LONG-TERM SURVIVAL AFTER HEART TRANSPLANTATION: THE EXPERIENCE OF THE REPUBLIC OF SERBIA HEART TRANSPLANTATION PROGRAM

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Summary

Introduction/Aim: Heart transplantation (HTX) is the gold standard for the treatment of patients in symptomatic terminal stadium of heart failure. This study aimed to investigate the long-term results of the HTX and to determine the independent survival predictors after HTX within The Serbian Heart Transplantation program.

Methods: A retrospective observational study was performed. The study included 44 patients that were subjected to heart transplantation from 2013 to 2021 within the The Serbian Heart Transplantation program. All the patients were included in the National heart transplantation waiting list according to the contemporary ISHLT criteria. The study included all the patients subjected to HTX, as well as the ones who received long-term circulatory support preoperatively. The data were obtained from the medical history records and follow-up visits.

Results: The average survival of all patients was 1611.8 days (1306.9 - 1916.7). The median length of patient follow-up was 637.4 days (1-2028 days). Six-year patient survival was 70.5%. Cox's regression analysis determined that independent predictors of worse outcome were as follows: age of the recipient, body mass index of the recipient, previous CVI, preoperative chronic renal insufficiency, pulmonary hypertension, infection in the postoperative course, as well as the need for mechanical circulatory support in the immediate postoperative course.

Conclusion: The Serbian Heart Transplantation program demonstrated the survival rate comparable to the HTX centers worldwide and in ISHLT registry. The independent risk factors should be carefully analyzed for our study population and taken into consideration when planning the procedure.

Keywords: heart transplantation, survival, independent predictors
INTRODUCTION

Terminal stage of heart failure is defined by repetitive hospitalizations due to decompensation, progressive worsening of symptoms, alteration of myocardial function and augmentation of heart cavities despite maximal medical and interventional therapy. (1, 2) This group of patients is classified in NYHA III and IV class, as well as stage D according to the classification of the American Heart Association. (3)

Heart transplantation (HTX) is the gold standard for the treatment of patients in symptomatic terminal stadium of heart failure. Despite the use of optimal medical therapy, resynchronization therapy, alternative surgical or interventional methods, patients with terminal heart failure should be considered as candidates for HTX. (4) Survival of these patients without HTX is 50% in 1-2 years. Primary indications for HTX in adults are non-ischemic cardiomyopathy (53%) and ischemic cardiomyopathy (38%), acquired valvular heart disease (3%) and retransplantation (3%). (5) Candidates are included in the National list of transplantation candidates after performing a wide range of diagnostic procedures. The most important diagnostic procedures for listing heart transplant candidates are cardiopulmonary exercise test and right heart catheterization. (6)

The first heart transplant in the Republic of Serbia was performed in 1989 at the Institute for cardiovascular diseases “Sremska Kamenica”, followed by four heart transplantations at the Institute for cardiovascular diseases “Dedinje” in 1990s. After the period of silence the program was re instituted in the year 2013. Since then until December 2022, 44 heart transplantations were performed and in more than 120 patients short and long-term mechanical circulatory support were implanted within the National transplantation program at the University Clinical Center of Serbia.

This study aimed to investigate the long-term results of HTX and to determine the independent survival predictors after HTX within the Serbian heart transplantation program.

MATERIALS AND METHODS

Study design

A retrospective observational study was conducted. The study included 44 patients who were subjected to heart transplantation form 2013 to 2021 in the Department for cardiac surgery, University Clinical Center of Serbia.

Indication for the HTX was given by heart failure. The team consisted of: cardiac surgeons, transplantation cardiologists, anesthesiologists, interventional cardiologists, echocardiographers and the other specialists if needed. All patients were included in the National heart transplantation waiting list according to the contemporary ISHLT criteria. (4) The study included all the patients subjected to HTX, as well as the ones who received long-term circulatory support preoperatively.

Surgical technique

All surgeries were done by different transplantation and explantation teams. The donor allocation process was led by the coordinator from the University Clinical Center of Serbia alongside the coordinators from local donor hospitals. Organs were explanted either within the University Clinical Center of Serbia or at local donor hospitals (Medical Military Academy, University Clinical Center of Nis, University Clinical Center of Vojvodina and University Clinical Center of Kragujevac).

