Open Access

OBM Transplantation

Original Research

Mortality Risk Factors in Patients who are in Heart Transplantation Waiting List

Petr A. Fedotov [1, *], Maria A. Simonenko [2, *], Yulia V. Sazonova [3], Mariya A. Bortsova [4], Artem N. Kostomarov [5], Mariya Yu. Sitnikova [6]

1. Heart Failure SRL, Almazov National Medical Research Centre, Saint-Petersburg, Russia; E-Mail: drheart@mail.ru
2. Heart Transplantation Outpatient Department, Cardiopulmonary Exercise Test SRL, Almazov National Medical Research Centre, Saint-Petersburg, Russia; E-Mail: dr.maria.simonenko@gmail.com
3. Cardiology Department №8, Thoracic Surgery SRL, Almazov National Medical Research Centre, Saint-Petersburg, Russia; E-Mail: yulia.via.sazonova@gmail.com
4. Cardiology Department №8, Almazov National Medical Research Centre, Saint-Petersburg, Russia; E-Mail: bortsova_ma@almazovcentre.ru
5. Post-graduate medical student, I.P. Pavlov First Saint-Petersburg State Medical University, Saint-Petersburg, Russia; E-Mail: art-kostomarov@yandex.ru
6. Heart Failure Research Centre, Almazov National Medical Research Centre, Saint-Petersburg, Russia; E-Mail: drsitnikova@mail.ru

* **Correspondence:** Petr A. Fedotov, Maria A. Simonenko; E-Mails: drheart@mail.ru; dr.maria.simonenko@gmail.com

Academic Editor: Haval Shirwan

Special Issue: Perspectives on Heart Transplantation

OBM Transplantation
2019, volume 3, issue 3
doi:10.21926/obm.transplant.1903077

Received: February 01, 2019
Accepted: July 29, 2019
Published: August 05, 2019

Abstract

***Background*:** To estimate the survival of patients in the heart transplantation waiting list (HTx WL) at Almazov National Medical Research Centre (V.A. Almazov NMRC), Saint-

Petersburg, Russia, from 2010 to 2017 and to define risk factors for death among these patients.

***Methods*:** It was a single-center retrospective study involving 151 patients with advanced chronic heart failure (CHF) in the HTx WL.

***Results*:** Mortality in the HTx WL for the period 2010–2017 was found to decrease. Based on the results of constructing the discriminant function, four factors predicting the survival of patients in the HTx WL, namely, ACE inhibitors/ARBs, beta-blockers, status 1 of UNOS, CHF NYHA class IV, were pointed out.

***Conclusions*:** The model has sufficient resolving power but is not capable of predicting the outcome in the presence of acute decompensation of CHF.

Keywords

Heart failure; advanced heart failure; cardiomyopathy; congenital heart disease; heart transplantation; heart transplantation waiting list

1. Introduction

Currently, in the Russian Federation, the prevalence of chronic heart failure (CHF) in the adult population is 14.9 million, 6 million of them suffer from CHF NYHA class III-IV [1]. The annual mortality of patients with the high functional class of CHF, even under the treatment in a specialized hospital, reaches 12% [2]. The only effective method of treating advanced CHF is heart transplantation (HTx) [3]. According to the International Society for Heart & Lung Transplantation (ISHLT) data, more than 5000 HTx are performed in the world every year [4]. Mortality in an HTx waiting list (HTx WL) could be about 5–15% per year [5-7]. In the Russian Federation, the number of patients in HTx WL is gradually increasing and it increased from 339 to 497 patients in the period 2012 to 2016. Further, the actual mortality in HTx WL was 12% in 2013 and 7.4% in 2016 [8, 9]. The aim of this study was to estimate the characteristics of patients' included in the HTx WL at Almazov National Medical Research Centre (V.A. Almazov NMRC), Saint-Petersburg, Russia during 2010–2017 and to evaluate their survival.

2. Materials and Methods

2.1 Collection of Data and Population

We assessed the data of HTx WL from V.A. Almazov NMRC from 2010 to 2017, which included 181 patients aged from 10 to 65 years. Following patients were excluded from the analysis: 15 patients (male =) who are still waiting for HTx, 5 refused HTx after being included in the HTx WL (all males) or removed from the list (n=10, male = 9) due to contraindications to HTx (stroke = 3 patients, obesity with BMI >35 kg/m^2 = 2 patients, with pulmonary embolism (PE) and pulmonary vascular resistance (PVR) > 5 Wood Units (W.U.) = 1 patient, 3 patients with low compliance, 1 patient with skin melanoma). In this way, 151 patients were finally considered in the study and five of them were children (females in the age range of 10–16 years).

This was a single-centered non-randomized retrospective study considering data for eight years (2010-2017). The study included a small number of patients (n = 151). During the eight years, the availability of surgical treatment methods (PSI, ICD, and MCS) has changed and the criteria for selecting patients for HTx with respect to concomitant pathology have expanded. This study considered a group of patients from the heart transplantation waiting list, which differed in compliance. The analysis did not include patients' laboratory parameters and there was no complete information about coronary angiography of the deceased patients.

2.2 Statistical Analysis and Conformity Assessment

All statistical analyses were performed using program STATISTICA 10.0 (StatSoft Inc., USA). All results are presented as mean value ±SD (M ±sd) for the normally distributed data or the median and lower and upper quartile values (Me [LQ;UQ]) for the non-normally distributed data. The shear effect and the reliability of the differences (p) were estimated using the nonparametric Kruskal-Wallis and Mann-Whitney tests for independent samples, and the Friedman and Wilcoxon test for dependent samples. A two-sided p-value < 0.05 was required to infer a statistical significance. The comparison of the frequencies of binary features was carried out using contingency tables with an estimate of Fisher's exact test ("Fisher p") in the unrelated groups and an evaluation of the McNemar criterion ("McNemar p") in the associated groups. In our investigation on the primary end-point, we used survival of topical patients in the HTx WL. The survival time was taken as the days spent in HTx WL before their removal from the list (due to transplantation, death, or improving condition). Survival rates between the two groups were calculated using the Kaplan-Meier method.

Within the framework of the general model of discriminant analysis of a set of indicators differing in groups, a step-by-step (with inclusion) procedure for constructing the discriminant function (DF) was applied.

