Original Article

A Comprehensive Retrospective Cohort Study on Heart Transplantation: Exploring Complications, Mortality Causes, and Survival Rates

Salma Nozhat[1], Mahmood Zamirian[1], Alireza Arzhangzade[1*], Sasan Shafiei[1], Keivan Sahebi[2]
Roozbeh Narimani Javid[3], Sarvenaz Salahi[4], Hassan Foroozand[2], Khalil Zarrabi[5], Masoud Shafiee[6]
Mohammad Rafati Navaei[5], Hosein Fatemian[2]

[1] Department of Cardiology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
[2] School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
[3] Student Research Committee, Hamadan University of Medical Sciences, Hamadan, Iran.
[4] Royan Stem Cell and Biotechnology Research Center, Tehran, Iran.
[5] Cardiovascular Surgery Department, Shiraz University of Medical Sciences, Shiraz, Iran.
[6] Shiraz Organ Transplant Center, Abu-Ali Sina Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.

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Highlights

- High Survival Rates: The study reported 1-year, 5-year, and 10-year survival rates of 80%, 51%, and 42%, respectively, for heart transplant recipients.
- Key Complications: Allograft rejection occurred in 23.8% of patients, significantly impacting survival, with a mean survival of 23.9 months for those with rejection versus 65.9 months without.
- Leading Cause for Transplant: Dilated cardiomyopathy was the most common underlying condition, accounting for 85.3% of heart transplant cases.
- Demographic Insights: The cohort had a mean age of 40.7 years, with 64% male recipients, and no significant survival differences based on sex or age.

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* **Corresponding Author:**
Alireza Arzhangzade
Assistant Professor of Cardiology, Department of Cardiology, School of Medicine, Shiraz University of Medical Sciences, Iran.
Tel: +989397603632
Email: Alirezaarjang@gmail.com

ABSTRACT

Background: Heart transplantation (HTx) has become the preferred treatment for certain individuals with advanced heart failure. However, the outcomes and complications of this procedure have not been thoroughly evaluated in the Iranian population. In this study, we aimed to provide a comprehensive understanding of the epidemiological characteristics of patients who underwent HTx, focusing on the indications for HTx, early and late complications, causes of mortality, and survival rates.

Methods: In this retrospective cohort study, we included all patients aged 18 years and older who underwent HTx between July 2013 and June 2023 at Namazi Academic Hospital, affiliated with Shiraz University of Medical Sciences. We collected baseline and clinical characteristics and 10-year follow-up data from medical records. The 10-year survival data were presented using the Kaplan-Meier curve. Subgroup survival analyses based on Allograft rejection status, sex, and age were also performed.

Results: We identified 75 patients who underwent HTx during the study period, including 48 males and 27 females. The most prevalent underlying cause for HTx was dilated cardiomyopathy, accounting for 85.3% of the surgeries. After the procedure, 15 patients showed signs of allograft rejection. The survival analysis indicated a mean survival of 71.3 ± 6.5 months. The 1-, 5-, and 10-year survival rates were reported at 80%, 51%, and 42%, respectively.

Conclusions: Overall, this study's findings offer valuable insights into the demographic and clinical characteristics of patients undergoing HTx and their outcomes. Additionally, our results enhance current knowledge regarding pre-HTx risk assessment and patient selection, early post-HTx diagnosis, and the management of significant complications.

Keywords: Heart Transplantation; Patient Outcome Assessment; Survival Rate

Introduction

Heart transplantation (HTx) has become the preferred treatment for specific patients with advanced heart failure (HF). Advancements in preoperative patient evaluations, selection processes, transplantation methods, organ preservation, postoperative care, and immunosuppressive strategies have increased survival rates and reduced complications.[1, 2]

The International Thoracic Organ Transplant Registry (ISHLT) has reported increased survival rates among HTx recipients based on a registry of over 66,000 cases, with approximately 3000 new cases each year. The survival rates were approximately 83% at the 1-year follow-up and 72% at the 5-year follow-up.[3] Nonetheless, some important complications still restrict patients' quality of life and long-term outcomes.[4]

