Patient-Related Preoperative Clinical Factors Influencing 1-Year Survival After Orthotopic Heart Transplantation – A Single Center Polish Experience

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Background: End-stage heart failure is a growing problem in Poland. Orthotopic heart transplantation remains the best treatment option. Although increasing, the number of heart transplants is disproportionately low compared with patient need. Therefore, it is crucial to identify factors contributing to improvement of heart transplantation outcomes. To find factors providing best survival and optimal recipient selection, we analyzed pretransplant patient-related clinical factors.

Material/Methods: Between May 2015 and May 2020, we performed 258 cardiac transplants at our institution. We reviewed possible patient-related clinical factors affecting the 1-year survival of our patients and analyzed factors related to survival. Mean age at transplant was 53.5 (±11.8) years; 22.9% of patients were women. Preoperative factors were analyzed using univariable and multivariable analyses.

Results: In this cohort, 31.8% were diabetic, 43% had ischemic etiology of heart failure, and 15.3% had reversible pulmonary hypertension. Mechanical circulatory support was used in 22%. During 1-year observation, 64 (24.8%) patients died. Univariable analysis showed ischemic etiology (hazard ratio [HR]=2.05, CI=1.227-3.429; P=0.01) and left ventricular assist device were associated with 1-year risk of death (HR=1.953, CI=1.090-3.499; P=0.02). Urgent listing trended toward worsened prognosis (HR=1.509, CI=0.95-2.397; P=0.08). Multivariable analysis showed ischemic etiology (HR=1.81, CI=1.075-3.059; P=0.03), total mechanical circulatory support (HR=1.93, CI=1.080-3.437; P=0.03), decreased eGFR (HR=0.987, CI=0.975-0.998; P=0.03), and protein level (HR=0.97, CI=0.951-0.998; P=0.04) were independently associated with worse 1-year survival after transplantation.

Conclusions: Ischemic etiology and mechanical circulatory support were the most important preoperative factors. Malnutrition and renal failure were additional risk factors. Age alone did not influence 1-year survival.

Keywords: Comorbidity • Heart Failure • Heart Transplantation • Prognosis

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Background

Heart failure in developed countries is still an ongoing pandemic. According to the current guidelines, orthotopic heart transplantation (OHT) is the treatment of choice in end-stage heart failure that is refractory to medical therapy [1]. However, this procedure is performed relatively rarely in comparison to the real needs of patients. According to the current data from the Polish Transplant Coordinating Center (Poltransplant) [2], 145 patients with end-stage heart failure were transplanted in 2019, whereas at the same time, 462 patients were listed for transplantation.

To assist in the development of a system to improve the use of scarce donor resources, we attempted to identify the major preoperative factors that might identify heart transplant recipients who would were most likely to survive the first year after transplantation in our institution. As this group has not been well studied, we felt that previously published data based on larger registries may not be representative of the Polish population. Another important issue is related to the discussion between the transplant team and a potential recipient when transplantation-related risk is unacceptably high and postoperative survival is poor.

Given that mortality is highest within the first year after transplantation, we tried to find the most significant pretransplant clinical factors influencing 1-year survival. There are some data related to different patient populations. However, they cannot be fully compared with those related to the Polish population.

To optimize the risk-benefit ratio in transplant recipients, we performed a clinical analysis of heart transplant recipients to assess recipient-related factors influencing 1-year survival after OHT.

Material and Methods

This was a retrospective single-center study assessing 1-year survival after OHT. All consecutive adult heart transplant recipients (258 patients) transplanted between May 2015 and May 2020 were enrolled in the study. Analyzed were recipient-related factors known at the time of patient listing that were available from the transplant questionnaire. The mean age at the time of transplantation was 53.5 (±11.8) years (range: 21-72, median age: 56.5 years), and 59 patients (22.9%) were women. Mechanical circulatory support included a preoperatively implanted left ventricular assist device in 40 patients (15.7%), extracorporeal membrane oxygenation (ECMO) in 4 patients (1.6%), intra-aortic balloon pump (IABP) in 22 patients (8.7%), or a combination of different devices (eg, IABP and ECMO in the same patient).

Baseline characteristics of the transplanted population are summarized in **Table 1**.