3. Results

3.1 General Characteristics of Patients in HTx WL

The general characteristics of the patients in HTx WL were as follows: age 47.4 ±12.8 years, male 113 (75%), left ventricle (LV) ejection fraction (LVEF) Simpson 20.8 ±7.9%, LV end-diastolic volume (LV EDV) 266 ±110 mL, TAPSE 1.3 ±0.5 sm, mean pulmonary artery pressure (PAP) 32 ±13 mmHg, and PVR 3.5 ±1.5 W.U. The causes of CHF were ischemic heart disease (IHD) in 61 (41%) patients, dilated cardiomyopathy (DCM) in 66 (45%) patients, restrictive cardiomyopathy (RCMP) in 2 (1%) patients, hypertrophic cardiomyopathy (HCM) in 2 (1%) patients, transferred myocarditis in 4 (3%) patients, chronic rheumatic heart disease (CRHD) in 3 (2%) patients, and other cardiomyopathies (CMP) in 13 (7%) patients. In the period from January 2010 to October 2017, in total 41 of the 151 (27.2%) patients included in the HTx WL died.

The mean duration spent by a patient in the HTx WL was 96 [31;192] days. In addition, 13 patients spent more than one year in the HTx WL, 10 of them underwent HTx, and 3 died. One patient has been waiting for HTx for 769 days. The patients were divided into two groups: group 1: survived in the HTx WL (n=110), including the 96 patients who underwent HTx and 14 patients who improved CHF; and group 2: the deceased patients in the HTx WL (n=41).

3.2 Mortality in HTx WL

The causes of death in HTx WL were as follows:

1. CHF progression - 20 patients (49%), time spent in the HTx WL to death was 39 [15;147] days (range 4–454 days); CHF progression was significantly more common than the other causes (Fisher's exact p, two-tailed: p=0,005)
2. Infectious complications - 8 (19%) patients, time spent in the HTx WL to death was 50 [3;143] days (range 3–480 days);
3. Sudden cardiac death - 7 (17%) patients, time spent in the HTx WL to death was 55 [15;178] days (range 2–379 days);
4. PE - 6 (15%) patients, time spent in the HTx WL to death was 35 [29;91] days (range 7–120 days).

The length of stay in the HTx WL in the deceased group was significantly less than that in the survivors (37 [15;120] days and 116 [48;223] days, respectively, p=0.004). In fact, 17 (41%) patients died within one month from the moment they were included in the HTx WL. The groups were comparable in age, gender, and for most clinical indicators (Table 1). Moreover, the parameters that showed significant differences in the deceased patients included a lower incidence of IHD (p=0.03), a higher incidence of PE (p=0.038), a greater percentage of patients with CHF class IV (NYHA) (p=0.0001), inotropes-dependent patients–UNOS 1B (p<0,0001); this corresponds to a lower level of systolic BP (p<0.0001) and diastolic BP (p=0.001), a larger LVED (p=0.02), LVES (p=0.01), and LV ESV (p=0.037) (Table 1).

Table 1 The comparative characteristics of survived and deceased patients in the HTx WL.

Indicators \ **Groups**		**Group 1 Survivors n=110**	**Group 2 Non-survivors n=41**	**p**
Age, years. Me[LQ;UQ]		51 [37;56]	50 [40;56]	0.86
Male, n (%)		83 (75%)	30 (73%)	0.83
IHD, n (%)		49 (45%)	12 (29%)	0.03
DCM, n (%)		43 (39%)	23 (56%)	0.04
RCMP, n (%)		2 (2%)	0	-
HMP, n (%)		1 (1%)	1 (2,4%)	-
Myocarditis, n (%)		3 (3%)	1 (2,4%)	-
Others CMP, n (%)		12 (11%)	4 (10%)	0.93
CHF NYHA class, n (%)	**Class III**	87 (79%)	**17 (42%)**	0.0001
	Class IV	23 (21%)	**24 (58%)**	
UNOS, n (%)	**status 2**	83 (75%)	**11 (27%)**	<0.0001
	status 1	27 (25%)	**30 (73%)**	
VAD (EXCOR, ECMO)		4 (4%)	3 (7%)	-
Permanent AFib, n (%)		22 (20%)	11 (27%)	0.38

Co-morbidities, n (%)	92 (84%)	35 (85%)	0.99
Obesity, n (%)	20 (18%)	3 (7%)	0.13
PHT, n (%)	25 (23%)	14 (34%)	0.21
History of sternotomy, n (%)	16 (15%)	3 (7%)	0.28
T2D, n (%)	19 (17%)	1 (2%)	-
PE, n (%)	37 (34%)	21 (51%)	0.038
CKD C3a, n (%)	4 (4%)	4 (10%)	0.21
COPD, n (%)	11 (10%)	8 (20%)	0.16
Stroke, n (%)	16 (15%)	5 (12%)	0.79
Infectious complications n (%)	5 (5%)	6 (15%)	0.07
Polymorbidity, n (%)	42 (38%)	18 (44%)	0.58
ICD, n (%)	20 (18%)	6 (15%)	0.81
CRT-D, n (%)	16 (15%)	5 (12%)	0.79
History of cardiac surgery in HTx WL (ICD/CRT-D, RFA AVN, PTCA, VAD), n (%)	49 (45%)	17 (41%)	0.85
BMI, kg/m2. Me[LQ;UQ]	24 [22;28]	23 [21;27]	0.63
H, beats per min. Me[LQ;UQ]	80 [72;90]	81 [71;97]	0.39
SBP mmHg. Me[LQ;UQ]	110 [100;120]	90 [90;105]	<0.0001
DBP mmHg. Me[LQ;UQ]	70 [62;75]	60 [60;70]	0.0006
$VO_{2\ peak}$, mL/min/kg. Me[LQ;UQ]	11.9 [10.2;14.8]	10.8 [8.9;13.3]	0.11
LVEF%. Me[LQ;UQ]	20 [16;24]	20 [14;22]	0.36
LVED, mm. Me[LQ;UQ]	64 [48;71]	70 [60;77]	0.02
LVES, mm. Me[LQ;UQ]	55 [33;62]	61 [52;69]	0.01
LV EDV, ml. Me[LQ;UQ]	243 [187;311]	256 [181;336]	0.54
LV ESV, ml. Me[LQ;UQ]	156 [58;205]	186 [134;271]	0.037
LV SV, ml. Me[LQ;UQ]	57 [43;72]	54 [33;70]	0.18
TAPSE, cm. Me[LQ;UQ]	1.3 [1.1;1.6]	1.1 [0.8;1.5]	0.056
Mean PAP baseline, mmHg. Me[LQ;UQ]	30 [23;36]	31 [25;38]	0.53
Mean PAP after reduction test, mmHg. Me[LQ;UQ]	31 [25;38]	30 [29;38]	0.41
PVR baseline, Wood Units. Me[LQ;UQ]	3.2 [2.3;4.2]	3.0 [2.5;4.0]	0.96
PVR after reduction test, Wood Units. Me[LQ;UQ]	2.6 [1.8;3.0]	2.9 [2.6;3.2]	0.17
MR, grade. Me[LQ;UQ]	2 [2;3]	2 [2;3]	0.36
TR, grade. Me[LQ;UQ]	2 [1;3]	2 [1;3]	0.12
Treatment (including all drugs that patients were managed with while they were in HTx WL)			
Spironolactone, n (%)	110 (100%)	41 (100%)	-
Torasemide, n (%)	108 (98%)	36 (88%)	0.01
I.V. Furosemide, n (%)	38 (35%)	33 (80%)	0.0001

