Hemodynamic Profile of Patients with ESKD Referred to Heart Failure Department of Rajaie Heart Center, A Data from Right Heart Catheterization Registry

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Introduction. Cardiovascular disorders are the leading cause of mortality and morbidity in patients with end-stage kidney disease (ESKD). We aimed to describe different patterns of cardiovascular abnormalities, the hemodynamics and the outcomes of ESKD patients referred to a tertiary center for heart failure programs, in detail.
Methods. In this cohort, all ESKD patients who were referred by nephrologists for cardiovascular consultation and scheduled for right heart catheterization between July 2009 to October 2021, were assessed. The outcome of the selected patients in terms of all-cause mortality or successful kidney transplantation was followed up until January 2022.
Results. A total of 73 patients (54.7% male) were selected. With the exception of four patients who had a specific cardiovascular disease, the remainder were referred due to a low left ventricular ejection fraction or pulmonary hypertension in order to determine the potential for kidney transplantation. Most of the patients (63%) were categorized as heart failure with reduced ejection fraction (HFREF). More than 87% of study population had pulmonary hypertension (PH). Post capillary PH (isolated or combined) was the most common type of PH (81%). The median interquartile range (IQR) of time to kidney transplantation or all-cause mortality was 1 (0.5 to 2) year. Twenty-five (36.2%) patients received a successful kidney transplant. The all-cause mortality rate was 28.8%. Older age, lower left ventricular ejection fraction (LVEF) and presence of pericardial effusion were independent predictors of all-cause mortality in multivariate analysis.
Conclusion. ESKD patients with HFREF and/or pulmonary hypertension will have remarkable improvement in terms of their cardiac performance parameters following kidney transplantation.

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Original Paper

INTRODUCTION

The intimate link between the heart and kidneys is a well-known fact. In order to have a better understanding of the pathophysiologic issues and select the optimal managing strategy, investigators have classified this relationship into five classes of cardiorenal syndrome.[1-3] Cardiovascular disorders are the leading cause of mortality and morbidity in

patients with chronic kidney disease, particularly those with end- stage kidney disease (ESKD) who are on renal replacement therapies.[4-8]

Both traditional cardiovascular risk factors such as diabetes mellitus, hypertension, smoking and hyperlipidemia and the novel and uremic related risk factors accelerate the progression of cardiovascular problems in ESKD patients; regardless of the etiology, these patients will have very poor outcomes.[7,9-12]

Given the presence of cardiovascular risk in individuals with chronic kidney disease, many ESKD patients are likely to have some degree of cardiovascular abnormalities at any stage of their disease. On the other hand, regardless of a high incidence of cardiovascular abnormalities in ESKD, it has been shown that many of these abnormalities remarkably improve following a successful kidney transplantation.[7,12-16]

Despite the fact that individuals with ESKD have a poor prognosis even when treated with cardiovascular-specific medications, prompt initiation of kidney transplant program will save their cardiovascular health.[12-15,17,18]

In the current study, we aimed to have a detailed description of different patterns of cardiovascular abnormalities, the hemodynamic profile, and the outcome of ESKD patients referred to the heart failure department of a tertiary center for cardiovascular assessment and registered in right heart catheterization registry of Rajaie Heart Center (RHC-RHC).

MATERIALS AND METHODS

The RHC-RHC registry was founded in 2009 and is operational at present. The data of all right heart catheterizations is registered in specific registry forms in hospital information system (HIS). In this cohort, we enrolled all ESKD patients referred to our heart failure department by nephrologists for a comprehensive cardiovascular assessment and scheduled them for hemodynamic study by right heart catheterization (RHC) for further planning of cardiovascular therapies and/or decision making for kidney transplantation. The HIS was queried for all adult patients with the diagnosis of ESKD who had undergone RHC between July 2009 and October 2021 in heart failure and transplantation department of Rajaie Cardiovascular Medical and Research Center, Tehran, Iran.

The following inclusion criteria were used to enroll the patients:

1- History of ESKD on routine hemodialysis for at least one year

2- Right heart catheterization for the first time

Patients with considerable missing data, missed follow- up and those who were on peritoneal dialysis were excluded.

Demographic data, clinical characteristics, echocardiography and laboratory variables were all extracted from HIS and patients' hospital documents.

