SINGLE-CENTER EXPERIENCE OF HEART TRANSPLANTATION AT THE HEART CENTER OF ASTANA

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Abstract

Background. Chronic heart failure is a major global health issue. As a complication of most cardiovascular diseases, it affects 4% of the population. Heart transplantation is the gold standard in the treatment of patients with end-stage heart failure. Objective of the study was to evaluate early and long-term outcomes of heart transplants performed at the Heart Center University Medical Center (Heart Center) over a 10-year period.

Materials and methods. Cross-sectional study was conducted from 2012 to 2022, 86 orthotopic heart transplants were performed at the Heart Center. The analysis of the obtained results was conducted retrospectively.

Results. From August 2012 to December 2022, 114 patients were on the waiting list for heart transplantation. Of these, 86 (75.4%) patients underwent transplantation; 10 (8.7%) patients were excluded. Among the 86 patients, 49 (56.9%) had previously undergone cardiac surgery. Of these, 42 (48.8%) had a left ventricular assist device implanted earlier, 3 (3.4%) had a fully artificial heart, and 2 (2.5%) were on temporary mechanical support (central veno-arterial Extracorporeal membrane oxygenation). Hospital mortality was 8 (9.3%) recipients. In 2.7% of cases, the cause of death was an acute cerebrovascular accident on the second day post-surgery. Postoperative renal dysfunction was noted in 28 (32.5%) patients. An analysis of all performed heart transplantation cases showed a 30-day survival rate of 94%, a 1-year survival rate of 84.3%, and a 5-year survival rate of 64.7%.

Conclusion. In the hospital period and the first 6 months after heart transplantation, infectious-septic complications were predominant, whereas in later periods, rejection reactions were more common.

Introduction

Chronic heart failure (CHF) is a major global health issue. As a complication of most cardiovascular diseases, it affects 4% of the population. The mortality rate within a year for this group, even with treatment in specialized hospitals, is 10.2%.[1] For patients with refractory CHF, the one-year mortality rate can reach 50%.[2] The number of patients reaching the end stage of CHF is constantly increasing. This is due to both the rise in life expectancy and the improved effectiveness and quality of cardiovascular disease treatments. Heart transplantation (HT) is the gold standard in the treatment of patients with end-stage heart failure.

Modern pharmacotherapy includes the use of beta-blockers, angiotensin-converting enzyme inhibitors, sacubitril/valsartan, dapagliflozin and empagliflozin, and diuretics, including aldosterone receptor antagonists.[3] As a complement to pharmacological therapy, cardiac resynchronization therapy

(CRT) is used.[4] The use of CRT in patients with left ventricular dyssynchrony can prevent or delay the need for heart transplantation or serve as a bridge to transplantation.[5,6] For patients, with severe mitral regurgitation, the mitral clipping technique—transcatheter mitral valve repair—can be applied.[7] Heart transplantation is performed only when all other measures have failed to produce the desired results. Due to the increasing number of patients with end-stage heart failure and the limited availability of donor organs, not everyone in need of a heart transplant can receive one.[8] Survival rates after heart transplantation are significantly higher compared to the natural progression of terminal heart failure. According to the latest data provided by the International Society for Heart and Lung Transplantation, the 1-year survival rate is 84.5% and the 5-year survival rate is 72.5%.[9] These survival rates have significantly improved compared to the 1980s, when the 1-year survival rate was 76.9% and the 5-year survival rate was 62.7%. At the University Hospital Zurich in Switzerland, a 20-year survival rate of 55.6% was reported.[10] Over the past decades, there has been a significant improvement in heart transplantation outcomes, primarily related to increased survival during the first year post-operation. In the longer term, patient survival is significantly influenced by complications such as chronic transplant vasculopathy, malignancies, infectious complications, transplant rejection, and renal failure.[8] Until 2011, surgical treatment for heart failure was virtually unavailable in Kazakhstan. In 2011, our Center performed the first implantation of a left ventricular assist device (LVAD). We anticipated that the implementation of our mechanical circulatory support program would serve as a catalyst for developing the first heart transplantation program in our country. This vision came to fruition when the first heart transplantation was successfully performed in August 2012.

The aim of our study was to evaluate the early and long-term outcomes of heart transplantations performed at the Heart Center of University Medical Center over a period of 10 years.