Sildenafil was given to all patients with reversible pulmonary hypertension, defined as pulmonary vascular resistance >2.5 Wood units, with a concomitant decline of <2.5 Wood units (sodium nitroprusside vasodilator test) without a decrease in systemic systolic blood pressure <85 mmHg.

The bicaval method was used in all patients. The mean ischemic time was 164±51 min. Donor hearts were eligible for transplantation based on the echocardiographic examination and hemodynamic measurements. Donor heart harvesting, preservation, and transportation were performed in the same manner by an experienced transplantation team. All patients received a similar immunosuppression regimen, including tacrolimus, mycophenolate mofetil, and steroids. The dose was gradually lowered and weaned within the first year. After transplantation, all patients were additionally given acetylsalicylic acid in small doses and statins if not contraindicated. The biopsy protocol was the same in the entire group of patients.

We analyzed preoperative recipient-related clinical factors to identify the patient-related prognostic factors that had the greatest influence on 1-year survival.

The retrospective study was performed in accordance with the Declaration of Helsinki. The Bioethics Committee of the Medical University of Silesia waived the need for separate permission to keep the retrospective transplant database and to perform this analysis because of anonymized data (decision no. PCM/CMN/0022/KB/185/21). Informed consent was not necessary because the data analysis did not meet the criteria of a medical experiment.

Statistical Analysis

Categorical variables are presented as counts and percentages. Continuous variables are presented as the mean and standard deviation for normally distributed data or the median with lower and upper quartile. The Shapiro-Wilk test was used to verify the normal distribution of data. The chi-squared test was used to compare categorical variables, whereas the t test or Mann-Whitney U test was utilized to compare continuous variables, as appropriate. Cox proportional hazards regression was used to determine the predictors of 1-year mortality. Variables with $P<0.3$ in the univariable Cox proportional hazards regression were included in the multivariable model. The backward selection method was used to retain only statistically significant variables in the multivariable model. In the case of quantitative variables, hazard ratio (HR) was calculated for the difference by 1 unit. A P value <0.05 was considered statistically significant. SAS software version 9.4 (SAS Institute Inc., Gary, NC, USA) was used for all calculations.

Table 1. Clinical baseline characteristics of patients and factors associated with 1-year survival (univariable analysis).

Clinical factor	Total (n=258)		Hazard ratio, (range), confidence interval: 95%	P
Sex (female)	59	(22.9%)	1.692, (0.862-3.323)	0.13
Age, years	53.5	(±11.8)	1.023, (1.000-1.046)	0.05
Body weight, kg	73.72	(±14.5)	1.028, (1.010-1.047)	0.06
Height, m	1.72	(±0.09)	4.551, (0.203-102.294)	0.34
BMI, kg/m^2	24.5	(±3.9)	1.106, (1.036-1.181)	0.28
Urgent list	113	(53.6%)	1.509, (0.95-2.397)	0.08
Diabetes	81	(31.8%)	1.403, (0.827-2.382)	0.21
Impaired glucose tolerance	18	(7%)	1.061, (0.377-2.990)	0.91
COPD	17	(6.7%)	0.196, (0.027-1.415)	0.11
Stroke/TIA	43	(18.6%)	1.013, (0.551-1.862)	0.97
Ischemic etiology	99	(43%)	2.051, (1.227-3.429)	0.01
Reversible pulmonary hypertension	35	(15.3%)	0.907, (0.407-2.017)	0.81
Mechanical circulatory support	56	(21.96%)	1.474, (0.842-2.580)	0.17
LVAD	40	(15.7%)	1.953, (1.090-3.499)	0.02
ECMO	4	(1.6%)	3.502, (0.855-14.34)	0.08
IABP	22	(8.7%)	0.164, (0.023-1.186)	0.07
Serum creatinine, mmol/L	116.97	(±46.4)	1.004, (1.000-1.008)	0.09
GFR <60 mL/min/1.73 m^2	82	(35.6%)	0.989, (0.977-1.000)	0.06
PVR (Wood units)	2.04	(±1.17)	1.013, (0.803-1.277)	0.92
Aspartate transaminase, U/L	64.72	(±294)	0.998, (0.994-1.003)	0.44
Alanine aminotransferase, U/L	62.8	(±240.5)	0.998, (0.993-1.002)	0.32
Bilirubin, mmol/L	17.8	(±18.4)	1.005, (0.993-1.017)	0.41
Albumin level, g/L	42	(±6.6)	0.978, (0.943-1.015)	0.25
Protein level, g/L	70.2	(±9.98)	0.982, (0.960-1.006)	0.13

A P value <0.05 was considered statistically significant. BMI – body mass index; eGFR – estimated glomerular filtration rate; COPD – chronic obstructive pulmonary disease; LVAD – left ventricular assist device; ECMO – extracorporeal membrane oxygenation; IAB – intraaortic balloon pump; TIA – transient ischemic attack; PVR – pulmonary vascular resistance.