Primary graft dysfunction (PGD), defined as the onset of cardiac dysfunction within the first 24 hours following transplantation and in the absence of a clear secondary etiology, accounts for approximately 40% of mortality after HTx. This positions PGD as the leading cause of early death after HTx.[5] Post-HTx patients may also experience acute cellular rejection (ACR) or antibody-mediated rejection (AMR).[6, 7] Additionally, the administration of immunosuppressive drug regimens in transplant recipients predisposes patients to various malignancies and infections.[8, 9]

Current studies on HTx recipients in Iran, especially concerning their complications, survival outcomes, and causes of death, are still limited.

Different HTx institutions have reported varied survival rates and complications, such as the type and severity of existing cardiac conditions, based on the characteristics of the recipient and donor. This study aimed to provide a comprehensive understanding of the epidemiological characteristics of patients in our academic HTx center, focusing on indications, early and late complications, causes of mortality, and survival rates.

Methods

Study design and population

In this 10-year observational retrospective single-center study, we included all patients aged 18 years and older who underwent HTx between July 2013 and June 2023 at Namazi Academic Hospital, affiliated with Shiraz University of Medical Sciences. A data collection form was designed and completed for each patient by reviewing their medical records. Data collected from inpatient and outpatient medical records encompassed the patients' baseline characteristics, medical and surgical history, mortality and causes of death, complications (e.g., allograft rejection, infection, cardiac allograft vasculopathy [CAV]), laboratory results, and medications.

The following outcomes were collected for the first 10 years after HTx surgery: (1) mortality/survival (the incidence of death, causes of death, and length of survival); (2) rejection (the incidence, timing, and types of rejection); and (3) the incidence of early and late post-transplant complications (infection, respiratory failure, stroke, CAV, cancer, new-onset steroid-induced diabetes, and severe renal dysfunction [defined as a serum creatinine>2.5 mg/dL, a diagnosis of renal failure, or being on dialysis, based on the ISHLT definition]). Allograft rejection was confirmed through endomyocardial biopsies, and an expert pathologist conducted rejection grading according to ISHLT guidelines.[10]

We reviewed patient charts to obtain all transfused blood products, including packed red blood cells, platelets, fresh frozen plasma, cryoglobulin, comprehensive drug history, and the pre-HTx ejection fraction. We also obtained pre-HTx laboratory findings, including serum fasting blood sugar, total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride levels.

The ethics committee of Shiraz University of Medical Sciences approved the study (IR.SUMS.MED.REC.1401.212).

Statistical analysis

Quantitative and categorical variables were presented as mean±SD and frequencies and percentages, respectively. The overall 10-year survival rate was reported using the Kaplan-Meier method. Unadjusted survival rates for sex (female/male) and age (younger than 50, 50, or

older) were estimated using the Kaplan-Meier method, and the differences between the curves were assessed utilizing the log-rank test. Statistical significance was defined as a *P*-value≤0.05. SPSS version 25.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

A total of 75 patients, consisting of 48 males (64%) and 27 females (36%), underwent HTx during the assessment period. The mean age of the recipients at the time of HTx was 40.7 ± 11.4 years, ranging from 18 to 63 years. In this cohort of patients, the most common comorbidities were hypertension and hypothyroidism, followed by diabetes mellitus and hyperlipidemia. (Table 1) shows the baseline characteristics and clinical features of patients who underwent HTx.