Materials and Methods

This study was an observational, analytical, cohort, retrospective analysis of 86 orthotopic heart transplantations conducted at the Heart Center of University Medical Center from 2012 to 2022. The analysis of the obtained results was conducted retrospectively.

Ethical approval. The study was conducted in strict accordance with the principles outlined in the Helsinki Declaration. Prior to commencement, the study received approval from the Local Bioethics Committee of the Corporate Foundation "University Medical Center," protocol #3 dated 14/07/2023.

Statistical Analysis. Statistical analyses were performed applying Stata (version 3.6.3). The significance level for all statistical tests was set at 0.05. Data were presented as mean values ± standard deviation (SD) or medians for quantitative variables and percentages for qualitative variables. The 30-day survival rate adds the 1-year survival rate was calculated by Kaplan-Meier survival analysis. The analysis of the main etiological factors in the development of terminal chronic heart failure and the corresponding causal relationship was assessed by calculating the odds ratio (OR).

Results

Recipients From August 2012 to December 2022, there were 114 patients on the heart transplant waiting list. Of these: 86 patients (75.4%) underwent heart transplantation.10 patients (8.7%) who were in the hospital setting died due to progressive heart failure with no possibility of heart transplantation or use of mechanical support as a bridge to transplantation. 4 patients (3.5%) exited the hospital setting for various reasons. One patient achieved disease remission, showing improved hemodynamic parameters and ejection fraction due to tailored therapy. The etiology of terminal heart failure among the recipients was: Dilated cardiomyopathy in 52 patients (60.4%). Ischemic cardiomyopathy in 22 patients (25.8%). Valvular pathology in 7 patients (8.1%).

Other causes (arterial hypertension, hypertrophic cardiomyopathy) in 5 patients (5.8%).

There were 68 male patients (79.5%) and 18 female patients (20.5%). The

average age of recipients was 42 ± 9.4 years (ranging from 17 to 64 years). The average duration of illness at the time of transplantation was 4.33 ± 2.51 years.

By the time of the operation, 60 recipients (69.7%) were classified as NYHA functional class IV of chronic heart failure according to the New York Heart Association (NYHA) classification.

Characteristics of recipients and the etiology of terminal heart failure were detailed in Tables 1 and 2.

Table 1.
Characteristics of recipients

Data	Quantity (percentage)
Men	68 (79.5%)
Women	18 (20.5%)
Age	42 ± 9.4 years
Diabetes	9 (7.7%)
Cardiorenal syndrome	17 (19.7%)
Chronic obstructive pulmonary disease	19 (22.1%)
History of acute cerebrovascular accident	7 (8.1%)
Previously undergone surgery	49 (56.9%)
Left ventricular assist device	42 (48.8%)
Artificial heart for adults *CARMAT*	3 (3.4%)
Extracorporeal membrane oxygenation	2 (2.5%)

Table 2.
Etiology of terminal chronic heart failure

Disease	Men (n-68)	Women (n-18)	OR	95%CI	P value
Dilated cardiomyopathy	38	14	0.316 ᵞ	[0.10;1.21]	0.997
Cardiac ischemia	20	2	3.333 ᵅ	[0.70;15.85]	0.130
Rheumatic disease	3	1	0.785 ᵞ	[0.08;8.03]	0.838
Congenital heart disease	3	-	3.648 ᵅ	[0.18;74.46]	0.400
Hypertensive cardiomyopathy	2	-	1.391 ᵝ	[0.06;30.26]	0.834
Hypertrophic cardiomyopathy	1	1	0.253 ᵞ	[0.02;4.07]	0.341
Ivemark Syndrome	1	-	0.822 ᵞ	[0.03;21.03]	0.906

ᵅ - OR>1 means that the event is directly related and has a chance of occurring in the first group;
ᵝ - OR=1 means that the odds are equal in both groups;
ᵞ - OR<1 means that the event is directly related and has a chance of occurring in the second group

The echocardiographic data were characterized by significantly reduced left ventricular myocardial contractility - left ventricular ejection fraction (LVEF) of 17.6 ± 4.9% (range 8–27%), cardiomegaly (end-systolic left ventricular dimension of 71.3 ± 9.8 mm (range 35–95 mm), end-diastolic left ventricular volume of 273.25 ± 84.2 ml (range 52–524 ml), and high pulmonary hypertension (mean pulmonary artery pressure of 55.6 ± 13.27 mmHg (range 25 to 82 mmHg).