The method for RHC has been described elsewhere in detail.[19]

Definitions

According to the European heart failure guideline, heart failure is defined as a clinical syndrome that is characterized by the primary symptoms and signs of dyspnea, fatigue, peripheral edema, lung crackles and elevated jugular venous pressure. It is further divided into three categories including heart failure with reduced ejection fraction (HFREF), heart failure with mildly reduced ejection fraction (HFMREF) and heart failure with preserved ejection fraction (HFPEF).[20]

Additionally, normal, high and low cardiac output (CO) are defined as a resting CO of 2.5 to 4 L/min, more than 8 L/min and less than 2.5 L/min, respectively.[21]

Pulmonary hypertension (PH) is defined based on the updated clinical classification as a mean pulmonary artery pressure (PAP) of ≥ 20 mmHg detected in right heart catheterization.

According to the most current version of the PH guideline, the followings are the PH categories:

1- Precapillary PH: mean PA*P* > 20 mmHg, pulmonary capillary wedge pressure (PCWP) ≤ 15mmHg and pulmonary vascular resistance (PVR) ≥ 3 Wood unit

2- Isolated post capillary PH: mean PA*P* > 20 mmHg, PCW*P* > 15 mmHg and PVR < 3 Wood unit

3- Combined pre- and post-capillary PH: mean PA*P* > 20 mmHg, PCW*P* > 15 mmHg and PVR ≥ 3 Wood unit[22]

Outcome of Interest. We divided the study population into 4 groups based on the recommended plans from the RHC report sheet as the followings:

1- Kidney transplantation possible

2- Medical therapy and further re-evaluation of cardiovascular function for decision making
3- Heart and kidney transplantation recommended
4- Specific addressing of the cardiovascular problem and follow- up recommended

The outcome of the selected patients in terms of all-cause mortality or successful kidney transplantation until January 2022 was monitored by reviewing their hospital records or by phone contact. We also asked those patients who had received a kidney transplant to refer for a follow-up visit and undergo a new echocardiogram, to assess their cardiovascular function following transplantation.

Statistical Analysis

All analyses were conducted using IBM SPSS 19. One sample Kolmogorov Smirnov test was used to assess the normal distribution of variables.

Continuous variables were presented as mean (± standard deviation) and median (interquartile range), and were compared using the Mann-Whitney *U*-test, the Student's *t*-test, ANOVA and the Kruskal-Wallis tests, or Wilcoxon signed ranks test, as appropriate. Categorical data were presented as numbers and percentages and were compared by the χ^2 test or Fisher exact test. Binary regression multivariable analysis was used for multivariable analysis. Kaplan Meier estimator was used to show the survival of study population during the follow- up time. All reported probability values were two-tailed, and a *P* value of < .05 was considered statistically significant.

The current study was approved by the research and ethic committee of our center with the ethical code of IR.RHC.REC.1400.073.

RESULTS

Out of almost 2000 patients who were scheduled for RHC, a total of 73 patients (54.7% male) were selected according to the inclusion / exclusion criteria.

With the exception of four patients who required treatment for specific cardiovascular or valvular problems, others were referred for heart failure consultation due to a significant cardiovascular problem (reduced ejection fraction or pulmonary hypertension) in order to assess the potential of kidney transplantation.

Tables 1 to 5 depict demographic, clinical, laboratory, echocardiographic, and hemodynamic data of all study population; respectively.

Table 1. Demographic Data of Study Population (n = 73)

Variables (n = 73)	Value
Age, y [mean (SD)]	37.7 (10.4) [Range = 19 to 69]
Sex, n (%)	
Male	40 (54.7)
Weight, kg [mean (SD)]	64.4 (13.9) [Range = 37 to 100]
Body Surface Area, m^2 [mean (SD)]	1.7 (0.2)
Hemodialysis Duration, y [median (IQR)]	2 (1.25 to 4)
Hypertension, n (%)	63 (86.6)
Diabetes Mellitus, n (%)	12 (16.4)
Coronary Artery Disease, n (%)	13 (17.8)
Coronary Revascularization, n (%)	9 (12.3)
Dyslipidemia, n (%)	10 (13.7)
Smoking, n (%)	10 (13.7)
Drug Abuse, n (%)	2 (2.7)
Hypothyroidism, n (%)	8 (11)
History of Stroke, n (%)	1 (1.4)
Peripheral Vascular Disease, n (%)	1 (1.4)
Alcohol, n (%)	0
Connective Tissue Disease, n (%)	0

Figure 1 shows the different types of heart failure. The median Interquartile range

(IQR) of left ventricular ejection fraction in HFREF was 25% (20 to 33).

