Outcome of Heart Transplant Candidates Based on a High Volume Heart Transplant Center Experience in Iran

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ABSTRACT

Background: The waiting list for heart transplants is a valuable data registry that would offer very useful information on the characteristics of patients who have various outcomes while waiting in the list.

Objective: The purpose of this study was to look at the prognosis of those waiting for heart transplants as well as the factors that increase mortality.

Methods: Advanced heart failure patients' demographic, clinical, hemodynamic, and echocardiographic results, as well as their prognosis, were retrieved from the national registry for heart transplantation between 2011 and 2018. The study population was defined and compared in four groups: 1) Death while awaiting HTX, 2) Death after HTX, 3) Alive without a transplant, 4) Transplanted and alive.

Results: The data of 207 patients [75% male, mean (SD) age of 34(10) years] were analyzed. The most common etiology of heart failure was idiopathic dilated cardiomyopathy. A total of 86 patients (41%) were successfully transplanted, with a median (IQR) time between listing and transplantation of 84 (30-219) days, 54 patients (26.1%) were dead and 32% were still alive. The multivariate analysis showed right atrial pressure, pulmonary capillary wedge pressure, cardiac index, and systolic blood pressure at the time of listing as independent predictors of death.

Conclusion: The study on HTX waiting list is very useful for both allocation strategies and administrative planning for patients with advanced heart failure by development of accurate models and scoring systems using predictors of death in the waiting list.

KEYWORDS: Heart transplantation, Waiting list, Mortality

INTRODUCTION

Despite advances in medical and device therapy, the prognosis and quality of life of patients with advanced heart failure (HF) remain dire. Heart transplantation (HTx) is still a lifesaving therapy for patients with end-stage refractory heart failure [1]. Compared to the natural course of end-stage HF, the survival after HTx is excellent with a median survival of 10 years for all and 13 years for those surviving to 1 year [2, 3]. According to the International Society of Heart and Lung Transplantation (ISHLT) current 1-year and 5-year survival after HTx is about 85% and 72.5%, respectively [2, 3].

Iran celebrated the first successful HTx in 1993. Since then, the number has increased significantly thanks to improving experiences. [4] All HTx centers in Iran register recipients in a unified HTx waiting list endorsed and owned by the Iran's Ministry of Health

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Table 1: List Baseline characteristics of study population (n= 207).

Variables	Value
Sex (Male/Female), number(%)	155/52 (74.9/25.1)
Age, year, mean (SD)	34 (10)
Etiology, number(%)	
DCM	166 (80.2)
ICMP	13 (6.3)
HCM	4 (1.9)
ARVC	7 (3.4)
PPCM	6 (2.9)
Valvular CMP	7 (3.4)
RCM	3 (1.4)
CHD	1 (0.5)
Blood group, number(%)	
A	56 (27.1)
B	47 (22.7)
AB	17 (8.2)
O	80 (38.7)

Abbreviations: DCM: Dilated Cardiomyopathy; ICMP: Ischemic Cardiomyopathy; HCM: Hypertrophic Cardiomyopathy; ARVC: Arrhythmogenic Cardiomyopathy; PPCM: Post-Partum Cardiomyopathy; RCM: Restrictive Cardiomyopathy; CHD: Congenital Heart disease

(MOH) according to the "Heart Transplantation Protocol" which was developed and edited in 2010 based on the united network for organ sharing (UNOS) and ISHLT latest guidelines [1, 5]. This protocol also guides the donor heart allocation [6, 7].

The demand for a donor heart has continued to exceed the supply worldwide. The problem of death in the waiting list has been altered significantly by the presence of durable mechanical circulatory support systems (MCS) in many countries. The best treatment for refractory heart failure in our country, however, is still HTx due to limited access to MCSs and high donation rates.

Patients who are listed for HTx differ in characteristics and ultimate outcome [8-11]. Waiting list data are not only useful in developing validated models for predicting the mortality risk in HTx recipients (which is also useful for donor allocation strategies), but also, it could be highly instructive and helpful for administrative systems like the MOH to properly prepare for future requirements of heart failure therapies like durable MCSs.