The evaluation included a test assessing the degree of heart failure (6-minute walk test), which averaged 210.08 ± 96.6 meters. 60 recipients (69.7%) were classified as NYHA functional class IV, while the remainders were classified as NYHA functional class III.

According to the results of right heart catheterization, pulmonary vascular resistance was 2.4 ± 1.7 Wood units (ranging from 1.0 to 7.4 Wood units). Peak oxygen consumption (VO2max) was determined using cardiopulmonary exercise testing. The average VO2max value was 11.7 ± 2.73 ml/kg/min.

The evaluation aimed at determining eligibility for heart transplantation also included assessment of a wide range of clinically significant comorbidities. Type 2 diabetes mellitus was present in 9

(7.7%) patients, cardiorenal syndrome in 17 (19.7%), chronic obstructive pulmonary disease (COPD) in 19 (22.1%), prior cerebrovascular accident in 7 (8.1%) recipients, and a frontal lobe cavernoma in 1 (1.2%) patient.

In 49 (56.9%) cases, patients had previously undergone cardiac surgery, including 42 (48.8%) who had received a left ventricular assist device, 3 (3.4%) who had a total artificial heart *CARMAT*, and 2 (2.5%) who were on temporary mechanical support (central veno-arterial extracorporeal membrane oxygenation (ECMO).

Donors. The main causes of death among donors were acute cerebrovascular events - 66.6%, traumatic brain injury - 31%, and isolated brain tumors - 2.1%. The average age of donors was 36 ± 0.7 years (ranging from 20 to 67 years). There were 53 (61.2%) males and 33 (38.7%) females. The most significant limiting factor for performing heart transplantation is the insufficient number of donor organs available. Therefore, we considered donors with expanded criteria, including those older than 50 years and those with significant myocardial hypertrophy (more than 1.4 cm). When selecting donor-recipient pairs, body weight was considered, with a maximum difference of 30% between the donor and recipient.

Surgical Features. Considering various factors such as a significant proportion of patients previously implanted with various long-term mechanical circulatory support systems and the geographical distance between donor hospitals and the transplant center, the ex vivo donor heart conditioning system (OCS) was utilized in 56 (65.11%) cases. Bicaval and biatrial techniques were applied in 57 (66.3%) and 29 (33.7%) cases, respectively. Temporary parameters included: cross-clamp time of 248.4 ± 86.7 minutes (ranging from 108 to 672), anoxia time of the donor heart when using the OCS system was 68.9 ± 15.4 minutes (ranging from 45 to 129), average duration of normothermic perfusion in the Organ Care System apparatus was 275 ± 104 minutes, and the mean operative time was 386.7 ± 129.5 minutes (ranging from 185 to 775). In 32 (37.2%) cases, central veno-arterial ECMO was implanted intraoperatively with an average duration of 7.7 days. Additionally, in 6 cases, superior vena cava reconstruction was performed using a xenopericardial patch. The average length of stay in the intensive care unit was 12.2 ± 8.67 days.

Immunosuppressive Therapy. During heart transplantation, we utilized induction therapy aimed at reducing the risk of acute rejection and delaying the administration of nephrotoxic calcineurin inhibitors. In our case, induction immunosuppression included:

Oral administration of tacrolimus (Prograf) at a dose of 0.1 mg/kg over 3-6 hours before the operation,

Infusion of anti-thymocyte globulin (ATG) at a dose of 1.5 mg/kg. One-third of the ATG dose should be infused before clamping the aorta, and the remainder after unclamping, to be continuously infused for up to 6 hours,

Administration of methylprednisolone 500 mg intravenously over 30 minutes to 1 hour before surgery. In the first three days, ATG is administered every 24 hours for 6 hours under CTD monitoring. During the first day post-transplantation, methylprednisolone 125 mg was administered intravenously every 8 hours (3 times a day). On the second day, methylprednisolone 100 mg was administered intravenously every 8 hours. After extubation, patients received a three-component tablet immunosuppressive therapy based on their blood tacrolimus levels: Prograf (tacrolimus), CellCept (mycophenolic acid) 2000 mg/day, and prednisolone 1 mg/kg orally with a reduction of 5 mg every other day. The immunosuppressive therapy was tailored to minimize the toxic effects of the medications on the recipient. Histological evaluation of biopsies was conducted according to the ISHLT-2005 classification. The average length of stay in the hospital for recipients was 46.4 ± 11.4 days.