After the potential donor was declared brain dead, he/she was subjected to the necessary diagnostic procedures according to the national transplantation protocol in order to be declared as suitable for organ procurement by a network of coordinators. After the donor was declared suitable and the approval was given, the explantation team was directed to the donor hospital. For the donors who had a high level of alosenztisation (PRA>20%) the result of cross match was obtained before the organ procurement. After the arrival in the donor hospital, the final assessment of the organ was done by the head of the organ harvesting team and the head of the transplantation team was informed and made the final decision regarding the beginning of the procedure. The donor heart was arrested and rinsed by the Custodiol HTK solution and transported in three sterile bags submerged in the same solution stored in the medical refrigerator. All implantation procedures were done with the use of extracorporeal circulation, using bicalvial or biatrial technique according to the surgeon preference. After surgery, graft rejection was monitored with regular endomyocardial biopsies, alongside coronary angiography and intravascular ultrasound according to the local protocol.

Data procurement

Data were obtained from the medical history records and follow-up visits. Demographic characteristics, comorbidities, hemodynamic measurements, operative characteristics, postoperative complications and inhospital mortality. Mortality and organ rejection in the follow-up period were registered from the electronic database and from documentation of follow-up visits. Variables were defined according to the variable definitions from ISHLT guidelines, Euroscore and STS-score definitions.

Statistical analyses

Descriptive statistics was calculated for the baseline demographic and clinical features and treatment outcomes.
Graphical and mathematical methods tested the normality of distribution. As appropriate, continuous variables were presented as means with standard deviations or medians with 25th-75th percentiles. Categorical variables were presented as numbers and percentages. Differences between groups were analysed using Student’s t-test for continuous variables (or the Mann-Whitney test) and the Pearson chi-squared test for categorical variables. Survival analysis was performed using the Kaplan-Meier method, and the groups were compared using the log-rank test. In addition, Kaplan-Meier survival curves were truncated at a timepoint in follow-up, when at least 10% of patients were still at risk, to avoid visual misinterpretation.(7) The significance level was set at 0.05, and all testing was two-sided. Statistical analysis was performed using the IBM SPSS Statistics for Windows, version 21.0. (Armonk, NY, USA) package.

RESULTS

Patient characteristics

Forty four patients who underwent heart transplantation were included in the study. The average age of transplanted patients was 46 years (16-64 years). Out of the total number of patients, 39 (88.6%) were male, while 5 (12.4%) transplanted patients were female. Most patients had dilated cardiomyopathy (63.6%) and ischemic cardiomyopathy (29.5%). The majority of patients had A blood group whereas 40.9% had O blood group. The average donor age was 41.6 years, while the youngest donor was 15 years old, and the oldest was 66 years old. Male donors made up for 65.9%, 43.2% of them had A blood group while 40.9% had O blood group. The average duration of extracorporeal circulation was 161.6 ± 51.8 minutes. Biatrial transplantation technique was performed in 33 (78.6%) patients, while bicaval technique was performed in 9 (21.4%) patients.

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<th>Table 1. Preoperative characteristics of patients</th>
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Values are presented as n (%). CKD - chronic kidney disease, COPD - chronic obstructive pulmonary disease, DM - diabetes mellitus, HLP - hyperlipidaemia, HTA - arterial hypertension, PVD – peripheral vascular disease, BMI – body mass index, LVAD – left ventricular assist device, ICD- intracardial defibrillator.

Survival and organ rejection

The average survival of all patients was 1611.8 days (1306.9-1916.7). The median length of patient follow-up was 637.4 days (1-2028 days). Six-year patient survival was 70.5%. By comparing survival in patients, no statistically significant difference was found between male and female patients (log-rank p=0.734). Also, no statistically significant difference was found in the survival of patients who underwent a previous cardiac surgery (log-rank p=0.085). Graph 1 shows the survival analysis of patients who had mechanical circulatory support previously implanted as a bridge to transplantation. No statistically significant difference in survival was found in this group of patients (log-rank p=0.228). Patients with preoperatively diagnosed pulmonary hypertension had statistically significantly worse survival than other patients (log-rank p=0.023, Graph 2).