Table 1. The baseline characteristics, clinical features, and procedural details of patients who underwent heart transplantation

		Total (n=75)
Sex, n (%)		
	Male	48 (64.0%)
	Female	27 (36.0%)
Age, mean (SD)		40.7 (11.4)
Comorbidities n (%)		
	Hypertension	9 (12.0%)
	Hypothyroidism	6 (8.0%)
	Diabetes mellitus	4 (5.3%)
	Hyperlipidemia	3 (3.9%)
	Chronic kidney disease	2 (2.7%)
	Ischemic heart disease	2 (2.7%)
	Cirrhosis	2 (2.7%)
	Cerebrovascular accident	1 (1.3%)
	Neurofibromatosis	1 (1.3%)
	Hemochromatosis	1 (1.3%)
Social History n (%)		
	Smoker	3 (4.0%)
	Opium addict	2 (2.7%)
Underlying Causes n (%)		
	DCMP	64 (85.3%)
	alcoholic CMP	2 (2.7%)
	ICMP	2 (2.7%)
	RCMP	2 (2.7%)
	HCM	1 (1.3%)
	HOCM	1 (1.3%)
	ARVC (bivent)	1 (1.3%)
	Unknown CMP	2 (2.7%)
Surgical Techniques n (%)		
	Bicaval	57 (76%)
	Biatrial	17 (22.7%)
	Redo	1 (1.3%)
Blood Product Transfusion mean (SD)		
	pRBC	4.3 (5.8)
	FFP	7.6 (9.6)
	Cryoglobulin	0.76 (3.3)
	Platelet	9.7 (27. 6)

SD: standard deviation, DCMP: dilated cardiomyopathy, CMP: cardiomyopathy, ICMP: idiopathic cardiomyopathy, RCMP: restrictive cardiomyopathy, HCM: hypertrophic cardiomyopathy, HOCM: hypertrophic obstructive cardiomyopathy, ARVC: arrhythmogenic right ventricular cardiomyopathy, pRBC: packed red blood cells, FFP: fresh frozen plasma.

The most common underlying cause of HF and subsequent HTx was dilated cardiomyopathy, accounting for 85.3% of cases, followed by alcoholic cardiomyopathy, hypertrophic cardiomyopathy, idiopathic cardiomyopathy, and restrictive cardiomyopathy. One patient had arrhythmogenic cardiomyopathy, and the underlying causes of cardiomyopathy in 2 patients were unknown.

Regarding the causes of early mortality, 12 patients (15.8%) died during or shortly after the operation. Among these 12 patients, 4 (33.3%) lost

their lives due to PGD. Three patients (25%) experienced septic shock following surgery, and 2 (16.6%) died from COVID-19 infection while hospitalized. Sudden cardiac death caused by unexplained tachyarrhythmia, right ventricular failure, and bleeding each accounted for 1 death (8.3%) during this period.

Among the 63 early post-HTx survivors, 41 (65.1%) were male and 22 (34.9%) were female. Fifteen patients (23.8%) showed evidence of allograft rejection, with 9 patients (14.3%) having ACR and 6 patients (9.5%) having AMR. The time between HTx and rejection was categorized as either acute or chronic, using a cutoff point of 6 months. Accordingly, 11 patients experienced acute rejection, while 2 patients had multiple rejection episodes. For those patients with multiple episodes, the acute or chronic nature of the rejection was determined by the time of the first rejection episode (Table 2).

All HTx recipients were administered 3-drug immunosuppressive treatment following our protocol. We administered rabbit antithymocyte globulins as an induction treatment. Azathioprine was given at a dosage of 4 mg/kg 1 hour prior to HTx. Solumedrol, at a dose of 1000 mg, was provided after the aortic cross-clamp was removed. The administration of rabbit antithymocyte globulin at a dosage of 1.5–2.5 mg/kg/day was maintained for 5 days after HTx. Oral cyclosporine was also started within 5 days post-HTx, with doses adjusted according to renal function and drug levels. The drug levels were maintained at trough values of 300–500 ng/mL during the first 3 months after transplantation and then maintained at 200–300 ng/mL for 1 year. Following transplantation, azathioprine was also continued at a dosage of 1–2 mg/kg/day. The administration of prednisone at a dosage of 0.5 mg/kg/day began on the second day after surgery and gradually decreased to 0.2 mg/kg/day during the first month.