Beta-blockers, n (%)	107 (97%)	33 (80%)	0.001
ACE inhibitors/ARBs, n (%)	91 (83%)	11 (27%)	0.0001
Dobutamine, n (%)	16 (15%)	19 (46%)	0.0001
Dopamine, n (%)	34 (31%)	35 (85%)	0.0001
Episodes of adrenaline/noradrenaline, n (%)	7 (6%)	5 (12%)	0.31
Digoxin, n (%)	6 (5%)	5 (12%)	0.17

IHD: ischemic heart disease, CMP: cardiomyopathy, DCM: dilated cardiomyopathy, RCMP: restrictive CMP, HCM: hypertrophic cardiomyopathy, CHF NYHA class III: chronic heart failure NYHA class III, UNOS: United Network for Organ Sharing: Status 1A, 1B, 2; AFib: atrial fibrillation, BMI: body mass index, PHT: pulmonary hypertension, T2D: type 2 diabetes, PE: pulmonary embolism, CKD C3a: chronic kidney disease, COPD: chronic obstructive pulmonary disease, ICD: cardioverter-defibrillator, CRT-D: cardiac resynchronization therapy device with defibrillator, RFA AVN: radio-frequency ablation of the atrioventricular (AV) node, PTCA: percutaneous transluminal coronary angioplasty with stent implantation, VAD: ventricular assist device (EXCOR/ECMO), H: heart rate, SBP/DBP: systolic/diastolic blood pressure, $VO_{2\ peak:}$ peak oxygen consumption, EF: ejection fraction, LV: left ventricle, LVED: left ventricle end-diastolic diameter, LVES: left ventricle end-systolic diameter, EDV: end-diastolic volume, ESV: end-systolic volume, SV: stroke volume; TAPSE : tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure, PAP: pulmonary artery pressure, PVR: pulmonary vascular resistance, MR: mitral regurgitation, TR: tricuspid regurgitation, ACE inhibitors/ARBs: angiotensin converting enzyme inhibitors/Angiotensin II receptor blockers.

In the analysis of the correlation of the revealed indicators with death in the HTx WL and after excluding the factors with internal interaction, three independent indices (Figure 1), namely, UNOS classes (r= –0.45, p<0.0001, r=0,21), IHD (r=–0.24, p<0,006, r=0.06), and LVES (r=0.23, p<0.008, r=0.06), were used. The patients who died during the first month of their enrolment in the HTx WL, compared with the patients who died in the long term, showed a greater severity of mitral regurgitation in the recipients with less survival in HTx: MR 3[2;3] grades, 2[2;3] grades, respectively; p=0,036.

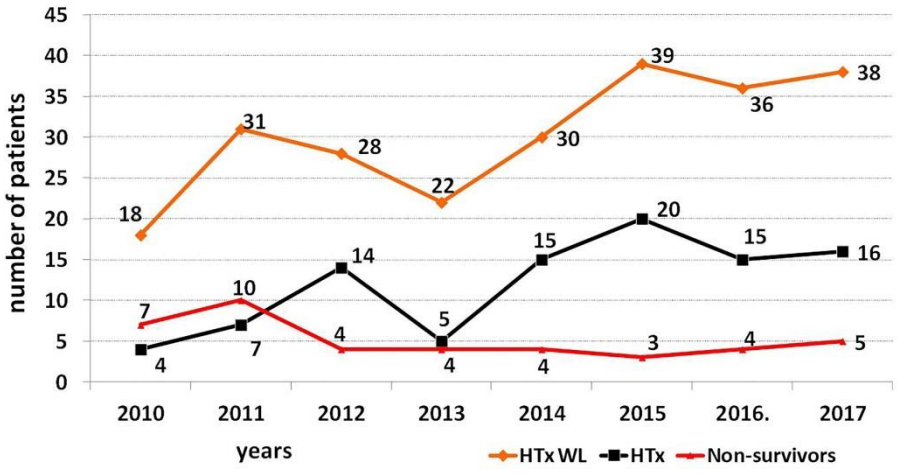

Figure 1 The total number of patients in the HTx WL and the number of deceased and heart transplanted patients from 2010 to 2017.

3.3 Changing the Characteristic of Patients in the HTx WL from 2010 to 2017

A decrease in mortality in the HTx WL from 2010 to 2017 was observed (the lowest mortality was observed in 2015, i.e., 8% (3 patients out of 39) (Figure 1).

In order to analyze the causes of the decrease in mortality, we formed three subgroups depending on the period of inclusion in the HTx WL: those included in the HTx WL in 2010–2011, those in 2012–2014, and those in 2015–2017. The patients in these subgroups were comparable by gender, anthropometric, echocardiographic, and clinical (diagnosis, BP, H, VO_{2peak}) indicators. However, in contrast to the period 2010–2011, the number of patients with renal dysfunction (CKD C3a), past-sternotomy, PHT, and a combination of significant co-morbidity was increased in the subsequent period. From 2010–2011 to 2012–2014 and 2015–2017, the frequency of surgical treatment of CHF (ICD, CRT-D, RFA AVN, VAD implantation, palliative PTCA) was significantly increased (Table 2).

Table 2 The occurrence of concomitant conditions in patients included in the HTx WL in different years.

	2010–2011 years n=40	2012–2014 years n=49	2015–2017 years n=62	p
	1	2	3	
CKD C3a, n (%)	2 (5%)	7 (14%)	12 (19%)	1 and 3 p=0.04
Pulmonary hypertension (PVR >3,0 W.U. after reduction test), n (%)	10 (25%)	40 (82%)	50 (81%)	1 and 2 p=0.0001 1 and 3 p=0.0001
Past-sternotomy, n (%)	1 (2.5%)	12 (24%)	19 (31%)	1 and 2 p=0.005 1 and 3 p=0.0003
Combination of concomitant diseases, n (%)	14 (35%)	37 (76%)	58 (94%)	1 and 2 p=0.0002 2 and 3 p=0.01 1 and 3 p<0.0001
Surgical treatment of CHF, n (%)	8 (20%)	27 (55%)	31 (50%)	1 and 2 p=0.001 1 and 3 p=0.003

CKD: chronic kidney disease, PVR: pulmonary vascular resistance, CHF: chronic heart failure.