More than 87% of our study population had PH. Post capillary PH (isolated or combined) was the most common type of PH (81%) (Figure 2).

About one third of the patients had high cardiac output syndrome. The median (IQR) of cardiac index in this group was 5.1 (4.6 to 7.7) L/min / m^2. All of these patients had arteriovenous fistula (AVF) for hemodialysis and they were advised for AVF closure before transplant (Figure 3).

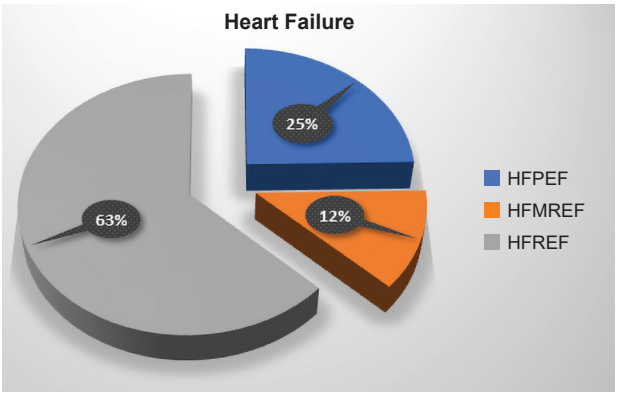

Figure 1. Different Types of Heart Failure, Considering the Heart Failure Definition (n = 73)

Table 2. Clinical Findings of Study Population (n = 73)

Variable	Value
Symptoms and Signs	
Dyspnea	73 (100)
NYHA Function Class, n (%)	
I	13 (17.8)
II	24 (32.9)
III	36 (49.3)
IV	0
Orthopnea, n (%)	36 (49.3)
PND, n (%)	30 (41.1)
Peripheral Edema, n (%)	46 (63)
Ascites, n (%)	22 (30.1)
Electrocardiogram	
Sinus Rhythm, n (%)	71 (97.3)
AF Rhythm, n (%)	2 (2.7)
Wide QRS, n (%)	4 (5.4)
Vascular Access, n (%)	
Catheter	11 (15.1)
AV Fistula	62 (84.9)
Indication for Right Heart Catheterization, n (%)	
Left Ventricular Dysfunction	54 (73.9)
Pulmonary Hypertension Without LV Dysfunction	19 (26.1)
LV Dysfunction and PH	44 (60.3)
Recommendation After Catheterization, n (%)	
Kidney Transplant	27 (37)
Kidney and Heart Transplant	2 (2.7)
Specific Addressing the Cardiovascular Problem and Follow-up	4 (5.4)
Medical Therapy and Further Re-evaluation of Cardiovascular Function for Decision Making	40 (54.8)
Cardiovascular Medications	
Diuretics, n (%)	33 (45.2)
ACEI/ARB, n (%)	59 (80.8)
Calcium Channel Blocker, n (%)	35 (47.9)
Minoxidil, n (%)	2 (2.7)
Prazosin, n (%)	20 (27.4)
Methyldopa, n (%)	1 (1.4)
Beta Blocker, n (%)	52 (71.2)
Hydralazine, n (%)	16 (21.9)
Nitrate, n (%)	9 (12.3)
MRA, n (%)	5 (6.8)
Digoxin, n (%)	7 (9.6)
Warfarin, n (%)	1 (1.4)
ASA/Clopidogrel, n (%)	21 (28.7)
Statin, n (%)	11 (15)
PDE5I , n (%)	6 (8.2)

Abbreviations: AV, arterial venous; AF, atrial fibrillation; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LV, left ventricle; NYHA, New York Heart Association; MRA, mineralocorticoid receptor antagonist; PND, paroxysmal nocturnal dyspnea; PDE5I, phosphodiesterase type 5 inhibitors; PH, pulmonary hypertension.

All of the patients who were referred for pre-transplant evaluations, underwent selective coronary angiography. Eleven patients had significant coronary artery disease, coronary angioplasty and CABG was done for revascularization.