Discussion

86 patients were included in outpatient follow-up. Hospital mortality was observed in 8 (9.3%) recipients. The most common cause of early mortality was infectious-septic complications and multiorgan failure (MOF), accounting for 54% of the fatalities. Specifically, the combi-

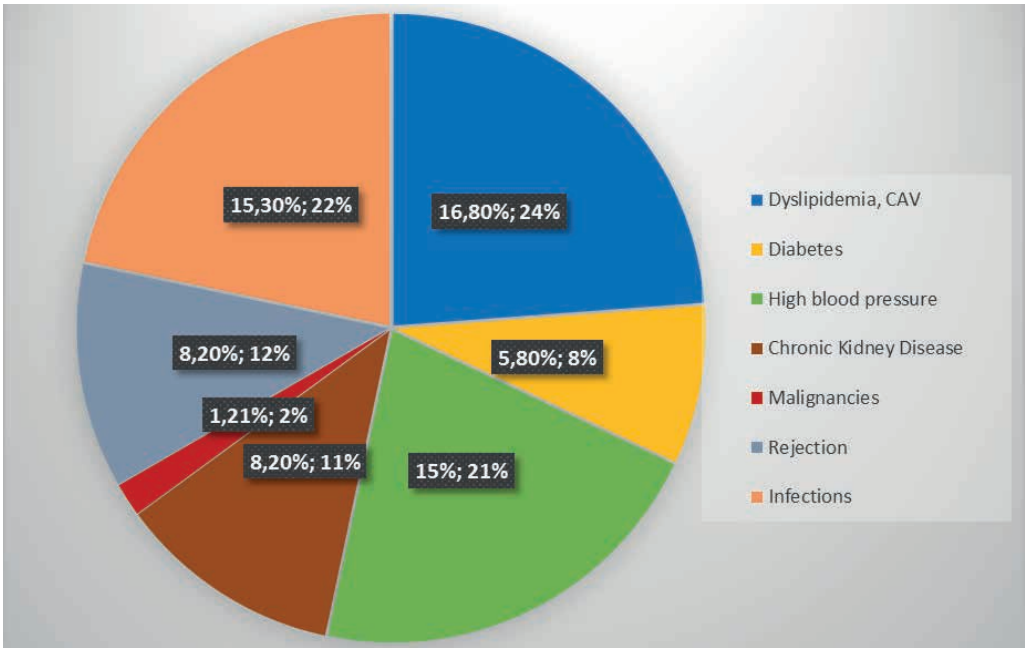
nation of sepsis and MOF led to death in 32%, while 30% succumbed solely due to sepsis. In 2.7% of cases, death occurred due to stroke on the 2nd day.

Postoperative renal dysfunction was noted in 28 (32.5%) patients. Among them, 11 recipients experienced oliguria, progressing to anuria, with significant increases in potassium, urea, and creatinine concentrations, necessitating hemodiafiltration (HDF), with the number of sessions varying from 1 to 13 per patient. In 13 recipients, renal function fully recovered after HDF was performed.

Infectious complications during the hospital period were represented by bacterial pneumonia in 18.3% of cases among patients.

Complications after heart transplantation are presented in Figure 1.

Figure 1.
Frequent complications after transplantation



Acute rejection episodes (ARE) during the hospital period were diagnosed in 4 (4.6%) recipients. To manage acute rejection crises, pulse therapy with methylprednisolone was administered (at a dose of 1000 mg over 4 hours, for 3-5 days). For cytomegalovirus infection prophylaxis, all patients received antiviral medications (valganciclovir 900 mg/day).