In 2015–2017, compared with 2010–2011, the mortality rate of patients significantly decreased (Cox's F-Test: p=0.04) (Figure 2). However, regardless of the period, in 50% of deceased patients, the time to death was less than 30 days from the moment of inclusion in HTx WL.

In all periods between the live and deceased patients in the HTx WL, there was a difference (p<0.01) in the severity of UNOS status, but among the survivors in the list, there were no differences in the severity for UNOS during these periods.

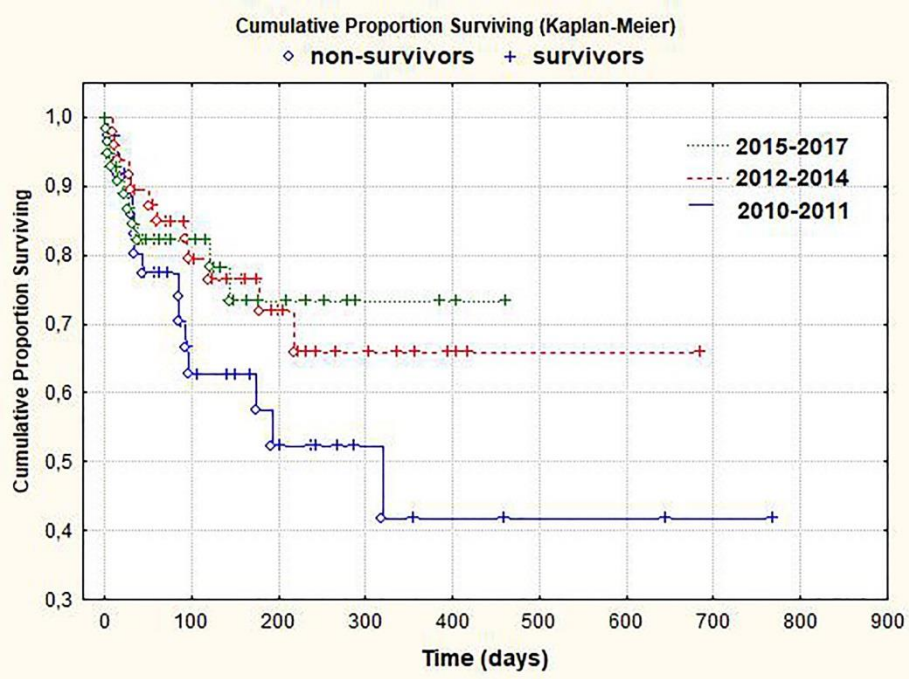

Figure 2 The Kaplan-Meier survival of patients according to their inclusion year in the HTx WL.

In the group of the deceased patients, compared with survivors, the frequency of dopamine use was higher in all periods (p<0.002). In 2015–2017, the patients were significantly more likely to receive dobutamine (p<0.0001) and adrenaline/noradrenaline (p=0.01) (Table 3). In 2015–2017, this group showed a lower incidence of beta-blockers (p=0.04) and greater frequency of intravenous furosemide (p<0.0001). In 2010–2011 and 2015–2017, ACE inhibitors/ARBs were administered less frequently in this group (p<0.0001), but in 2015–2017, these drugs were used more often in the group of survivors than those in 2010–2011 (p=0.03). In patients with status 1B UNOS, who received ACE inhibitors/ARBs or beta-blockers in the HTx waiting period, survival was higher compared to the patients who did not receive such therapy (p=0.0007 and p=0.009, respectively) (Figure 3).

Table 3 Characteristics of patients in the HTx WL at different time periods.

	2010–2011 years n=40		2012–2014 years n=49		2015–2017 years n=62		p
	survivors n=23	non-survivors n=17	survivors n=38	non-survivors n=11	survivors n=49	non-survivors n=13	
	1	**2**	**3**	**4**	**5**	**6**	
Time before the removal from the HTx WL, days Me [LQ;UQ]	140 [64;267]	44 [29;97]	156 [76;232]	55 [22;108]	76 [28;163]	29 [7;143]	p > 0,05

UNOS 1A	2 (9%)	2 (12%)	1 (3%)	2 (18%)	2 (4%)	1 (8%)	-
UNOS 1B	6 (26%)	11 (65%)	12 (32%)	7 (64%)	6 (12%)	8 (62%)	1 and 2 p=0.02 5 and 6 p=0.0007
UNOS 2	15 (65%)	4 (23%)	25 (66%)	2 (18%)	41 (84%)	4 (31%)	1 and 2 p=0.01 3 and 4 p=0.007 5 and 6 p=0.0005
Digoxin, n (%)	2 (9%)	2 (12%)	1 (3%)	1 (9%)	3 (6%)	2 (15%)	-
Dopamine, n (%)	8 (35%)	16 (94%)	14 (37%)	10 (91%)	12 (24%)	11 (85%)	1 and 2 p=0.0002 3 and 4 p=0.002 5 and 6 p=0.0001
Dobutamine, n (%)	4 (17%)	8 (47%)	8 (21%)	4 (36%)	4 (8%)	8 (62%)	5 and 6 p=0.0001
Episodes of adrenaline/ noradrenaline, n (%)	3 (13%)	0	2 (5%)	1 (9%)	2 (4%)	4 (31%)	5 and 6 p=0.01
Spironolactone, n (%)	23 (100%)	17 (100%)	38 (100%)	11 (100%)	49 (100%)	13 (100%)	p=1.0
Torasemide, n (%)	23 (100%)	14 (82%)	38 (100%)	10 (91%)	47 (96%)	12 (92%)	p > 0.07
I.V. Furosemide, n (%)	12 (52%)	14 (88%)	15 (39%)	9 (82%)	11 (22%)	12 (92%)	5 and 6 p< 0.0001 1 and 5 p=0.02
Beta-blockers, n (%)	22 (96%)	12 (71%)	36 (95%)	10 (91%)	49 (100%)	11 (85%)	5 and 6 p=0.04
ACE inhibitors/ARBs, n (%)	17 (74%)	2 (12%)	28 (74%)	5 (45%)	46 (94%)	4 (31%)	1 and 2 p=0.0001 5 and 6 p<0.0001 1 and 5 p=0.03
Cardiosurgical treatment, n (%)	4 (17%)	4 (24%)	22 (58%)	5 (45%)	23 (47%)	8 (62%)	1 and 3 p=0.01 1 and 5 p=0.0001

UNOS: United Network for Organ Sharing: Status 1A, 1B, 2; ACE inhibitors/ARBs–angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers; HTx WL: heart transplantation waiting list.