Results

During the 1-year observation period, 64 (24.8%) patients died. In the univariable analysis, ischemic etiology (P=0.01) and left ventricular assist device support (P=0.02) were significantly correlated with 1-year mortality risk. The analyzed pretransplant conditions and the outcomes of univariable analysis are presented in **Table 1**.

The multivariable analysis showed that ischemic etiology (HR=1.813, CI=1.075-3.059; P=0.03), all types of preoperative mechanical circulatory support (HR=1.927, CI=1.080-3.437; P=0.03), low protein level (HR=0.974, CI=0.951-0.998; P=0.03), and decreased eGFR calculated by the Modification of Diet in Renal Disease Study equation (HR=0.987, CI=0.975-0.998; P=0.03) were related to a higher mortality rate during 1-year follow-up (**Table 2**).

Table 2. Multivariable analysis.

Clinical factor	Hazard ratio	95% Confidence interval (range)	P
Ischemic etiology	1.813	1.075-3.059	0.03
eGFR	0.987	0.975-0.998	0.03
Protein level	0.974	0.951-0.998	0.03
Mechanical circulatory support (total)	1.927	1.080-3.437	0.03

eGFR – estimated glomerular filtration.

Univariable analysis demonstrated a nonsignificant P value for all types of mechanical circulatory support (P=0.17), whereas in multivariable analysis, considering the influence of independent variables, the P value reached significance (P=0.03) (**Tables 1, 2**).

Discussion

Many factors, such as donor heart ischemic time, perioperative conditions (prolonged bleeding, need for high inotropic support, delayed return of graft function), and donor status, influence patient and graft survival after transplantation [3]. At the time of patients' listing, these factors are unpredictable or can be only partially modified. On the other hand, recipient listing is a multi-stage, complex process requiring a detailed interdisciplinary approach and decision making, and we claim that some factors available at this stage may determine the course after OHT.

To find patients with the best survival after OHT, we analyzed the recipient population from a single transplant center for 5 years. We tried to concentrate on recipient clinical factors that most affected 1-year survival and could influence the decisions of transplant teams regarding the choice of the most optimal treatment for a particular patient.

A large amount of clinical data is available from the International Thoracic Organ Transplant (TTX) Registry [4]. However, the recipient population from different transplantation centers worldwide may not be fully comparable to our recipient population. Our center, similar to other Polish heart transplant centers, did not participate in the TTX Registry, and therefore the TTX Registry may have different findings. For example, in our population, the mean age at transplant was 53.5 (±11.8) years, whereas in Leiden [5], the mean age was 49 (±14) years; the difference may not be significant but shows a trend toward younger recipients. Furthermore, in the Brazilian population, the cause of transplantation was related to Chagas disease in 17.2% of patients [6], in contrast to our population, which had no cases of Chagas disease. Differences are also related to donors, organ procurement, immunosuppression, and periprocedural strategies [7].

When compared with the International Society for Heart and Lung Transplantation (ISHLT) population between 2010 and 2018, our cohort included slightly older recipients (median age 56.5 vs 55 years in the ISHLT registry), ischemic etiology was more often the indication for transplantation (43% vs 32%), and diabetes was a more prevalent comorbidity in our population (31.8%), whereas it was diagnosed in the European population in only 13.6% of cases according to the ISHLT registry [8]. However, aside from diabetes, these differences may not be statistically significant.

However, compared with that of the ISHLT registry, the 1-year mortality in our study seems to be surprisingly high. Part of the explanation may be that the statistical data available in this large registry comprise different populations, mostly outside of Europe. When compared with a German or Hispanic population, which are also included in this registry, the current 1-year mortality rate is rather similar, equally around 20% [9,10].