Table 3. Laboratory Findings of Study Population (n = 73)

Variable	Value
Hemoglobin, mean (SD)	11.3 (1.8)
WBC Count, median (IQR)	6100 (5100 to 8700)
Platelet Count, median (IQR)	164000 (152000 to 195000)
FBS, median (IQR)	88 (77 to 105)
Triglyceride, median (IQR)	94 (79 to 130)
Cholesterol, mean (SD)	130 (41)
HDL, median (IQR)	37 (34 to 41)
LDL, mean (SD)	69.6 (24)
BUN, median (IQR)	44 (34 to 58)
Creatinine, median (IQR)	7.6 (6.2 to 9.3)
Sodium, median (IQR)	139 (138 to 140)
Potassium, median (IQR)	4.9 (4.3 to 5.2)
Magnesium, median (IQR)	2.3 (2.2 to 2.5)
Uric Acid, mean (SD)	6.3 (5.7 to 6.6)
ALT, median (IQR)	14 (11 to 37)
AST, median (IQR)	17 (12 to 23)
LDH, median (IQR)	426 (339 to 469)
Total Bilirubin, median (IQR)	1 (0.8 to 1.1)
TSH, median (IQR)	3.4 (2.6 to 4.3)
T4, median (IQR)	7.1 (5.3 to 7.9)
T3, median (IQR)	0.8 (0.8 to 0.9)
NT-Pro BNP, median (IQR)	25000 (16500 to 35000)

Abbreviations: FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoproteins; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone; NT-pro-BNP, N-terminal pro b-type natriuretic peptide.

Follow Up Data and Outcomes

The median (IQR) follow-up duration from index RHC was 6 (2 to 7) years. The median (IQR) of time to kidney transplantation or all-cause mortality was 1 (0.5 to 2) years. The median (IQR)

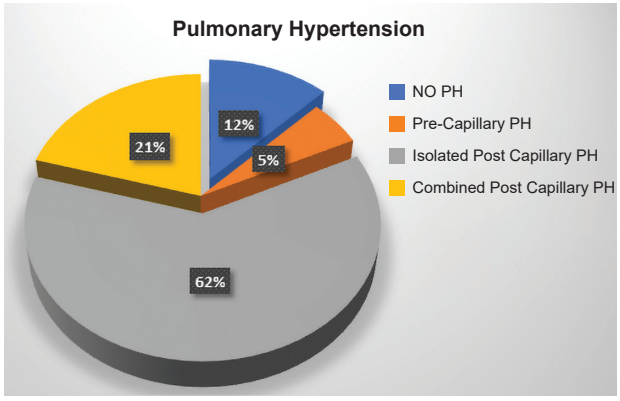

Figure 2. Different Types of Pulmonary Hypertension, Considering the Hemodynamic Definition of Pulmonary Hypertension (n = 73)

Table 4. Echocardiographic Findings of Study Population (n = 73)

Variable	Value
LVEF, % [median (IQR); range]	25 (20 to 40); 10 to 55
LVEDD, mm [median (IQR); range]	61 (54 to 64); 42 to 70
LVESD, mm [median (IQR); range]	47 (39 to 51); 29 to 59
LVEDVI, mm^3 [median (IQR); range]	87 (78 to 115); 54 to 217
LVOT-VTI, cm^2 [median (IQR); range]	20 (14 to 24); 5.9 to 29
RV Sm, cm/s [median (IQR); range]	10 (8 to 12); 6 to 15
TAPSE, mm [median (IQR); range]	18 (15 to 21); 11 to 26
TRG, mmHg [median (IQR); range]	45 (30 to 55); 15 to 75
SPAP, mmHg [median (IQR), range]	60 (35 to 70); 30 to 80
E/E, [median (IQR), range]	18 (14 to 22); 5 to 30
LVH, n (%)	36 (49.3)
Severe LV Enlargement, n (%)	19 (26)
Severe RV Enlargement, n (%)	5 (6.8)
Valvular Heart Diseases, n (%)	
Mitral Regurgitation	
Mild / Moderate	51 (69.8)
Severe	14 (19.2)
Mitral Stenosis	
Severe	1 (1.4)
Aortic Regurgitation	
Mild / Moderate	26 (35.6)
Severe	2 (2.7)
Aortic Stenosis	
Mild / Moderate	4 (5.5)
Tricuspid Regurgitation	
Mild	18 (24.6)
Moderate	39 (53.4)
Severe	16 (21.9)
Reduced IVC Collapse (Normal Size), n (%)	1 (1.4)
Increased IVC Size (Normal Collapse), n (%)	19 (26)
Reduced IV Collapse (Increased Size), n (%)	31 (42.4)
Pericardial Effusion, n (%)	20 (27.4)

Abbreviations: LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDVI, left ventricular end-systolic volume index; LVOTVTI, left ventricular outflow tract velocity time integral; RV sm, right ventricle peak systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TRG, tricuspid regurgitation gradient; SPAP, systolic pulmonary pressure; LVH, left ventricular hypertrophy; IVC, inferior vena cava.

of time to kidney transplantation was 3 (2 to 6) months. The median (IQR) of time to death was 1 (0.7 to 1) year.

