonstrated survival greater than 20 years after heart transplant.⁴ However, survival continues to be below 80% at 5 years in various institutions.²,⁵

Survival after heart transplant is affected by several mortality factors from both the recipient and the donor.⁶ For the recipient, age, body mass index, high preoperative creatinine level, ischemic time, cardiovascular diseases or hematologic-associated causes, and the patient’s psychological state can affect survival.²,⁷-¹⁰ For the donor, higher age, donor diabetes mellitus history, and sex mismatch or race mismatch can increase the recipients’ mortality after heart transplant.⁹,¹¹

The principal causes of death after this procedure include cardiac graft vasculopathy, primary graft failure, graft rejection, infection, and neoplasia.¹²,¹³ In recent years, new developments to minimize the causes of death have been implemented, thus raising survival rates.¹⁴ These include the implementation of more protocols, strict sanitary policies, and the combination and use of better immunosuppressive therapy.⁶

Most studies have been done on populations other than Latin American. Hence, in this study, we sought to analyze the survival and the most frequent characteristics in deceased patients after heart transplant in a Latin American population. It is important to acknowledge how we measure with
regard to survival versus other countries and institutions and what aspects can be improved to provide and obtain a better life expectancy for our patients.

Materials and Methods

Patients and methods
This retrospective and analytic study was conducted by reviewing the medical records of 35 patients who underwent heart transplant between 2010 and 2015 at the “Instituto Nacional Cardiovascular” of Lima, Peru. The study was approved by the local institutional review board. The analyzed variables included sociodemographic, clinical, and surgical characteristics, explant diagnoses, and complications developed over the 5 years, all in relation to mortality. In addition, causes of death after heart transplant, in relation to the time they occurred, were described. We divided the population into 2 groups: deceased and alive, to determine the related characteristics.

Heart transplant and immunosuppression
The heart transplant procedures followed the Instituto Nacional Cardiovascular management guidelines. All recipients received grafts from a deceased donor. The surgical technique employed was the orthotopic bicaval unipulmonary technique. Before transplant, each recipient underwent histocompatibility analysis with the donor, in which the serology, infections, and previous colonizations were assessed. For induction therapy, basiliximab was used, and corticotherapy was started with methylprednisolone and later continued with prednisone. Cefepime (1 g intravenously every 8 hours for 7 days) was used for antibacterial prophylactic therapy; nevertheless, another drug was administered when an infectious complication presented. After heart transplant, patients received mycophenolate mofetil, tacrolimus, and corticosteroids as a triple immunosuppressive therapy. As additional prophylaxis, ganciclovir was added for 1 week and then valganciclovir for 3 months. Trimethoprim/-sulfamethoxazole was given for 1 year, and oral nystatin, topical cotrimoxazole, and oral ciprofloxacin were administered during the hospital stay.

Complications and follow-up
Complications were diagnosed by a multidisciplinary team of different specialists. All patients were clinically evaluated during their hospital stay (including receiving laboratory tests) and later received periodic checks every 2 weeks during the first 2 months, monthly between the 2nd and 6th months, and then every 2 to 3 months thereafter. Control examinations included laboratory tests and endomyocardial biopsies. Patients were hospitalized when complications had clinically manifested or when pathologic findings were identified during medical checks.

Statistical analyses
Descriptive variables were grouped in a table of frequencies. In the bivariate analysis, chi-square test was used for categorical and t test was used for continuous variables. For survival analyses, the Kaplan-Meier method was performed. Statistical significance was determined at P < .05. To assess survival in relation to cholesterol, lower total cholesterol was considered when the values were below 160 mg/mL, in accordance with a previous study. All analyses were done with the use of SPSS software version 23.0 (SPSS: An IBM Company, IBM Corporation, Armonk, NY, USA) and STATA software (StataCorp LP, College Station, TX, USA).

Results
Table 1 shows the demographic, clinical, and surgical characteristics of patients. The mean age of our study population was 39.49 ± 15.07 years. Most patients (66%) were less than 50 years old, and only 1 of the patients who died had an age > 50 years. There were few patients with comorbidities like hypertension and diabetes mellitus; nevertheless, a sustained amount of the patients had a positive medical history for chronic kidney disease (CKD). Interestingly 4 of the 5 patients (80%) who died had CKD stage 1. In addition, 71% of the population had pulmonary hypertension as a pretransplant diagnosis, with 80% of the patients who died having this diagnosis. Nevertheless, this result did not reach statistical significance for a frequent patient characteristic (P = .65).