To our knowledge, this is the first study on a HTx waiting list in Iran. We aimed to characterize the clinical, hemodynamic and echocardiographic findings of patients on heart transplantation waiting list in a tertiary center for heart failure care with an experience of 13 years in heart transplantation.

MATERIALS AND METHODS

Study Population

Our study is a retrospective cohort analysis of advanced heart failure adult patients who were registered in a web-based national registry for heart transplantation designed by Iran MOH. All registered adult patients who were listed by the Rajaie Cardiovascular Medical and Research Center (RCMRC) HTx team between 2011 and 2018 were included in this listing system, which has been in place since 2011. RCMRC is a tertiary center for cardiovascular medicine in Iran. Since 2006, the Heart Failure and Transplantation Department at the RCMRC has been devoted to offering patients with heart failure the most cutting-edge, knowledge-based clinical care. In 2008, the program was expanded to encompass the fellowship training program and a multidisciplinary approach to the management of patients with heart failure, and pulmonary hypertension. The current team includes board-certified cardiologists who are expert in heart failure and transplantation, dedicated cardiac surgeons, echocardiographers and cardiac imaging specialists, nurse practitioners, transplant coordinators, specialized heart failure certified nurses, pharmacists, geneticists, social workers, dieticians, exercise physiologists, psychologists and all other consultant physicians (nephrologists, infectious specialists, pulmonologists, gastroenterologists, neurologists, endocrinologists and psychiatrists).

Table 2: Comparison of hemodynamic findings between the four defined groups (n= 207).

	Death while awaiting HTX n= 54	Death after HTX n= 22	Alive without HTX n= 67	Transplanted and alive n= 64	P value
Age, year, mean(SD)	35 (11)	33 (11)	37 (11)	29 (8)	*0.4 #0.2
LVEF, %, median (IQR)	10 (10-15)	10 (10-11)	10 (10-15)	10 (10-15)	*0.4 #0.5
SBP, mmHg, median (IQR)	95 (89-100)	92(85-98)	103 (96-110)	95 (90-100)	*<0.0001 #0.1
DBP, mmHg, median (IQR)	65 (65-70)	65 (65-70)	70 (67-75)	70 (65-70)	*0.003 #0.09
PAP, mmHg, median (IQR)	40 (36-46)	34 (26-45)	35 (27-43)	35 (28-40)	*0.001 #0.7
RAP, mmHg, median (IQR)	20 (13-35)	17 (12-25)	13 (8-16)	14 (8-17)	*<0.001 #0.1
CO, Lit/min, median (IQR)	2.6 (2.2-3.3)	2.8 (2.3-3.6)	3.1 (2.5-3.6)	2.7 (2.2-4)	*0.02 #0.9
CI, Lit/min/m^2, median (IQR)	1.5 (1.2-1.8)	1.7 (0.35-2)	1.65 (1.4-2.1)	1.67 (1.37-2.2)	*0.05 #0.9
PVR, Wood unit, median (IQR)	2.1 (1.2-3.4)	1.7 (1.2-2.8)	1.8 (1.1-2.7)	1.89 (0.8-2.7)	*0.1 #0.6
SVR, Wood unit, median (IQR)	21 (15.9-25)	20 (17.5-23)	19.1 (16-22)	20 (17.5-25)	*0.2 #0.9
PCWP, mmHg, median (IQR)	30 (25-35)	26 (21-35)	25 (20-30)	25 (20-30)	*<0.001 #0.8

*P value for Death before HTX versus alive without HTX
#P value for Transplanted and alive versus death after HTX

Abbreviations: SD: Standard Deviation; LVEF: Left Ventricular Ejection Fraction; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PAP: Pulmonary Arterial Pressure; CO: Cardiac Output; CI: Cardiac Index; PVR: Pulmonary Vascular Resistance; SVR: Systemic Vascular Resistance; PCWP: Pulmonary Capillary Wedge Pressure; RAP: Right Atrial Pressure ; IQR: Interquartile Range; HTX: Heart Transplantation

RCMRC, as a center of excellence for heart failure care, is capable of performing most of the recommended heart failure therapies, including best in evidence pharmacologic treatment, device-based treatment, remote care and telemedicine, advanced failure care, rehabilitation, cardiac transplantation and limited MCS implantation.