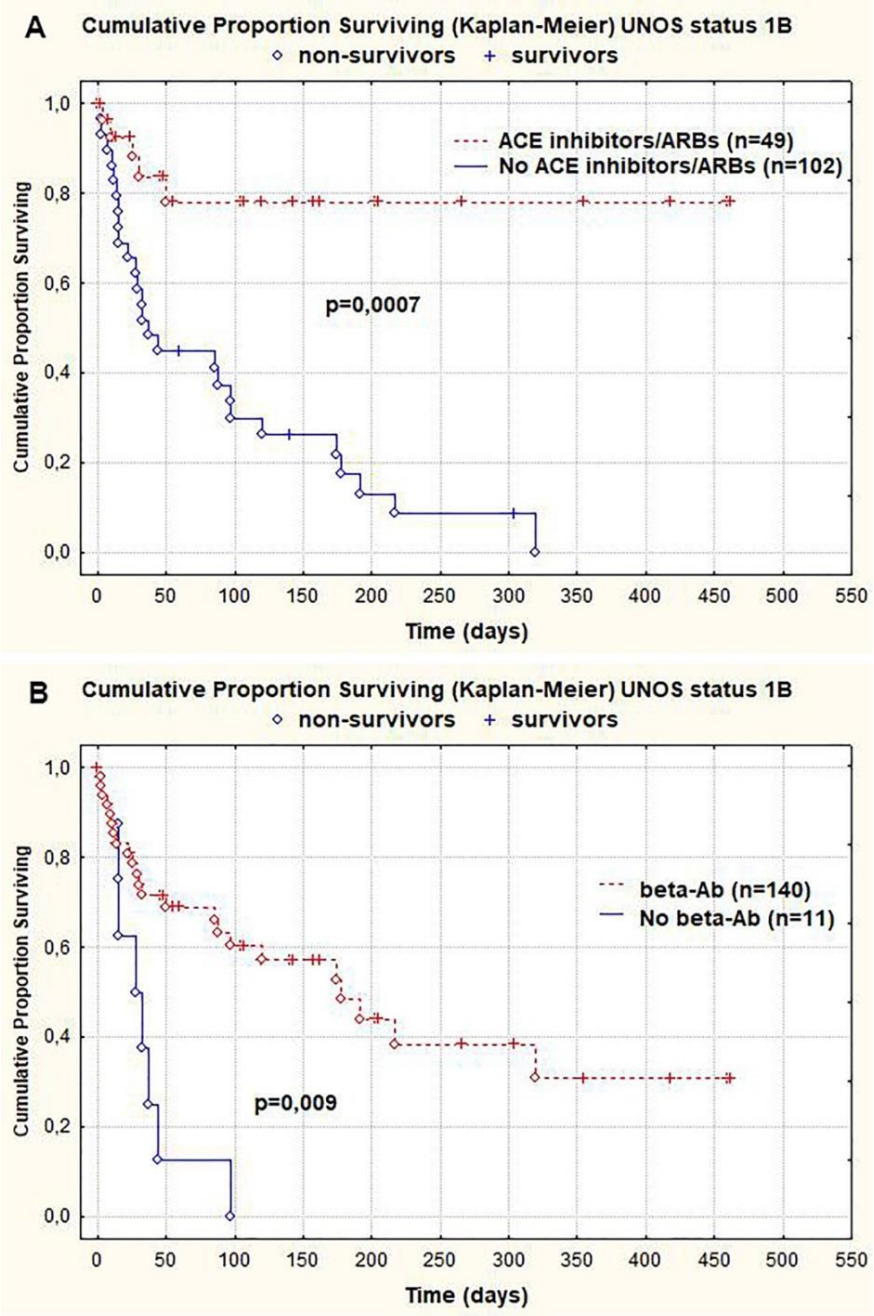

Figure 3 Survival of patients with status UNOS 1B, depending on the application: (A) ACE inhibitors/ARBs; (B) beta-blockers. UNOS status 1B: United Network for Organ Sharing: Status 1B; ACE inhibitors/ARBs: angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers; beta-Ab: beta-blockers.

3.4 Log Regression

In order to determine the possibility of predicting survival in the HTx WL (survivors/non-survivors), clinical and instrumental parameters were used (Model 1) to perform a regression analysis (logit regression). We used the following factors as the predictors of mortality in the HTx WL: class of CHF, UNOS classes, systolic and diastolic blood pressure, PE history, LVES, LV ESV, I.V. furosemide, beta-blockers, ACE inhibitors/ARBs, management with dobutamine, dopamine. With

the step-by-step inclusion of the listed indicators into the model, only three indicators were identified finally (UNOS1B, ACE inhibitors/ARBs, LVES) with the statistical significance for the prediction. This model is characterized by statistical significance (p <0.0001), high sensitivity (99%) and specificity (82%), high positive predictive value (97%), and negative predictive value (60%). The predictive power of the model is 97.74%.

Model 1 Predicted patients' survival in the HTx WL.

Model: Logistic regression (logit) N of 0's: 100 1's: 33 Dep. var: groups (1- **Survivors**, 2- **Non-survivors**) Loss: Max likelihood (MS-err. scaled to 1) Final loss: 23,763241521 Chi-square (df=3)=101,50 p=0,0000 Odds ratio: 445,50 Perc. correct: 94,74%				
	Const.B0	**UNOS 1B**	**ACE inhibitors/ARBs**	**LVES**
Estimate	–4,263211	2,040992	–6,289832	0,1140094
Standard Error	1,749866	0,8004157	1,351363	0,03579219
t (129)	–2,436308	2,549914	–4,654434	3,185316
p-level	0,01620286	0,01194465	0,000007952471	0,0018134
–95%CL	–7,725364	0,4573494	–8,963537	0,0431937
+95%CL	–0,8010592	3,624634	–3,616126	0,1848252
Wald's Chi-square	5,935596	6,502063	21,66376	10,14624
p-level	0,01484347	0,01077956	0,000003261729	0,001447348
Odds ratio (unit ch)	0,01407702	7,698238	0,001855073	1,120763
–95%CL	0,0004414863	1,579881	0,0001279928	1,04414
+95%CL	0,4488533	37,51097	0,02688663	1,203008
Odds ratio (range)		7,698238	0,001855073	2923,86
–95%CL		1,579881	0,0001279928	20,56435
+95%CL		37,51097	0,02688663	415717,4

Notes: LVES: left ventricle end-systolic diameter, ACE inhibitors/ARBs–angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers.