Table 2. The characteristics of allograft rejections

	Grade of Rejection		Time Frame of Rejection	
			Acute (≤6 months) (n)	Chronic (>6 months) (n)
ACR	Grade 1 R (n)	**6**		
	Grade 2 R (n)	**3**	**6**	**3**
	Grade 3 R (n)	**0**		
AMR	Grade 1 (n)	**2**		
	Grade 2 (n)	**3**	**5**	**1**
	Grade 3 (n)	**1**		

AMR: antibody-mediated rejection, ACR: acute cellular rejection.
AMR grading: grade 0: negative histologic and immunopathologic findings; grade 1: presence of positive histologic and immunopathologic findings; grade 2: presence of both histologic and immunopathologic findings; and grade 3: presence of severe histologic plus immunopathologic findings.
ISHLT ACR grading: grade 0: no rejection; grade 1 R, mild: interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage; grade 2 R, moderate: Two or more foci of infiltrates with associated myocyte damage; and grade 3 R, severe: diffuse infiltrate with multifocal myocyte damage, with or without edema, hemorrhage, or vasculitis.

During the follow-up, 3 patients experienced CAV, and 4 patients were diagnosed with cancer. One patient developed an intracerebral hemorrhage, and 2 had cerebrovascular accidents (one due to a left atrial clot). Notably, 1 of the 4 patients with cancer experienced dacryocystitis, followed by mucormycosis and eye enucleation just 5 days later. This patient's risk factors consisted of neutropenia, diabetes mellitus post-HTx, and the continuous use of oral steroids. A detailed report of infectious and non-infectious postoperative complications, as well as long-term complications, is presented in (Table 3).

Table 3. Infectious and non-infectious postoperative and long-term complications

		Early Survivors (n=63)
Sex, n (%)		
	Male	41 (65.1%)
	Female	22 (34.9%)
Cardiac allograft vasculopathy, n (%)		3 (4.5%)
Malignancy, n (%)		3 (3.9%)
	Leukemia	1 (1.6%)
	Kaposi sarcoma	2 (3.2%)

	Squamous cell carcinoma	1 (1.6%)
	Total	4 (6.3%)
Noninfectious Complications n (%)		
	Cerebrovascular accident	2 (3.2%)
	Intracranial hemorrhage	1 (1.6%)
	Cushing syndrome	1 (1.6%)
	Right diaphragmatic paralysis	1 (1.6%)
	Pericardial hematoma	1 (1.6%)
	Testicular abscess (orchiectomy)	1 (1.6%)
	Deep vein thrombosis	1 (1.6%)
	Severe aortic insufficiency (due to iatrogenic mechanical damage)	1 (1.6%)
	Atherosclerotic coronary artery disease	1 (1.6%)
	Mild pulmonary stenosis (at the anastomosis site)	1 (1.6%)
	Total	11 (17.5%)
Infectious Complications n (%)		
	Infectious diarrhea	3 (4.8%)
	Aspergillosis	1 (1.6%)
	cytomegalovirus infection	1 (1.6%)
	Total	5 (7.9%)

The survival analysis for HTx patients in this cohort showed a mean survival time of 71.3±6.5 months. According to the Kaplan-Meier curve, the survival rates were 80% after 1 year, 75% after 2 years, 71% after 3 years, 51% after 5 years, and 42% after 10 years (Figure 1).

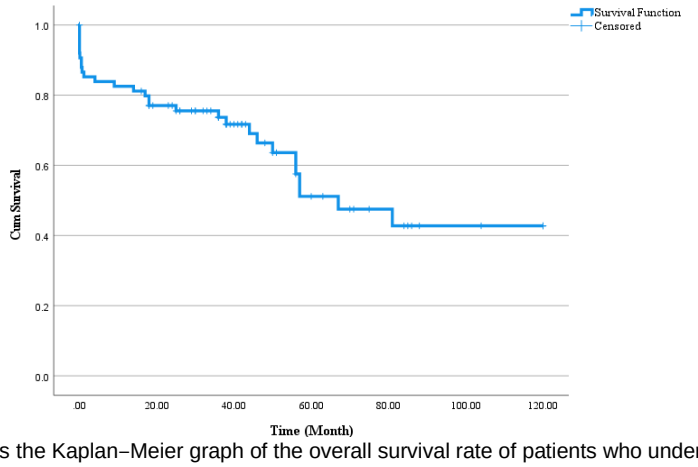

Figure 1. The image illustrates the Kaplan–Meier graph of the overall survival rate of patients who underwent heart transplantation.