All demographic, clinical and laboratory data including date of listing, etiology of heart failure, right heart catheterization, and echocardiographic findings were extracted from the data registry of stage D heart failure, patients' hospital records and/or database of the listing system of health ministry. A database maintained by the health ministry, patient hospital records, or phone calls were used to gather information on heart transplant waiting list mortality.

Ethical Considerations

The study was approved by research and ethics committee of our center with an ethics code of IR.IUMS.FMD.REC.1398.404.

Assessment of Heart Transplant Candidates

According to the Ministry of Health (MOH) protocol, adult patients with end-stage cardiac disease who are candidates for heart transplantation will be evaluated by a thorough echocardiogram in accordance with the guidelines of the American Society of Echocardiography [12, 13], a cardiopulmonary exercise testing (CPX) to evaluate their functional capacity, Heart Failure Survival Score (HFSS) [6] to evaluate their prognosis (particularly in those who have borderline CPX results) and standard right heart catheterization (RHC) to evaluate hemodynamics including pul-

Table 3: The adjusted associations between death and other predictors in multivariate analysis.

	BETA	Wald	P value	Odd Ratio (95% CI)
LVEF	0.068	2.302	0.129	0.93 (0.85-1)
SBP	0.069	5.852	0.016	1.07 (1.01-1.1)
RAP	0.132	11.331	0.001	0.8 (0.8-0.9)
CI	1.076	7.489	0.006	0.3 (0.1-0.7)
SVR	0.156	7.329	0.007	0.8 (07-0.9)
PCWP	0.112	10.367	0.001	0.894 (0.8-0.9)

Variable(s) entered on step 1: Age, LVEF, gender, RV, MR, TR, SBP, DBP, PAP, RAP, CO, CI, PVR, SVR, BSA, PCWP, ICD.

Abbreviations: BSA: Body Surface Area; ICD: Intracardiac Defibrillator; LVEF: Left Ventricular Ejection Fraction; SBP: Systolic Blood pressure; DBP: Diastolic Blood Pressure; RAP: Right Atrial Pressure; CO: Cardiac Output; CI: Cardiac Index; PCWP: Pulmonary Capillary Wedge Pressure; SVR: Systemic Vascular Resistance; PVR: Pulmonary Vascular Resistance; MR: The Severity of Mitral Regurgitation; TR: The Severity of Tricuspid Regurgitation

monary capillary wedge pressure (PCWP). Pulmonary arterial pressure (PAP) and right atrial pressure (RAP) were measured via a fluidfilled system. Cardiac output (CO), cardiac index (CI), pulmonary vascular resistance (PVR) and documentation of the absence of irreversible pulmonary hypertension were also recorded.

The potential comorbidities were assessed in all transplant candidates including obesity, frailty, diabetes mellitus, renal and hepatic dysfunction, peripheral vascular diseases, psychiatric and neurologic problems, malignancy, smoking, substance and/or drug abuse and social issues.

In patients for whom emergent listing is considered (cardiogenic shock and acute mechanical circulatory support) the assessment process were necessarily abbreviated.

For listed patients, we typically repeat crucial pre-transplantation work-ups every six months or if they exhibit clinical worsening (aggravation of symptoms necessitating frequent hospitalization, particularly with end-organ dysfunction [kidney/liver]), develop a significant comorbidity (pulmonary embolism, kidney/liver failure unrelated to cardiac failure), or infection.

Patients were defined in four groups: 1) Death without HTx, 2) Death after HTx, 3) Alive without HTx, 4) Transplanted and alive.

Statistical Analysis

Statistical analysis was performed using SPSS 22 for Windows (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). All variables were tested for normal distribution with the Kolmogorov- Smirnov test. The quantitative variables were expressed as mean [standard deviation (SD)] or median [interquartile range (IQR)] as appropriate and categorical variables as number (percentage). The comparisons were conducted using the chi-square, student t-test, or Mann-Whitney test, as appropriate. Multivariate analysis was performed using binary logistic regression to assess the independent predictors for death without heart transplantation. P values <0.05 were considered significant.