CHF patients in the HTx WL form a very heterogeneous group due to the differences in the causes of CHF, the severity of the disease, presence of comorbidities, and other indicators. This prediction model, based on three indicators, seems to be promising for future research in our population with the accumulation of data and other additional indicators. In order to find a model with large indicators, as well as visualization of the model's ability to predict outcomes in patients, a discriminative analysis was performed for the HTx WL (Table 4).

Table 4 Logit analysis of contingency tables.

Classification of Cases. Odds ratio: 445,50 Perc. correct: 94,74%			
	Prediction: Survivors	**Prediction: Non-survivors**	**Percent**
Survivors	99	1	99,00000
Non-survivors	6	27	81,81818

3.5 Discriminant Analysis

Within the framework of the general model of the discriminant analysis, a set of 21 indicators, which included the signs: UNOS status 1, management with dopamine, dobutamine, beta-blockers, ACE inhibitors/ARBs, Torasemide per os, I.V. Furosemide; the period of inclusion in the HTx WL (2010–2011, 2012–2014, 2015–2017); the number of HTx and removal year from the HTx WL; days in the HTx WL before the outcome; SBP, DBP, IHD, DCM, and CHF class at the time of inclusion in the HTx WL; and LVED, LVES, ESV, PE, surgical treatment in the HTx WL. A step-by-step (with inclusion) procedure for constructing the discriminant function (DF) was applied. The procedure included in the model had four dichotomous signs (Table 5, Figure 4).

Table 5 The raw coefficients and factor loading of the discriminant function.

Variables	DF coefficients	DF factor loadings
ACE inhibitors/ARBs	–3,221	–0,969
beta-Ab	–0,533	–0,464
UNOS status 1	0,689	–0,370
CHF class IV	0,284	–0,341
Constant	3,281	-

DF: discriminant function; ACE inhibitors/ARBs: angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers; beta-Ab: beta-blockers, UNOS status 1: status 1 by United Network for Organ Sharing; CHF class IV: chronic heart failure NYHA class IV.

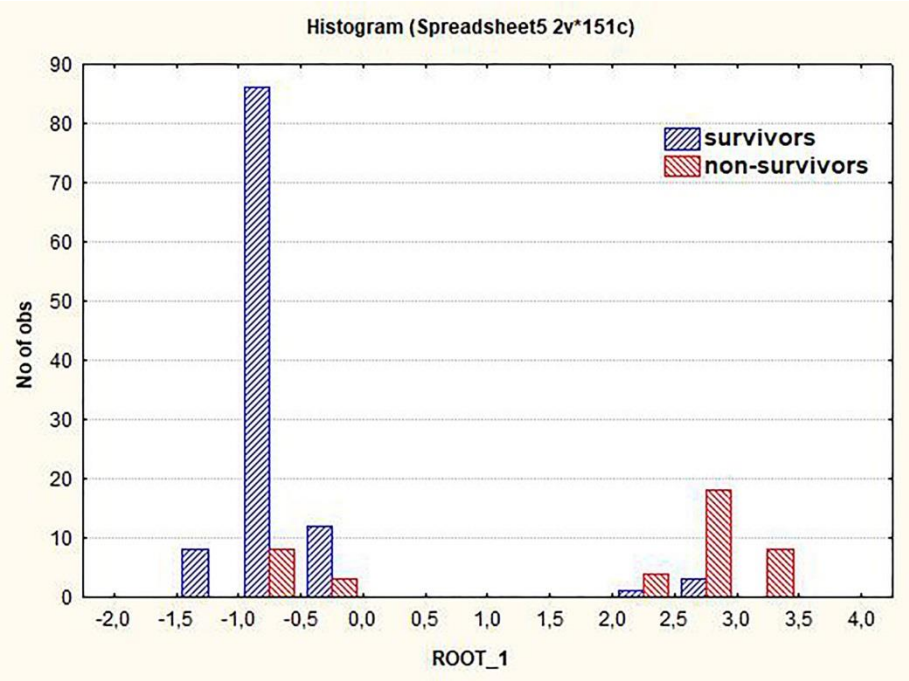

Figure 4 A joint histogram of the values of the discriminant function for the groups of deceased and living patients.

Odd ratio based on classification matrix is 72.3 with the confidence interval CI = [21.5; 243.4].

In the construction of DF, 11 inversions were detected in the group of survivors and 4 inversions in the group of deceased patients. According to the DF, "deceased" group included four survivors. All of them in the critical period had a successful HTx or BiVAD implantation. Among the deceased patients classified as "alive", a general pattern was revealed: regardless of the length of their stay in the HTx WL, they developed acute decompensation of terminal CHF, but neither HTx nor VAD was applied.

4. Discussion

In the Russian Federation, similar to the rest of the world, the number of patients requiring HTx is increasing [9] and so the number of patients awaiting a donor. Identifying reversible causes of death in this highly prognostic unfavorable group of patients can improve their survival. The decrease in the absolute risk of death of patients in the HTx WL, from 2010–2011 to 2012–2014 and to 2015–2017 in our sample was 20% and 24%, respectively.

First of all, the mortality of patients in an HTx WL depends on the severity of their condition and the duration of waiting for HTx [7, 10]. This corresponds to our observations, as mortality in the patients with status UNOS 1B was significantly higher than those with status 2 of UNOS. However, there were no differences depending on the length of their stay in the HTx WL, and in 17 (41%) patients, which had a higher grade of MR, death occurred within one month from the moment of their inclusion in HTx WL. MR due to LV dilatation causes its volumetric overload and further remodeling [11, 12]. According to Trichon et al., in case of HFrEF, regardless of the CHF cause, MR is an independent predictor of mortality, and the presence of MR grade 3–4 further increases these risks [13].

The difficulty to perform HTx in a short time led to the introduction of different mechanical circulatory support systems (MCS) in the clinical practices. In 2016, 42% of the patients in HTx WL were supported by the MCS system (International Society for Heart and Lung Transplantation Registry [14]). Among our patients, the frequency of MCS use was low (only 9.9%, i.e., 15 from 151 patients). Thus, in the first month after inclusion in HTx WL, the high mortality of patients was associated with the critical condition of patients, severe MR, lack of HTx capability in a short time, or failure to be supported by an MCS system. The researchers from a Washington Hospital Center confirmed these results by analyzing 48,000 patients from HTx WL between 1990 and 2005. The survival of patients with status 1 of UNOS depended on the possibility of emergent HTx or MCS, the lack of this assistance caused high and early mortality [15].

In most studies devoted to the prognosis of patients with CHF decompensation, the main echocardiographic risk factors were reported to be LVEF, LVED, and LVES [16-18]. In our study, there were no differences in the magnitude of LVEF between deceased and survived patients, but in the deceased ones, there was greater dilatation of the left chambers of the heart compared to survivors. Thus LVED, LVES, and LV ESV agree with the general idea of the negative effect of dilatation of the left heart chambers on the outcome of any heart disease [19, 20].