Average total cholesterol was 149.44 mg/dL, and all patients who had values below 160 mg/dL died. Likewise, high-density lipoprotein levels were also low in the deceased group, but, in contrast to total cholesterol, it did not reach statistical significance.
The mean weight and body mass index declined after transplant (mean weight: 60.95 ± 13.54 kg vs 58.29 ± 11.46 kg; body mass index: 23.15 ± 4.23 kg/m² vs 22.14 ± 3.40 kg/m²) but did not appear to be an important factor in relation to mortality. The average time of surgery was 377 minutes, with clamping time averaging 111.8 minutes. All patients who had more than 600 mL of blood loss during surgery died.
Regarding hematologic variables, on average, the presurgical hemoglobin level was 12.59 g/dL, which fell to 9.02 g/dL after surgery. Posttransplant leukocyte levels were above 11 × 10^3/mL in more than 60% of both groups. The posttransplant neutrophil levels above 75% were more common in the deceased group than in the living group (100% vs 86%). Despite this, these cell levels did not statistically influence mortality. Average albumin values were quite low (3.24 g/dL). Overall, mild malnutrition was the most common nutritional diagnosis (40%), which was more frequent in living patients (43% vs 20%). On the other hand, only 1 deceased patient had severe malnutrition; therefore, the distribution was equal in both groups (20% for each one). In addition, 29% of the patients were hospitalized for other pretransplant complications. The posttransplant infections and bacteremia had no significance on mortality, but the number of sepsis incidences was significant. The characteristics in the deceased group that reached statistical significance were CKD stage 1 (P = .049), total cholesterol values less than 160 mg/dL (P = .036), surgical bleeding of more than 600 mL (P = .013), and the number of sepsis (P = .03).

Table 2 shows the explant results for the 35 patients. The most frequent was dilated cardiomyopathy (80%). The other diagnosis had a similar distribution among them. The overall survival of our population was 85% at 5 years after heart transplant (Figure 1). All deaths that occurred happened in the first year after transplant. In addition, a total cholesterol level < 160 mg/dL was associated with mortality in these patients (P = .044). Although all patients with total cholesterol levels ≥ 160 mg/dL were alive, only 74% of those with lower levels had the same outcome at 5 years after heart transplant (Figure 2). A survival curve regarding the relation of sepsis was made, which showed P < .001.

<table>
<thead>
<tr>
<th>Result</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated cardiomyopathy</td>
<td>28 (80)</td>
</tr>
<tr>
<td>Ebstein anomaly</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Hypersensitivity myocarditis</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Lymphocytic cardiomyopathy</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Arrhythmogenic cardiomyopathy</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>1 (2.8)</td>
</tr>
</tbody>
</table>

The overall mortality was 14.33%, with 60% dying from graft failure or rejection. Although infections caused 40% of deaths, 1 patient with acute graft rejection had a ventilator-associated pneumonia by *Pseudomonas aeruginosa* and the other one had an abscess in an oral cavity that resulted in aspirative pneumonia. Both produced septic shock and death (Table 3).

Figure 1. Survival at 5 Years in the Total Study Population (85%)

Figure 2. Survival in Patients With Total Cholesterol Levels < 160 mg/dL

Results were statistically lower than for patients with values ≥ 160 mg/dL (Kaplan-Meier method with the long-rank test).

<table>
<thead>
<tr>
<th>Cause</th>
<th>Total Patients (N = 5) (%)</th>
<th>Days After Heart Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure or graft rejection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Acute graft rejection</td>
<td>2 (40)</td>
<td>114</td>
</tr>
<tr>
<td>• Acute right heart failure</td>
<td>1 (20)</td>
<td>250</td>
</tr>
<tr>
<td>Infected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ventilator-associated pneumonia</td>
<td>1 (20)</td>
<td>52</td>
</tr>
<tr>
<td>• Abscess in oral cavity</td>
<td>1 (20)</td>
<td>240</td>
</tr>
</tbody>
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**Discussion**

When faced with heart failure refractory to medical and surgical treatment, cardiac transplant is the treatment of choice. In this study, we examined our experience with patients at a national institute after heart transplant. Our findings focused on a Latin American population, in which the overall survival and mortality rates were 85% and 14.33%. In turn, it
was interesting to note that a low total cholesterol negatively influenced survival of our patients. According to the literature, high total cholesterol is a risk factor for decreased survival and increased mortality. However, low levels of cholesterol have been identified as markers for high mortality, thus resulting in the name “the cholesterol paradox.” For example, Nago and associates demonstrated that mortality with total cholesterol levels below 160 mg/dL had an age-adjusted hazard ratio (HR) of 1.49 (95% confidence interval [CI], 1.23-1.79) in male patients and 1.50 (95% CI, 1.10-2.04) in female patients. This association remained even when deaths were excluded from liver disease, which had an age-adjusted HR of 1.38 (95% CI, 1.13-1.67) for men and 1.49 (95% CI, 1.09-2.04) for women. In turn, Horwich and associates reported that low cholesterol levels (≤ 118 mg/dL) are not only associated with poor clinical outcomes in chronic diseases; in acute decompensated heart failure, patients had a higher mortality and longer hospital stay (P < .0001). These studies support our findings, in which we found that a low level of total cholesterol is a factor possibly related to mortality in these patients.