RESULTS

A total of 214 adult patients with a diagnosis of advanced HF were listed for heart transplantation in our center between 2011 and 2018, and after excluding those who failed to

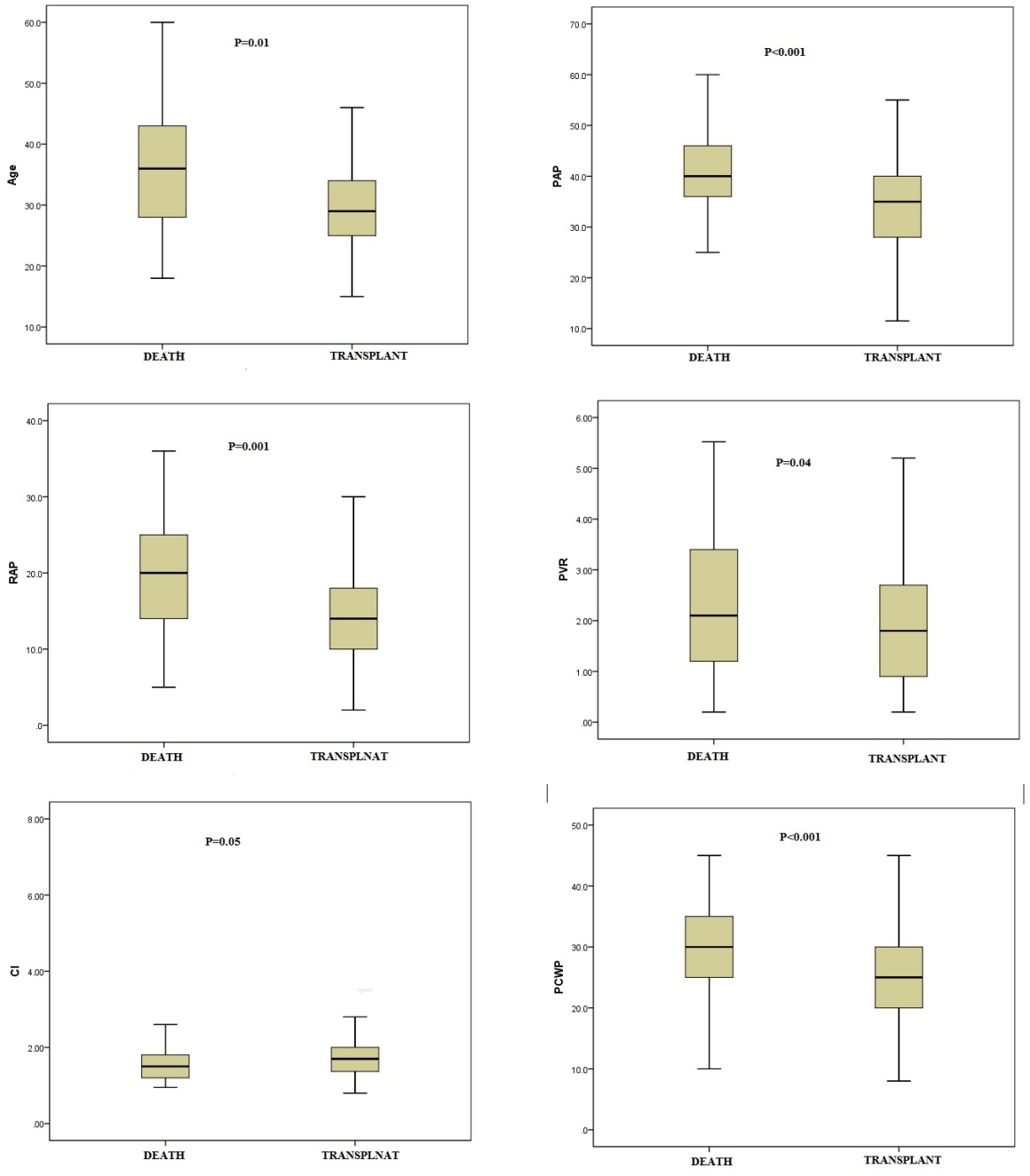

Figure 1: The comparison between patients who received a transplant and those who died while waiting for HTX.
Abbreviations: CI: Cardiac Index; PAP: Mean Pulmonary Artery Pressure; PCWP: Pulmonary Capillary Wedge Pressure; RAP: Right Atrial Pressure

follow-up, 207 patients' data were analyzed.