The presence of IHD in patients with CHF in the HTx WL was associated with a better prognosis in our population. This is contradictory to the notion that the ischemic origin of CHF, especially when there is a history of MI, is an unfavorable predictor of death [17, 21, 22]. We explain this fact with the increased frequency of palliative myocardial revascularization and ICD implantation in the

patients in HTx WL at our center. From 2010–2011 to 2012–2017, the frequency of cardiac surgery methods in patients from HTx WL increased from 20% to 50%.

Since 2013, the number of patients with concomitant pathology or a burdened background condition has increased at our center (Table 3). In 2012–2014, compared with 2010–2011, the number of patients with PVR above 3.0 W.U. was found to increase after the reduction test ($p = 0.0001$), with a history of median sternotomy ($p = 0.005$), and with combined co-morbidities ($p = 0.0002$). During the period (2015–2017), there was also an increase in the number of patients with PHT ($p = 0.0001$), combined pathology ($p<0.0001$), and those with CKD stage C3a ($p = 0.04$). This reflects the extension of the criteria for selecting patients for HTx [23] and the global trend of increasing patients with comorbid pathology in HTx WL [14, 24]. Despite the increased risk of cardiovascular events in the conditions of comorbidity in patients with CHF [25-28], the main predictor of death remains status 1 of UNOS [7, 15], thus in the group of patients with status 2 of UNOS, mortality was low. Further, despite the increase in the number of patients with comorbidities, which aggravates the forecast, a gradual decrease in the mortality in HTx WL was registered. One of the factors tragically affecting the prognosis is acute decompensation of advanced CHF.

The high mortality rate in our patients during 2010–2011 was due to insufficient HTx and MCS. This finding was in line with the UNOS data on high mortality in HTx WL during the period of 1990–1994 [15], when the use of MCS in HTx WL patients was about 9%, mortality in HTx WL patients with status 1 of UNOS was 25%, and that in status 2 of UNOS was 20%. Such a high mortality rate (26% of 434 patients) was also reported in an HTx WL group with only conservative therapy [29]. Based on the results of the discriminant analysis of our data, an increase in the number of HTx was not found to be a decisive factor in reducing mortality in HTx WL patients. Perhaps this is due to the lack of shortening the waiting time for the HTx.

The use of dobutamine, dopamine, and/or I.V. furosemide in therapy was higher in the group of the deceased patients, which corresponded to the severity of their condition and the status of UNOS. In contrast, the frequency of beta-blocker therapy and ACE inhibitors/ARBs was higher in the group of survivors in the HTx WL.

In order to unravel the factors that determine prognosis in HTx WL, we applied logistic regression. This indicated three factors to be involved: management with beta-blockers, ACE inhibitors/ARBs, and class 1 or 2 of UNOS. All other factors included in the model in conjunction with the above turn out to be non-significant. The risk factors, namely, beta-blockers, ACE inhibitors/ARBs, UNOS, are completely obvious and clinically understandable but do not reflect the complex model of our patients. The reason for the absence of additional factors could be explained by the small sample size and the characteristics of the studied population. Therefore, we carried out a discriminant analysis to solve the qualitative problem: using which set of indicators, a patient can be assigned to the group of surviving or deceased patients. As a result, we identified 21 risk factors affecting the prognosis. This information is clinically more significant because it focuses attention on the dependence of the prognosis on many components (severity of the patient condition, structural changes in TTE, and approaches to drug and surgical treatment methods). Moreover, the method allowed us to identify the patients who do not comply with this model and analyze the reason for this.

During the lack of routine use of MCS as a "bridge-to-transplant", all efforts were directed to further optimize the therapy of CHF in HTx WL patients. There is no doubt that the prognosis of

patients with CHF receiving ACE inhibitors/ARBs or beta-blockers is improving [3]. C. Campana et al. found that therapy by beta-blockers in HTx WL patients was optimized in 32% of them, ARBs in 7.5%, spironolactone in 42%, and diuretics in 35% [30]. However, the effectiveness of these drugs in the patients with the status 1B of UNOS has rarely been studied but their application seems reasonable [3, 31]. Active optimization of drug therapy made it possible to achieve a significant increase in the survival of patients with status 1B of UNOS compared with the patients who did not receive ACE inhibitors/ARBs or beta-blockers ($p = 0.0007$ and $p = 0.009$, respectively). When constructing a discriminant function (DF), the presence of ACE inhibitors or ARBs, in any of the periods in the HTx WL in the therapeutic regimen, was the most significant factor for classifying the patient in the surviving group.

Obviously, a large number of inversions make the constructed DF unreliable for prediction. The reason for this may be "random" due to factors not included in the study, such as the causes of acute decompensation of advanced CHF, the presence of vaccination against Pneumococcus or influenza, the reasons for the long-term presence of certain patients in the HTx WL, and others. The other reason may be a change in the prognostic significance of risk factors in the transition of a patient from a stable state to a decompensated one and vice versa [32, 33]. This creates difficulty in long-term prognosis with acute changes in patient status. Further investigations are required to determine the influence of such factors on the outcome.

5. Conclusions

1. At our center, the mortality in HTx WL patients for the period of 2010–2017 decreased, which is associated with the active use of cardiac surgical methods as a ”bridge” to transplantation and maximum drug therapy, including ACE inhibitors/ARBs and beta-blockers in patients receiving inotropic support (UNOS 1B).
2. Co-morbidities and IHD are not risk factors of death for patients included in an HTx WL.
3. Mortality in an HTx WL is significantly higher when CHF class 4, status 1 UNOS (with dobutamine, dopamine, I.V. furosemide), and the development of acute decompensation of advanced CHF are present.

The highest mortality in the first month after inclusion in the HTx WL is associated with the severity of MR, non-availability of urgent HTx, and MCS.

Author Contributions

PAF and MYS conceived the study. PAF, YVS and MAB provided the data. ANK had full access to all the data in the study and takes responsibility for its integrity and the data analysis. PAF performed statistical work for the study. MYS provided statistical guidance. PAF and MAS drafted the manuscript and take responsibility for the paper as a whole. All authors contributed substantially to its revision.

Competing Interests

The authors of this article have no conflicts of interest to disclose.