A total of 69 (94.5%) individuals were referred for pre-transplant cardiac consultation, out of which 25 (36.2%) were successfully transplanted. We did not have access to the peri-operative data of the transplanted group, but all were successfully discharged from hospital without any surgical related mortality.

Table 5. Hemodynamic Data of Study Population (n = 73)

Variable	Value
Body Surface Area, m^2 [mean (SD)]	1.7 (0.2)
Systolic Blood Pressure, mmHg [median (IQR)]	147 (130 to 173)
Diastolic Blood Pressure, mmHg [median (IQR)]	85 (70 to 100)
Mean Blood Pressure, mmHg [median (IQR)]	107 (95 to 123)
Heart Rate, beat/min [median (IQR)]	80 (75 to 90)
Fick Cardiac Output, L/min [median (IQR)]	5.9 (4.8 to 8)
Fick Cardiac Index, L/min /m^2 [median (IQR)]	3.5 (2.7 to 4.5)
RAP, mmHg [median (IQR)]	10 (8 to 15)
RV Systolic Pressure, mmHg [median (IQR)]	45 (40 to 60)
RV End-diastolic Pressure, mmHg [median (IQR)]	7 (5 to 10)
PASP, mmHg [median (IQR)]	43 (38 to 60)
PADP, mmHg [median (IQR)]	20 (16 to 30)
Mean PAP, mmHg [median (IQR)]	27 (25 to 40)
PCWP, mmHg [median (IQR)]	20 (15 to 25)
PVR, Wood Unit [median (IQR)]	1.6 (0.8 to 2.5)
SVR, Wood Unit [median (IQR)]	15 (12 to 20)
Pulmonary Artery Compliance [median (IQR)]	3 (2 to 4.4)
RA/PCWP [median (IQR)]	0.57 (0.4 to 0.7)
RVSWI [median (IQR)]	9.9 (6.5 to 15.6)
Pulmonary Artery Pulsatility Index [median (IQR)]	2.2 (1.5 to 3.6)

Abbreviations: RAP, right atrium pressure; RV, right ventricle; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; Mean PAP, mean pulmonary artery pressure (PASP+2*PADP/3); PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; RVSWI, right ventricle stroke work index (0.0136 × stroke volume index × (mean pulmonary artery pressure – right atrial pressure)).

All-cause mortality rate in all study population including kidney transplant candidates was 28.8 and 30.4%, respectively. After kidney transplantation, 13 out of 25 patients experienced an episode of allograft rejection and 3 of them died as a result

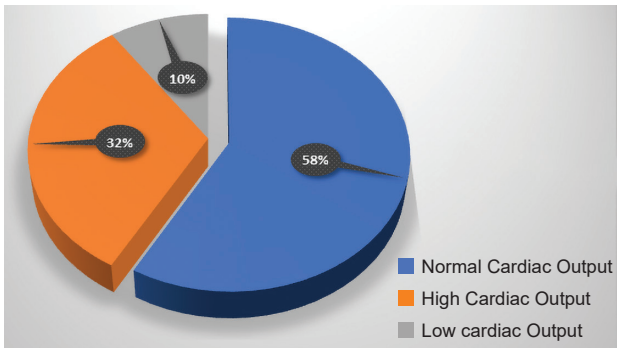

Figure 3. Study Sub Groups Based on Cardiac Output (n = 73)

of its complications. Two cases later underwent second transplantation.

According to our study, ESKD patients who are candidate of kidney transplantation are categorized into four groups:

Group 1 (Kidney transplantation would be possible): Twenty-seven (37%) patients (48.1% male) were included in this group. At the end of the follow- up period about one third of the patients in this group received a kidney transplant (9 of 27), 8 patients (29.6%) died and the rest of them are still on the waiting list for a kidney transplantation. One case passed away after a kidney transplant due to allograft rejection and the associated complications.

Group 2 (Medical therapy and further re-evaluation of cardiovascular function required for definite decision making): This group included 40 (54.8%) patients (60 % male). At the end of the follow up duration 16 (40%) patients successfully received a kidney transplant, 12 patients (30%) died and the rest of them are still waiting for further decision making or kidney transplantation. One of the deaths occurred after a kidney transplant as a result of rejection and its associated complications.