The analysis of survival in relation to the donor’s age found no statistically significant difference between the donors older than 45 years and those younger than 45 years (log-rank p=0.641). Besides, no statistically significant difference in survival was found between the patients operated with biastral technique and those operated with bicaval technique (log-rank p=0.239). Cox’s regression analysis determined that the following were independent predictors of worse outcome: recipient’s age, recipient’s body mass index, previous CVI, preoperative chronic renal insufficiency, pulmonary hypertension, infection in the postoperative course, as well as the need for mechanical circulatory support in the immediate postoperative course (ECMO, IABP) (Table 2).

In the postoperative follow-up, 13 (29.5%) patients developed some degree of organ rejection. Among the patients who developed rejection, 30.7% developed grade
1, 76.9% developed grade II, and only one patient developed grade III. There was no statistically significant difference in the survival of patients who developed some degree of graft rejection and those who did not (log-rank p=0.453). Cox’s regression analysis determined that the following were independent predictors of rejection: recipient’s age, recipient’s body mass index, preoperative allosensitization PRA>20%, as well as ischemic time (Table 3). Graft vasculopathy (CAV) developed in 4 (9.1%) patients. Patients who developed CAV did not have statistically significantly worse survival than other patients (log-rank p=0.213). Preoperative diagnosis of diabetes mellitus was determined as an independent predictor for the development of CAV, with a hazard ratio of 1.006 (CI 95% : 1.001- 1.012; P=0.018). In the postoperative follow-up period, the occurrence of infections requiring hospitalization was recorded in 3 (6.8%) patients. During the follow-up period, 9 (20.5%) patients developed renal insufficiency, while one patient developed malignancy.
As no therapeutic option has been found yet to reduce the mortality of patients in the terminal stage of heart failure, heart transplantation remains the gold standard in their treatment. However, 5,000-6,000 heart transplants are performed annually worldwide, although the need is much greater, due to the lack of donors this remains an option for a limited number of patients. 

Worldwide, over 50% of patients who are candidates for heart transplantation have been diagnosed with non-ischemic cardiomyopathy, 37% have been diagnosed with ischemic cardiomyopathy, while only 1% of them have been diagnosed with restrictive cardiomyopathy. In our study population, 63.6% had nonischemic cardiomyopathy, 29.5% had ischemic cardiomyopathy, while only 1.5% had restrictive cardiomyopathy. Survival analysis did not establish a difference between these groups of patients after a long-term follow-up period. The average age of transplant patients in the ISHLT report was 54 years. There was also a trend of an increase in the number of transplanted patients over 60 years of age, and a lower average age of patients can be explained by the fact that according to the protocol of our transplantation program, the upper limit for transplant candidates has been set at 65 years.

The entry into increasingly widespread clinical use of devices for long-term mechanical circulatory support as a bridge to heart transplantation has led to the fact that, according to the ISHLT registry, 36% of patients had this type of mechanical support implanted preoperatively. In our population, mechanical circulatory support was preoperatively implanted in 13.6% of patients. Survival analysis showed that patients with a preoperatively implanted LVAD had worse survival, while it was not identified as an independent risk factor.

Advances in immunosuppressive therapy led to the introduction of heart transplantation into clinical practice in the 1980s, and they are the main reason for the development of this method. The greatest risk of death is in the first year upon transplantation, when immunosuppressive therapy is most intensive. The greatest progress in the field of heart transplantation was made precisely in the reduction of mortality in the first postoperative year. In the largest number of world centers, mortality in the first year is around 10%. The most common causes of death in the first year are acute graft rejection, infection, CAV, malignancy, and renal failure. In our study population, infection was registered as an independent predictor of mortality after transplantation. After the first year, the median survival is 13 years. After 5 years, survival is 70-75%, which is confirmed by the results of our study, where six-year survival rate of 70.5% was recorded.

Elderly patients showed that recipient age was an independent predictor of both early and late post-transplant mortality. Patients in their 40s and mid-50s have the lowest risk. Patients younger than 40 years of age have a higher risk of worse outcome probably due to a stronger immune response and a higher risk of developing graft rejection. On the other hand, patients older than 60 years of age also have a higher risk of worse outcome due to a greater chance of developing malignancy and infection because of weakened immune system, as well as a higher frequency of comorbidities before transplantation. Also, in our study the age of the recipient was an independent predictor of mortality with a ratio of 1.077 (95% (36): 1.012-1.147; P=0.019).