Table 1 shows baseline characteristics of the study population. About 75% of patients were male. The mean (SD) age was 34 (10) with a range of 15-60 years.

The most common etiology of heart failure was idiopathic dilated cardiomyopathy (DCM)

(80.2%) and O positive was the most common blood group (36%)

Outcome of Transplanted Patients

A total of 86 patients (41%) were successfully transplanted and the median (IQR) time between listing and transplantation was 84 (30-219) days. Over half of patients (112 of 207) were listed between 2016 and 2018 and 44 were transplanted during this time.

Of 86 transplanted patients, a total of 16 passed away (6 in-hospital death [5 as a result of early refractory graft failure and one due to severe coagulopathy and bleeding]; 4 after discharge and in the first year [all occurred after the first month]).

About 75% of transplanted patients were alive at the end of 7 years. The one-year survival rate in our study population was about 88% (76 of 86).

Outcome of Listed Patients Who were not Transplanted

Of 121 listed patients who were not transplanted, 64% were listed after 2016, with the median (IQR) of time passed from listing to 2018 of 2 (1-3) years. At the end of the trial, 67 patients were still alive, and 54 (26%) of them had died. Almost all who passed away were supported by intravenous inotrope and/or temporary assist devices (such as extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pump (IABP) at hospital) or intermittent intravenous inotrope therapy, either at home or hospital infusion unit.

Hemodynamic and Echocardiographic Findings

Comparison of the hemodynamic findings in the four defined groups can be found in Table 2.

As shown, patients who died while waiting for HTx had lower systolic and diastolic blood pressure, higher filling pressures and cardiac output and index. There was no significant difference between the alive or dead group after HTx in terms of hemodynamic findings.

The echocardiographic findings were not different between the four study groups. More than 85% of the study population had significant (at least moderate) right ventricular dysfunction at the time of listing; and significant mitral and tricuspid regurgitation were seen in about 88%.

Fig 1 shows the comparison between all listed patients who received a transplant and those who died while waiting for HTx. Patients who passed away were older, had lower CIs, greater filling pressures, and higher pulmonary vascular resistance as compared to those who had transplantation.

The median (IQR) period from listing to death was 93 (87-108) days, which was not significantly different from the duration from listing to transplantation (between 20 days and a year) [Median (IQR)= 84 (30-219) days] (p= 0.3).

Regarding the echocardiographic findings, the prevalence of significant RV dysfunction was seen more frequently in those who died before transplantation than those who received HTx. (90% versus 84%, p= 0.01).

Although the overall frequency of blood groups was not different, O RhD negative and A RhD negative were two times more prevalent in those who died without transplantation.

There was a lower mortality rate among patients with intra-cardiac defibrillator (ICD) but this was not statistically significant (P= 0.08).

A binary logistic regression model with a backward elimination method was applied to assess the adjusted associations between death and other predictors which had been detected in the bivariate analysis. Our multivariate analysis showed that right atrial pressure, pulmonary capillary wedge pressure, cardiac index, systemic vascular resistance and systolic blood pressure at the time of listing could be considered as independent predictors of death of patients who were listed for HTX (Table 3).

DISCUSSION

The main aim of the present study was to show the outcome of patients in heart transplantation waiting list. Defining the prognosis of patients on the transplant waiting list is complex and of paramount importance. This study demonstrates the outcome of patients on the heart transplant waiting list of a tertiary center for cardiovascular care in Tehran, Iran between 2011 and 2018.

The clinical state and hemodynamic parameters of the HTx candidates that were lost made up roughly one third of the total (26.1%). As mentioned earlier, there is an important shortage of mechanical circulatory support systems in Iran. Though donation rates are proudly high, many patients die on waiting list who might survive with the help of durable MCSs, as shown by Trivedi et al [11].