Two patients (2.3%) received permanent pacemakers (PPM) due to post-transplant third-degree atrioventricular block and sick sinus syndrome. In the long-term period, 19 recipients deceased. The primary cause of late fatalities was rejection reaction, occurring in 10 (52.6%) cases, with 2 cases in combination with multiorgan failure. One patient passed away after 3 years due to prostate cancer development. One patient died from pulmonary tuberculosis 4 years after HTx. Two patients died from chronic renal failure (CRF) 5 and 6 years after HTx. In 5 cases, the cause of death was COVID-19 after HTx. As is known, long-term survival after HTx mainly depends on coronary artery disease (the main reason), infectious complications, and acute rejection of the transplant after the first year following HTx. In the long term, rejection reactions occurred in 6 cases, accounting for 6.9%, and infectious complications in the form of pneumonia of specific origin (mainly Pneumocystis etiology) were observed in 9 (10.4%) patients. After 5 years post-HT, coronary artery disease of the transplanted heart (CADTH) was verified in 1 patient, with coronary angiography (CAG) showing two-vessel disease of the coronary artery. Mammary-coronary bypass grafting of the anterior interventricular branch and aortocoronary bypass grafting of the obtuse marginal artery were performed. Subsequently, coronary angiography + graftography confirmed adequate functioning of the grafts. Vasculopathy post-HT was noted in 6 (6.9%) cases during scheduled CAG

and intravascular ultrasound (IVUS) examination. In all cases, intensified immunosuppression and lipid control were implemented. Follow-up IVUS examinations showed improvement.

According to various sources, the most significant kidney impairment develops within the first year post-HT and directly correlates with the level of tacrolimus in the blood. In this case, the main preventive measures include frequent monitoring of tacrolimus levels in the blood and maintaining fluid balance. In our case, renal dysfunction developed after HT within the first 6 months in 4 patients, and after this period, in 7 recipients.

An analysis of all performed HT cases was conducted. The 30-day survival rate was 94%, the 1-year survival rate was 84.3%, and the five-year survival rate was 64.7% (Figure 2 and 3).

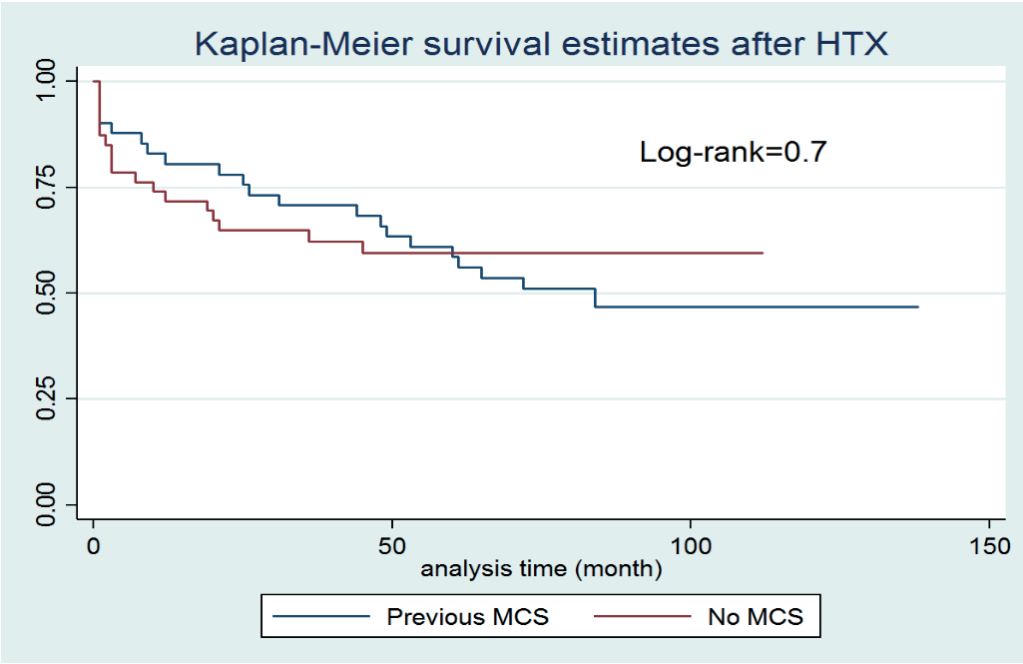


Figure 2.
Survival of patients who were previously on long-term mechanical support and without it: Previous MCS (Mechanical Circulatory Support) - patients with previously implanted long-term mechanical support devices.