Pulmonary hypertension proved to be one of the most important independent predictors of worse outcome, mostly due to the inability of the donor heart to cope with the increased afterload to which it had not been previously conditioned. Therefore, fixed pulmonary hypertension with pulmonary artery systolic pressure > 60 mmHg, TPG > 15 mmHg and PVR > 6 WU is an absolute contraindication for heart transplantation. In our population, preoperative pulmonary hypertension was identified as an independent predictor of mortality with a hazard ratio of 1.006 (95% (36): 1.001-1.012; P=0.018).

The incidence of graft rejection is highest in the first few months upon transplantation, while hyperacute rejection by preformed antibodies is certainly the most fatal complication in the immediate postoperative course. In our study, there was no hyperacute graft rejection.
which can be explained by the fact that in preoperatively verified allosensitive patients did not initiate procedures prior to obtaining crossmatch analysis. Previous allosensitization proved to be an independent predictor of rejection and increased postoperative mortality. A PRA test result >20% was shown to be a non-significant predictor of organ rejection with worse outcome after heart transplantation. In our study, allosensitization with PRA values >20% proved to be an independent predictor of postoperative rejection with a hazard ratio of 0.149 (95% (36): 0.031-0.724; P=0.018). The incidence of some degree of organ rejection varies between 15-36%, depending on the centre, and rejection was shown to be the cause of death in 9% of cases after the first post transplantation year.(13)

In our study, 13 (29.5%) patients developed some degree of organ rejection. Among the patients who developed rejection, 30.7% developed grade I, 76.9% developed grade 2, and only one patient developed grade 3. There was no statistically significant difference in the survival of patients who developed some degree of graft rejection and those who did not. As independent predictors of organ rejection, ischemic time, recipient’s BMI, and recipient’s age were singled out.

Graft vasculopathy is a form of coronary graft disease characterized by diffuse intimal proliferation. It is characterized by angiographic diffuse narrowing of the epicardial coronary arteries, with a decrease in the lumen of the distal segments and occlusion of small branches. Five years after heart transplantation, about 25% of patients develop some degree of CAV, while after 10 years, about 50% of patients develop some form of this entity. In our study, 9.1% of patients had CAV after a five-year follow-up period, and statistical analysis did not prove to be an independent predictor of mortality. In this population, diabetes mellitus proved to be an independent predictor of the development of CAV, which supports the fact that hypertension as a consequence of this disease can be the cause of CAV. The lower percentage of CAV in our population can be explained by the very low representation of marginal donors in our transplant program.(14)

On average, heart transplant patients can be expected to live 10 years, although many of them live much longer. Return to work, physical activity, pregnancy and good quality of life are today a reality for these patients. Graft dysfunction, CAV and the occurrence of malignancy are the main problems that limit long-term survival. New methods of immunosuppression, as well as monitoring the state of the immune system and better understanding of the pathophysiology of CAV will enable even greater long-term survival after heart transplantation.

CONCLUSION

The analysis of mortality within the group of patients who underwent a heart transplant as a part of the transplant program in the Republic of Serbia determined that six-year survival rate was 70.5%. Independent predictors of outcome after a long-term follow-up period were as follows: recipient’s age, recipient’s body mass index, previous CVI, preoperative chronic renal insufficiency, pulmonary hypertension, infection in the postoperative course, as well as the need for mechanical circulatory support in the immediate postoperative course (ECMO, IABP). Independent predictors of organ rejection after heart transplantation in our study population were as follows: recipient’s age, recipient’s body mass index, preoperative allosensitization PRA>20%, as well as ischemic time.

REFERENCES

UDALJENI REZULTATI NAKON TRANSPLANTACIJE SRCA: ISKUSTVO TRANSPLANTACIONOG PROGRAMA REPUBLIKE SRBIJE

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Sažetak

Uvod/ciljevi: Transplantacija srca predstavlja zlatni standard za lečenje pacijenata u simptomatskom terminalnom stadijumu srčane insuficijencije. Cilj studije bio je da ispita dugoročne rezultate posle transplantacije srca i da ispita nezavisne prediktore preživljavanja nakon operacije u okviru transplantacionog programa Republike Srbije.


Zaključak: Program transplantacije srca u Republici Srbiji pokazao je stopu preživljavanja koja je komparabilna sa centrima širom sveta u ISHLT registru. Nezavisne faktore rizika treba pažljivo analizirati u okviru naše populacije i uzeti ih u obzir prilikom planiranja procedure.

Ključne reči: transplantacija srca, preživljavanje, faktori rizika

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