References

1. Mareev VY, Fomin IV, Ageev FT, Begrambekova YL, Vasyuk YA, Garganeeva AA et al. Clinical Guidelines. Chronic heart failure (CHF) on behalf of Society of Heart Failure Specialists, Russian Cardiac Society. Heart Failure Journal. 2017: 18: 3-40.
2. Mareev VY, Ageev FT, Arutyunov GP, Koroteev AV, Mareev YV, Ovchinnikov AG et al. National Guidelines of diagnostics and management of chronic heart failure on behalf of Association of Heart Failure Specialists, Russian Cardiac Society and Russian Scientific Medical Society of Physicians (4th edition). Heart Failure Journal. 2013; 14: 379-472.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2016. Eur Heart J. 2016; 37: 2129-2200.
4. Journal of Heart and Lung Transplantation, 2018; 37: 1155-1206.
5. Dominguez-Gil B, Matesanz R. Newsletter Transplant International figures on donation and transplantation 2016. 2017; 22: 1-70. https://www.swissinfo.ch/blob/43613866/825b24970155b5877fba0263f928dba7/newsletter-transplant--international-figures-on-donation-and-transplantation–2016-data.pdf
6. Matesanz R. Newsletter Transplant International figures on donation and transplantation 2014. 2015; 20: 1-64. https://www.edqm.eu/sites/default/files/newsletter_transplant_2015.pdf
7. Trivedi JR, Schumer E, Black M, Massey HT, Cheng A, Slaughter MS. Risk factors of waiting list mortality for patients awaiting heart transplant. J Heart Lung Transplant. 2016; 35: S214.
8. Gautier SV. Transplantology: Outcomes and perspectives, vol. IV. 2012. Tver': OOO «Publishing house «Triada», 2013; p. 368.
9. Gautier SV. Transplantology: Outcomes and perspectives, vol. VIII. 2016. Tver': OOO «Publishing house «Triada», 2017; p. 368.
10. Khush KK, Zaroff JG, Nguyen J, Goldstein BA. Longer waiting time increases mortality in heart transplantation: an instrumental variable analysis. J Heart Lung Transplant. 2015; 34: S71.
11. Spinale FG, Ishihra K, Zile M, DeFryte G, Crawford FA, Carabello BA. Structural basis for changes in left ventricular function and geometry because of chronic mitral regurgitation and after correction of volume overload. J Thorac Cardiovasc Surg. 1993; 106: 1147-1157.
12. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: Pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol. 2015; 65: 1231-1248.
13. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol. 2003; 91: 538-543.
14. Lund LH, Khush KK, Cherikh WS, Goldfarb S, Kucheryavaya AY, Levvey BJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report—2017; focus theme: Allograft ischemic time. J Heart Lung Transplant. 2017; 36: 1037-1046.
15. Lietz K, Miller LW. Improved survival of patients with end-stage heart failure listed for heart transplantation. Analysis of organ procurement and transplantation network/U.S. United Network of organ sharing data, 1990 to 2005. J Am Coll Cardiol. 2007; 50: 1282-1289.

16. Oh C, Chang H-J, Sung JM, Kim JY, Yang W, Shim J, et al. Prognostic estimation of advanced heart failure with low left ventricular ejection fraction and wide QRS interval. Korean Circ J. 2012; 42: 659-667.
17. Koseki Y, Watanabe J, Shinozaki T, Sakuma M, Komaru T, Fukuchi M, et al. Characteristics and 1-year prognosis of medically treated patients with chronic heart failure in Japan Chronic Heart Failure Analysis Registry in Tohoku District (CHART). Circ J. 2003; 67: 431-436.
18. Volpe M, Francia P, Tocci G, Rubattu S, Cangianiello S, Rao MAE, et al. Prediction of long-term survival in chronic heart failure by multiple biomarker assessment: A 15-year prospective follow-up study. Clin Cardiol. 2010; 33: 700-707.
19. Lee TH, Hamilton MA, Stevenson LW, Moriguchi JD, Fqnarow GC, Child JS, et al. Impact of left ventricular cavity size on survival in advanced heart failure. Am J Cardiol. 1993; 72: 672-676.
20. Gupta A, Sharma P, Bahl A. Left ventricular size as a predictor of outcome in patients of non-ischemic dilated cardiomyopathy with severe left ventricular systolic dysfunction. Int J Cardiol. 2016; 221: 310-313.
21. Abtahi DM, Kpaeyeh JA, Gold MR. Risk stratification of sudden cardiac death: A multi-racial perspective. Int J Heart Rhythm. 2016; 1: 24-32.
22. Hsich EM, Rogers JG, McNamara DM, Taylor DO, Starling RC, Blackstone EH, et al. Does Survival on the heart transplant waiting list depend on the underlying heart disease? JACC Heart Fail. 2016; 4: 689-697.
23. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, et al. The 2016 ISHLT listing criteria for heart transplantation: A 10-year update. J Heart Lung Transplant. 2016; 35: 1-23.
24. Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirieth Official Adult Heart Transplant Report–2013; focus theme: Age. J Heart Lung Transplant. 2013; 32: 951-964.
25. Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. Am J Cardiol. 1996; 77: 1017-1020.
26. Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: Rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005; 149: 209-216.
27. Hawkins NM, Huang Z, Pieper KS, Solomon SD, Kober L, Velazquez EJ, et al. Chronic obstructive pulmonary disease is an independent predictor of death but not atherosclerotic events in patients with myocardial infarction: Analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). Eur J Heart Fail. 2009; 11: 292-298.
28. Mentz RJ, Schulte PJ, Fleg JL, Fiuzat M, Kraus WE, Piña IL, et al. Clinical characteristics, response to exercise training, and outcomes in patients with heart failure and chronic obstructive pulmonary disease: Findings from Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION). Am Heart J. 2013; 165: 193-199.
29. Nägele H., Rödiger W. Sudden death and tailored medical therapy in elective candidates for heart transplantation. J Heart Lung Transplant. 1999; 18: 869-876.

30. Campana C, Alessandrino G, Striuli L, Agnesina L, Dequarti MC, Ghio S, et al. The tailored medical therapy in patients with advanced heart failure referred for cardiac transplantation. Transplant Proc. 2008; 40: 1999-2000.
31. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, et al. Recommendations on pre-hospital & early hospital management of acute heart failure: A consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. Eur J Heart Fail. 2015; 17: 544-558.
32. Prokopova LV, Sitnikova M.Yu, Dorofeykov VV, Lelyavina TA, Kashuba SM. The place of non-routine HF-lEF in evaluation of one-year survival: Where does the road go from "available prognosis"? Russian Heart Failure Journal. 2016; 17: 82-90.
33. Prokopova LV, Kashuba SM, Galenko VL, Fedotov PA, Smirnov BI, Sitnikova MY. Role of simple clinical laboratory parameters in one-year prediction of lEF HF course in the epoch of high-tech methods of health care: The Available Prognosis study. Russian Heart Failure Journal. 2015; 16: 137-144.