Based on the multivariable model, in our population, we showed adverse effects of decreased eGFR calculated by the Modification of Diet in Renal Disease Study equation on 1-year survival. This finding is comparable to the observations of other studies [11-13]. Similarly, in the present study, we found that patients with ischemic etiology of heart failure had less favorable survival, which is in line with the results of other studies. Coronary artery disease is a part of the generalized atherosclerotic processes, and patients with coronary artery disease are more prone to vascular complications, such as ischemic stroke.

Of note, neither diabetes nor age at the time of transplant was correlated with survival in our group of patients. However, we suppose that the influence of these factors could reach statistical significance in the long-term follow-up. A similar observation was made in terms of pulmonary vascular resistance in our patients. According to the current guidelines [14], we did not perform transplants in patients with irreversible pulmonary hypertension. However, patients with reversible pulmonary hypertension type 2 were given sildenafil orally if it was not contraindicated. It may also be a result of appropriate patient selection (the sodium nitroprusside vasoreactivity test was performed in the whole group of patients as the part of qualification) and adherence to the ISHLT guidelines.

The ISHLT registry showed some differences between patients with higher and lower body mass indexes (BMI). In our study, univariable or multivariable analyses showed no influence of BMI on survival, which may have been related to the relatively small number of patients.

We observed that poor nutritional status, defined by protein concentration and not by BMI, was a factor for a poorer prognosis. In our cohort of patients, a higher protein level, but not albumin, was correlated with better survival. We think that frequent supplementation of an intravenous albumin preparation in cases of hypoalbuminemia may disturb this correlation that is observed in available studies [15]. A low protein level in patients is associated with poorer postoperative wound healing, poor rehabilitation, and decreased immune defense against infections [14]. Therefore, it seems reasonable to try to improve patient nutritional status before transplantation.

Worsened survival of OHT patients after previous left ventricular assist device implantation should be interpreted with caution. The long-term observation of patients with a left ventricular assist device is ongoing, and it cannot be excluded that transplantation might be the best long-term option for this group of patients, despite an elevated risk of complications as compared with that in other transplant patients.

Furthermore, in univariable analysis, mechanical circulatory support (in total) did not influence survival, whereas in multivariable analysis, the relationship reached statistical significance. In univariable analysis, particular types of mechanical circulatory support influenced survival in opposite directions (IABP improved survival), which may suggest that the whole group of circulatory support is inhomogeneous and the group of short-term circulatory support has a different clinical profile from the long-term group. Multivariable analysis considering the differences between these 2 groups showed less favorable outcomes in the group with mechanical circulatory support. This is in line with speculations, as this group of patients is the most seriously ill subgroup of patients awaiting transplantation.

Studies have shown that the 2-year survival after left ventricular assist device support was as good as after OHT, which suggests that destination therapy may be a better option than subsequent OHT in some patients with multimorbidity (limiting survival) after long-term mechanical circulatory support implantation [16].

In some cases, the risk-benefit ratio may be unacceptably high, and conservative treatment would be the best option for some patients and those listed for transplantation with a more favorable clinical profile. If the decision to transplant is made, the patient and the transplant team should be aware of the high risk of adverse events.

Further directions may be implementing nutritional programs in patients with advanced heart failure listed for heart transplantation. Notable is also the visible discrepancy in number and percentage of transplanted women and men. Also, the overt difference between 1-year mortality in European countries and the whole TTx registry needs further explanation.

Conclusions

Ischemic etiology and preoperative demand for mechanical circulatory support were the most important preoperative factors worsening 1-year survival rates in heart transplant recipients in the single-center Polish population. Malnutrition and renal failure were additional risk factors. Age alone did not influence 1-year survival. Our results show differences between the ISHLT registry population and our cohort. Data and conclusions from large registries covering different populations should be interpreted with caution. Long-term studies are needed to show the potential benefit of long-term mechanical circulatory support over subsequent transplantation in multimorbid patients.

We did not analyze death cases because they were influenced by many factors. Due to the relatively small number of patients, the analysis of particular death cases and endpoints were not performed. We also did not concentrate on perioperative and donor-related risk factors because they are unpredictable at the time of patients' listing. A multicenter analysis of Polish recipients could more accurately answer some of these questions.

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