Intraoperative bleeding of more than 600 mL was frequent in the deceased group. A similar result was reported by Buchs and associates, who demonstrated that bleeding of more than 500 mL is a risk factor for high mortality. To prevent excessive bleeding and to reincorporate loss of blood, several globular packages were given to the patients, according to their needs. It is interesting to note that only CKD stage 1 was a marker of mortality in our study and not CKD stages 2 or 3, although decreased creatinine clearance is associated with higher mortality. Our result did not show a very strong significance level, which may be due to the number of patients analyzed. Another approach is that patients with CKD stage 2 or 3 are unlikely to have a surgical procedure and therefore were not included in medical records for analyses.

We found that the variable sepsis was statistically associated with survival. A plausible explanation could rely on a deceased patient who had 3 sepsis episodes, thus possibly affecting the survival curves and results. In addition, 1 study reported that sepsis killed 2 of 10 patients studied, but it was not categorized as a mortality factor after heart transplant. Another study stated that 9 of 117 patients died due to sepsis, but it was not classified as a mortality factor.

Survival after heart transplant has improved over time. However, there are inconsistencies in the results of various institutions. For example, 1 study evidenced a 90% survival at 1 year. In Karamlou and associates, however, survival rates at 1 and 5 years were 87% and 71%, respectively, with rates of 75% and 63% for patients with congenital heart disease. In our study, survival at 5 years was 85%, which is higher than the reported literature. This could evidence an improvement compared with them. Our follow-up could be a factor that explains this high survival. In our case, the follow-up period differs from other studies. For example, one study followed patients continually for only the first month after heart transplant, every 2 weeks for the next 2 months, and monthly for the other 3 months; this study reported a survival at 5 years of 79%. Another group mentioned that patients were followed weekly for the first several weeks and then once every 3 months, with a survival rate of approximately 60% at 5 years. In our study, patients remained hospitalized for a brief period of time, during which routine biopsies and laboratory tests were conducted. After that, patients were seen every 2 weeks for the first 2 months, monthly up to 6 month, and then every 2 to 3 months.

On the other hand, a multidisciplinary approach from health care workers benefits survival. Van Bakel and associates showed that factors such as a greater number of transplant cardiologists (P = .01), presence of a thoracic surgery fellowship (P < .0001), a surgeon or cardiologist taking donor calls (P = .0003), and a routine screening for antibody-mediated rejection (P < .0001) lower mortality. In our institution, we lack some of these variables; implementation of this could lead to a better outcome and diminished morbidity after heart transplant.

Immunosuppressive therapy after transplantation was also previously studied. Coutance and associates found that the mortality of 20 patients was 80% at 1 month and 50% at 1 year, despite patients receiving a high immunosuppressive therapy regimen (100% received methyprednisolone, 90% received intravenous immunoglobulin, 85% received plasmapheresis, and 45% received rituximab). Holmes and associates used cyclosporine and mycophenolate for their immunosuppressive therapy, in which patient survival was lower than ours. In our population, the immunosuppression regimen differed with that mentioned above, as our patients received a triple therapy (mycophenolate mofetil, tacrolimus, and
corticosteroids). Nevertheless, the mortality was lower. On that basis, it can be mentioned that survival depends on several factors, including population demographic and biologic factors. Nevertheless, we cannot discharge the influence of the population number, which could have affected our results.

High pulmonary vascular resistance has been a known risk factor for increased mortality. However, a recent study stated that, over time, this has ceased to be, as long as the donor obtains a suitable heart. For example, Patel and colleagues mentioned that recipients with elevated pulmonary resistance who received a heart with an unappropriated measure had lower survival. In our experience, 71% of all patients had pulmonary hypertension; however, our univariate analysis showed that this condition was not significant for mortality. Given this, we can add some evidence that appropriate clinical practices would avoid raising mortality from this cause.

The main causes of death were acute graft rejection and infection. Karamlou and colleagues reported similar results, with their study showing 665 of 8496 patients dying from acute graft rejection and 271 dying from infection. In turn, Tallaj and associates reported that, over a 19-year period, infections caused 24% of deaths, with 14% from graft failure (within 30 days) and 12.5% from acute rejection. Although, the numbers of patients in both studies differed from ours, we managed to corroborate that these are the most common causes of death in patients after heart transplant.

The present study has some limitations, such as the population number; hence, this limited the statistical analysis and the results could be affected. However, we identified some variables related to mortality. Another limitation is lack of medical information from donors, except for one case. Because of this, donor infection status, donor age, and donor’s previous drug therapy were not known, restricting further analyses.

In conclusion, this research found that overall survival at 5 years in our national institute is higher and the mortality is lower than shown in currently reported data. We attribute this result to the institute’s guidelines used for these patients and the proper management implemented by the health care workers. In addition, patients with low total cholesterol values, defined as less than 160 mg/dL, had a lower survival rate. Nevertheless, further studies involving larger populations and more accurate data should be performed, to obtain more meaningful results.

References