The subgroup analysis based on allograft rejection status revealed an estimated mean survival of 65.9±7.4 months for patients without signs of allograft rejection and 23.9±6.4 months for those with signs of rejection. The log-rank test showed a P-value of 0.032, indicating a significant decrease in the survival rate among patients exhibiting signs of allograft rejection (Figure 2).

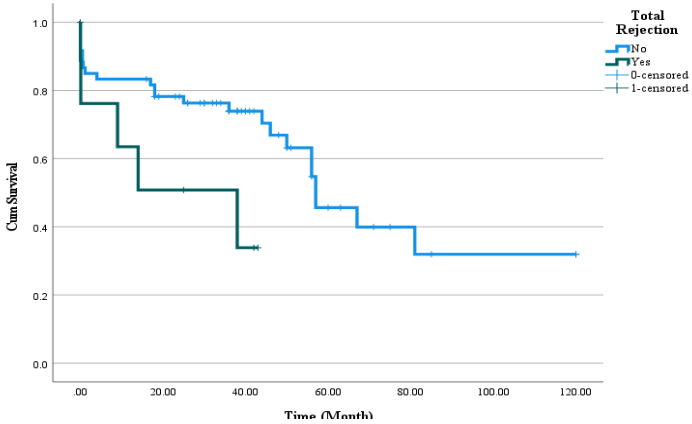

Figure 2. The image presents the Kaplan-Meier graph for comparing survival between patients with and without allograft rejection.

Subgroup analysis for age revealed an estimated mean survival of 66.5±7.7 months for patients aged 50 and younger, and 85.4±12.0 months for those older than 50 years. The log-rank test yielded a *P*-value of 0.159, indicating a nonsignificant difference between these 2 subgroups (Figure 3).

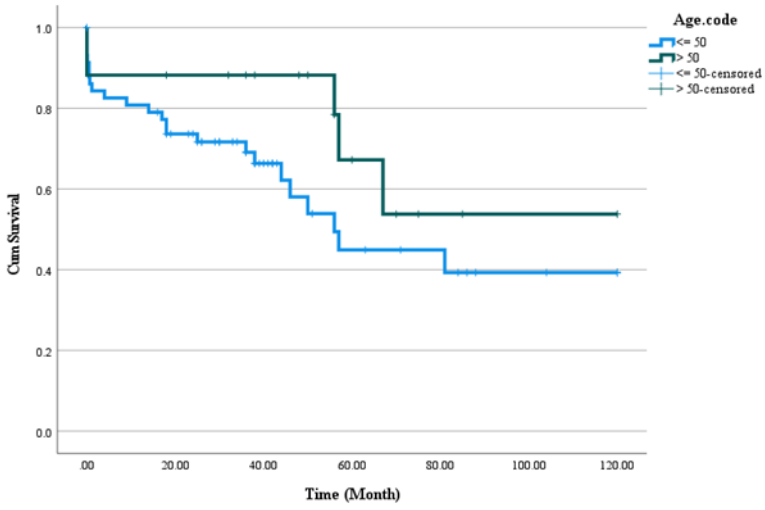

Figure 3. The image showcases the Kaplan-Meier survival curves comparing post-transplantation outcomes between recipients aged ≤50 years and >50 years.

Subgroup analysis based on sex also revealed an estimated mean survival of 68.7 ± 8.6 months for males and 69.3±8.1 months for females. The log-rank test yielded a P-value of 0.417, indicating a nonsignificant difference in this context (Figure 4).