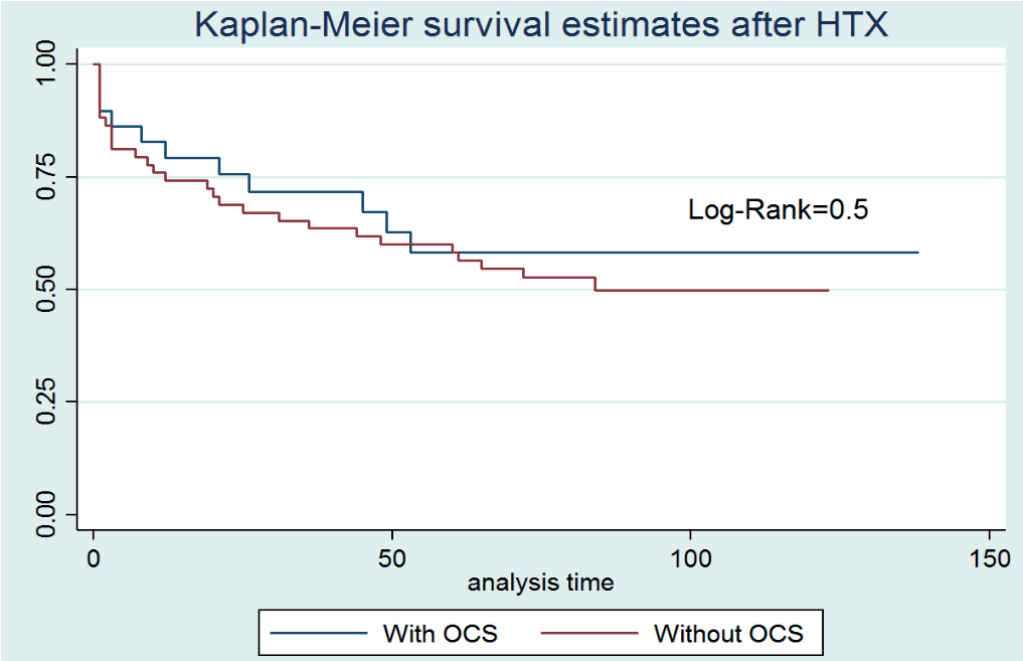


Figure 3.
Patient survival with and without OCS (Organ Care System) for donor heart conditioning.

Limitations: This study has potential limitations. Small sample size may restrict the generalizability of the findings and increase the potential for bias. Moreover, this study describes the experience of one center and we can't gener-

alize the findings of this research. Future research with a larger number of studies and more standardized methodologies would be beneficial to confirm and extend these findings.

What's known? Heart transplantation is the gold standard in the treatment of patients with end-stage heart failure. Survival rates after heart transplantation are significantly higher compared to the natural progression of terminal heart failure.

What's new? During the hospitalization period and the first 6 months post-HT, infectious and septic complications predominated, while rejection reactions were more common in later periods. To reduce complications after HT optimization of immunosuppressive therapy is essential. Implementation of non-invasive diagnostic markers for detecting organ rejection should be integrated into practice.

Conclusion

Based on a 10-year experience, it can be unequivocally stated that heart transplantation is an effective treatment method for patients with severe heart failure. It increases patient survival rates, improves tolerance to physical activity, enhances quality of life, and enables most patients to return to active life. During the hospitalization period and the first 6 months post-HT, infectious and septic complications predominated, while rejection reactions were more common in later periods. To reduce complications after HT in both the hospital and long-term settings, optimization of immunosuppressive therapy is essential. Implementation of non-invasive diagnostic markers for detecting organ rejection should be integrated into practice. The decade-long experience of HT in our center has demonstrated survival rates comparable to those reported by the International Society for Heart and Lung Transplantation.

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Authors' Contributions: YuP, GSh, SP– Collection and preparation of data, primary processing of the material and their verification. AG, ShA, YY– Statistical processing and analysis of the material, writing the text of the article (material and methods, results). SN, GD, AA – Writing the text of the article (introduction, discussion). SN, YuP, AA – Concept, design and control of the research, approval of the final version of the article. All authors approved the final version of the manuscript

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