Forty one percent of the waiting list candidates were transplanted with a one-year survival rate of 88% which is comparable to the high volume transplant centers worldwide [3, 4, 14, 15]. We did the first heart transplantation in 2007 and since 2013, we have succeeded in performing a high volume of cardiac transplantation (heart transplants for adults and children have ranged from 27 to 49 each year during the last four years) mostly on very sick patients. We assume the presence of a dedicated multi-disciplinary team including heart failure specialists, consultants (nephrologists, infectious specialists, pulmonologists, gastroenterologists, neurologists, endocrinologists and psychiatrists), trained nurse practitioners, social workers, physiotherapists, dieticians and many other who help the transplantation program; standardized follow-up care which leads to close follow up of patients and early detection of transplant related complications including rejection and infection have contributed to HTx success rate and should be followed in all centers interested in performing heart failure care and cardiac transplantation. As mentioned earlier, we lost 10 patients (~12%) in the first post transplantation year, mostly due to refractory graft failure in the first month (6 of 10). Optimizing graft survival requires better organ protection before and during procurement, decreasing ischemic time, and proper support after surgery. MCSs are undoubtedly useful in supporting graft dysfunction, particularly those refractory to available medical treatment. However, ICU protocols should be revised to perform timely and best in evidence and experience care to the patients. For example, right ventricular failure is an ominous problem after transplantation and should be monitored closely and treated quickly. In our experience, we keep an eye on blood gas, lactate level, urine output and hemodynamic parameters and handle the problem using prostaglandins, phosphodiesterase 5 inhibitors, combination of inodilators and vasopressors, early renal replacement therapy and rarely ECMO. These should all be considered before, provided timely and delivered properly according to the center's protocol.

Another crucial issue in transplant medicine is the prioritizing of patients on the waiting list. Numerous studies have been conducted all over the globe to establish a predictive model for predicting waiting list mortality and to achieve the best use of the donated heart [8-10, 16].

Currently, prioritization of patients on transplant waiting list is mostly based on the need for hospitalization, inotropes or mechanical circulatory support devices and it seems that more predictive models and scoring systems using waiting list data are also needed.

Krakauer et al. concluded that factors other than the probability of death enter into the decision of whom to transplant after finding that the survival benefit is greater for patients who are seriously ill and regrettably there is no correlation between the probability of death while awaiting a heart transplant and the probability of receiving a transplant [16].

Smits et al. used simple clinical parameters including the hemodynamic findings to predict waiting list mortality [10]. Jasseron et al. developed an accurate predictive model named Candidate Risk Score (CRS) using 4 items including: short-term MCS use, plasma concen-

trations of natriuretic peptides, glomerular filtration rate and total bilirubin level for France and this score is currently being used there to develop a modified allocation system for heart transplantation [9].

Although there is a unique national heart transplant waiting list for each province, an accurate scoring system for organ allocation is not available and the prioritization of patients for receiving a transplant is based on the estimation of severity of heart failure by the patient's physician considering ventricular function, cardiac output and index, filling pressures, need for hospitalization and inotropes, hepatic and renal function as well as serum natriuretic peptides and electrolyte levels particularly the serum sodium level. With the contribution of air-transfer, we believe that a unified, national list for all heart recipients can benefit the sickest patients by better allocation. Prioritizing patients on the waiting list is a constant challenge that calls for taking into account several aspects, such as clinical and para-clinical data. A more accurate model and scoring systems for prognosis which is individualized for Iranian people may be useful for this purpose.

These scoring systems may be more useful in deciding for the outpatients who have prolonged waiting time. The clinical condition, laboratory tests, the severity of the illness and the probability of death may change in a patient with heart failure and some of the listed patients may get better over time, so the patients in waiting list should be reevaluated frequently using these scoring systems instead of receiving a high priority because of accumulated waiting time.

The strength and uniqueness of this study may lie in the precise depiction of the fate of patients who were waiting for heart transplants in Iran for the first time. This study only involves one center; hence a multicenter trial would be preferable. A multicenter study on heart transplant waiting list would be very helpful in recognition of barriers in better management of heart failure patients.

The absence of key important prognostic indicators such kidney and liver function, the amount of natriuretic peptides in the blood, and the serum sodium level in our analysis may be another limitation of the current study. We opted to solely take into account hemodynamic and echocardiographic results in a patient with advanced heart failure in whom their measures have relatively changed less over time, since these variables' serial changes may be more significant than their spot measurements at the time of listing.

In conclusion, it seems that a national multicenter study on HTx waiting list in Iran is crucial for both allocation strategies and administrative planning for patients with advanced heart failure.

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