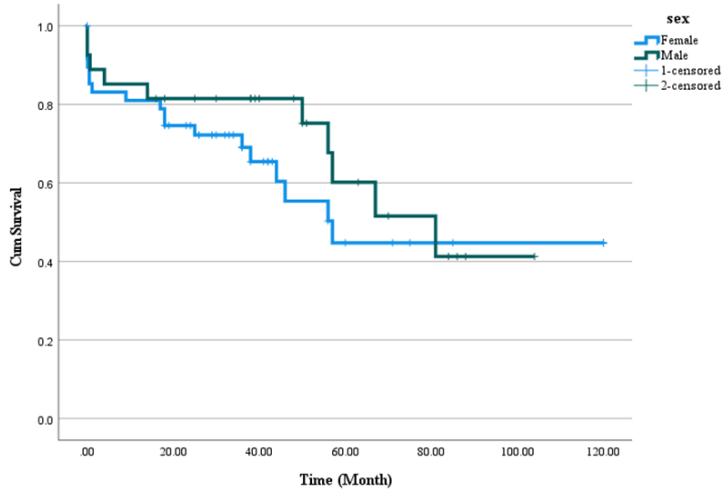

Figure 4. The image presents the Kaplan–Meier graph for comparing survival between males and females.

A Cox regression model was employed to adjust for multiple variables regarding all-cause mortality. Individuals older than 50 years had a hazard ratio of 0.50 (95% CI, 0.19 to 1.34), with a nonsignificant *P*-value (0.17) compared to those aged 50 years and younger. For sex, females exhibited a hazard ratio of 0.73 (95% CI, 0.34 to 1.58) when compared to males, with a nonsignificant *P*-value (0.424). In the rejection category, rejection had a hazard ratio of 2.857 (95% CI, 1.03 to 7.9), with a significant *P*-value (0.043) relative to non-rejected cases. Multivariable analysis indicated that age, sex, and transplant rejection were not statistically significant predictors of all-cause mortality in HTx patients.

Discussion

In this observational retrospective cohort study of 75 HTx patients, we analyzed demographic characteristics, clinical profiles, and outcomes. The mean age of the HTx recipients was 40.7±11.5 years, with 64% being male. The patients

presented with various medical conditions, among which hypertension (12%) and hypothyroidism (8%) were most prevalent. Survival analysis of the cohort revealed a mean survival rate of 71.3 ± 6.5 months. The patients exhibited survival rates of 80% at 1 year, 75% at 2 years, 71% at 3 years, 51% at 5 years, and 42% at 10 years.

The mean age of approximately 40 years in our cohort is consistent with existing literature, which suggests that HTx is primarily performed in middle-aged adults. The optimal age cutoff for HTx recipients remains a topic of debate due to the discrepancy between chronological and physiological age, organ availability, and inconsistent guidelines.[11]

The proportion of female patients in our study (36%) aligns with trends observed in other research.[12-14] A 25-year cohort study by María D García-Cosío et al.[15] involving 6740 HTx operations reported that 20.6% of the procedures were performed on women, with a slight but statistically insignificant increase in the rate of HTx for women over the study period. The observed increase in female patients undergoing HTx may be influenced by evolving lifestyles among women and the expansion of HTx eligibility criteria to encompass all patients in advanced stages of HF, regardless of the underlying cardiac condition.[16, 17]

Our cohort presented with diverse comorbidities, with hypertension (12%) and hypothyroidism (8%) being most common. Dilated cardiomyopathy was the primary cardiomyopathy leading to HTx, accounting for 85.3% of cases. This finding is consistent with existing literature that recognizes dilated cardiomyopathy as the leading cause of HF.[18,19] Although HTx has significantly improved life expectancy and quality of life for patients with refractory HF, it is crucial to recognize the potential risks and complications associated with this treatment option. Some of these factors are directly related to the characteristics of the graft and its interaction with the recipient's immune system, while others are dependent on donor characteristics and the adverse effects of immunosuppressive medications.[20]

PGD is a condition marked by impaired graft function within 24 hours following HTx, typically characterized by a left ventricular ejection fraction below 40%, with or without the need for mechanical circulatory support.[21] The precise pathophysiological mechanisms responsible for PGD development remain unclear. Nevertheless, several proposed mechanisms may contribute to cardiac dysfunction, including processes associated with the donor organ prior to procurement, during transportation, during implantation, and after reperfusion in the recipient. These various pathophysiological injuries ultimately result in the clinical manifestation of transplanted organ dysfunction.[22, 23]

Allograft rejection can be classified as ACR or AMR and may be further categorized as acute or chronic. ACR, the more common form, is primarily mediated by T cells, while AMR involves an immunological response with antibody production by B cells. Although acute allograft rejection remains a substantial contributor to morbidity and mortality following transplantation, advancements in immunosuppressive therapies have led to a decrease in its occurrence and impact on graft survival over time.

Post-transplantation, all patients should receive a combination of 3 types of immunosuppressive medications: glucocorticoids, calcineurin inhibitors (cyclosporine and tacrolimus), and antiproliferative agents.[24]

The first-line treatment for AMR typically consists of high-dose intravenous corticosteroids in combination with plasmapheresis and/or low-dose intravenous immunoglobulin. Rituximab may be added as an adjunctive therapy to reduce the risk of recurrent rejection. For symptomatic ACR, high-dose intravenous corticosteroids are the recommended initial treatment, irrespective of the ISHLT biopsy grade. According to ISHLT guidelines, antithymocyte antibodies should be administered in cases of hemodynamic compromise or if no clinical improvement is observed within 12 to 24 hours following intravenous corticosteroid therapy.[25]

In our study, 15 patients (23.8%) experienced allograft transplant rejection during the post-HTx period, consistent with rejection rates reported in other studies. For instance, Kamath et al. 13 found that 16 out of 72 patients had biopsy-confirmed allograft rejection following HTx.

A key finding of our study was the significant impact of rejection on survival rates. As detailed in the Results section, patients without rejection showed notably higher survival rates (65.9 vs. 23.9; P=0.032), emphasizing the importance of early diagnosis and proactive management of rejection to enhance survival outcomes.

CAV is a unique form of coronary occlusive disease that affects transplanted hearts. Unlike traditional coronary artery disease, CAV is characterized by a diffuse and concentric process. Local and systemic inflammation contribute to endothelial damage, leading to smooth muscle cell proliferation and reduced arterial lumen diameter, ultimately resulting in CAV development.

Several preventive strategies have been proposed to reduce the risk of CAV, including statin therapy, which slows CAV progression and improves survival rates following heart transplantation.[26] Angiotensin-converting enzyme inhibitors may also be beneficial, as they alleviate allograft microvascular endothelial dysfunction, decrease endothelin activation, and have been associated with plaque regression.[27] Calcium channel blockers are another recommended option, as they appear to delay CAV progression.[28] Further, sirolimus, an immunosuppressive agent, has been linked to slower CAV progression.[29]

Infection poses a significant risk for transplant patients, contributing to over 20% of deaths within the first year. Pre-transplant vaccinations against pneumococcal and influenza infections are essential for all patients. Post-surgery, preventive treatment for Pneumocystis carinii, Herpes simplex virus, and oral candidiasis should be initiated in all patients. Moreover, valganciclovir treatment is recommended for Cytomegalovirus-seronegative recipients with Cytomegalovirus-seropositive donors.

The clinical presentation of sepsis can vary among transplant patients, ranging from mild or atypical symptoms to severe refractory shock. Treatment typically involves administering broad-spectrum antibiotics, along with antiviral and antifungal medications, guided by clinical suspicions. In some cases, reducing the dosage of immunosuppressive therapy may be considered, based on the infection's severity.

As many recipients require steroids for months or years following transplantation, stress doses of steroids should be administered during acute infectious periods.[24]

Our survival analysis revealed no significant differences in survival rates between sexes or age groups. Still, a slight trend toward improved survival was observed in individuals over 50 years old, particularly among females. This finding contradicts the observations by Alyaydin et al.,[30] who reported that male sex was associated with a better prognosis. This discrepancy could be attributed to the increasing recognition of heart disease in women, which may result from increased awareness, advancements in medical technologies, and more comprehensive screening programs. These factors contribute to the early diagnosis and management of heart disease in women before it reaches an advanced stage.

Consistent with our study, Kuczaj et al.[31] found that age at the time of HTx was not correlated with survival rates. The overall survival in our study is encouraging, demonstrating that despite the complexities and comorbidities associated with HTx, patients can still achieve a reasonable lifespan following the procedure.

The latest International Society of Heart and Lung Transplantation registry data reports a 1-year survival rate of 84.5% and a 5-year survival rate of 72.5% for HTx patients.[32] These survival rates have significantly improved compared to the 71.9% 1-year survival rate and 62.7% 5-year survival rate observed in the 1980s. Long-term survival rates were higher in select experienced hospitals.[33,34] Furthermore, our approximately 20% 1-year mortality rate chimes with findings from German and Hispanic populations.[35,36]

A notable strength of our study is the long-term follow-up of patients. By monitoring patients over an extended period, we were able to gather valuable information on their outcomes and disease progression. Additionally, our comprehensive data collection method ensured that we obtained a complete dataset from each patient, allowing us to thoroughly analyze various factors and variables that may influence the results.

While this study offers valuable insights into contemporary HTx patients and their outcomes, it

is important to recognize several limitations. The retrospective design of the study and the relatively small sample size may affect the interpretation of the results. In addition, the absence of donor data is another limitation. To strengthen the generalizability of our findings, it is essential to validate them through larger, multi-center prospective cohorts.

Conclusion

Overall, this study provides important insights into the demographic, clinical characteristics, and outcomes of HTx patients. The identification of common comorbidities and underlying causes of HTx can aid clinical decision-making and improve patient care. The observed rate of transplant rejection highlights the importance of appropriate post-transplant management and surveillance. Moreover, findings on survival rates can help establish realistic expectations for patients and their families.

It is essential to acknowledge the limitations of this study, particularly its small sample size, and emphasize the need for further research to validate these findings in larger populations. As we continue to expand our understanding of pre-HTx risk assessment and patient selection, early post-HTx diagnosis, and management of significant complications, we can ultimately enhance the long-term outcomes and quality of life for HTx patients.

Declarations:
Ethical Approval

This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethics committee of Shiraz University of Medical Sciences approved the study (IR.SUMS.MED.REC.1401.212).

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Conflict of Interest

The authors declare that they have no conflict of interest.

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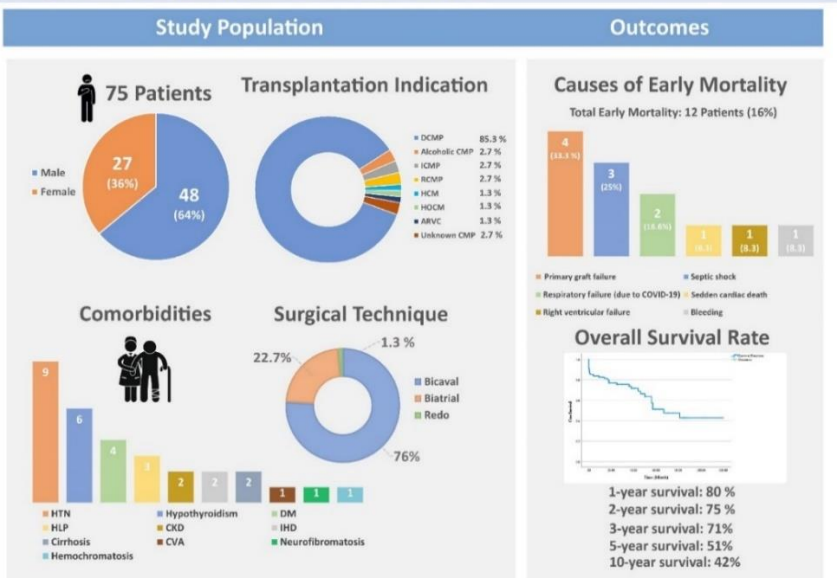
Graphical Abstract A comprehensive retrospective study on heart transplantation: complications, mortality Causes, and survival rates



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