Figure 4 shows the outcome of the study population in groups 1 and 2. There was no statistically significant difference between the two sub-groups in terms of outcomes. Furthermore, there was no statistically significant difference between the groups in term of the hemodynamic, echocardiographic data or duration of dialysis.

Table 6 compares the clinical, hemodynamic, and echocardiographic data of the groups 1 and 2 in terms of three main outcomes.

Group 3 (Heart and kidney transplantation): Two (2.7%) patients of this group had HFREF, with high filling pressures and low cardiac output, and one of them died during the follow up period.

We recommended to all patients in groups 1 to 3 to receive guideline-directed medical therapies for heart failure, including appropriate blood pressure control, hemodialysis optimization, and volume overload management in those with high filling pressures and congestion. Regular follow-up (every 1 to 3 months before and after kidney transplantation) in a heart failure clinic or regular visits by a dedicated cardiologist was also suggested.

Table 6. Comparison of Echocardiographic and Hemodynamic Variables Between Two Groups of Recommendation

	Group 1 (n =27)				Group 2 (n = 40)					
	Kidney Transplant	Dead	Alive	*P* (In Group 1)	Kidney Transplant	Dead	Alive	*P* (In Group 2)	*P* (Between Groups)
Age	42 (12)	43 (9)	39 (11)	> .05	37 (10)	40 (11)	35 (9)	0.6	> .05
LVEF	40 (30 to 40)	35 (17 to 50)	25 (25 to 25)	> .05	20 (15 to 35)	17 (10 to 32)	45 (45 to 50)	0.4	> .05
LVEDVI	82 (79 to 101)	87 (81 to 102)	100 (78 to 111)	> .05	94 (83 to 110)	108 (88 to 125)	80 (73 to 95)	0.7	> .05
TRG	50 (30 to 50)	58 (51 to 62)	38 (33 to 40)	> .05	45 (31 to 50)	45 (30 to 56)	42 (30 to 45)	0.5	> .05
TAPSE	19 (17 to 21)	19 (15 to 22)	19 (18 to 22)	> .05	16 (15 to 18)	16 (14 to 19)	18 (16 to 23)	0.6	> .05
RVsm	10 (9.5 to 10.5)	13 (11 to 14)	12 (10 to 12)	> .05	9 (7 to 10)	9 (7 to 11)	10 (8 to 12)	0.4	> .05
CO	5.3 (5.2 to 5.6)	7.9 (5 to 10)	5.8 (5.5 to 7.6)	> .05	5 (4.5 to 5.6)	4.6 (3.7 to 5.7)	6.7 (6.2 to 6.9)	0.6	> .05
CI	3.3 (3.1 to 3.4)	4 (2.7 to 5.5)	3.7 (3.3 to 4.1)	> .05	2.9 (2.6 to 3.3)	2.6 (2.2 to 2.8)	3.9 (3.4 to 4)	0.5	> .05
Mean PAP	21 (19 to 29)	35 (26 to 45)	26 (26 to 30)	> .05	29 (26 to 40)	36 (27 to 46)	40 (31 to 46)	0.9	> .05
Mean BP	106 (103 to 114)	101 (88 to 118)	100 (93 to 110)	> .05	101 (90 to 114)	103 (96 to 110)	100 (95 to 115)	0.4	> .05
RAP	8 (7 to 10)	12 (8 to 13)	8 (8 to 8)	> .05	11 (9 to 18)	10 (10 to 12)	15 (15 to 17)	0.7	> .05
PCWP	14 (14 to 15)	25 (18 to 32)	20 (20 to 20)	> .05	20 (19 to 22)	27 (20 to 37)	25 (25 to 30)	0.3	> .05
PVR	1.3 (1 to 2.5)	1.1 (0.9 to 2)	1.9 (0.9 to 2)	> .05	2.2 (1.5 to 2.7)	2.8 (1.7 to 3.5)	1.6 (1.1 to 1.9)	0.6	> .05
SVR	17 (16.8 to 19.5)	10.5 (8 to 23)	15.8 (13 to 24)	> .05	16.6 (15 to 19.5)	20 (15 to 26)	14.4 (13 to 15)	0.5	> .05

Abbreviations: LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-systolic volume index; RVsm, right ventricle peak systolic velocity; TAPSE, tricuspid annular plane systolic excursion; CO, cardiac output; CI, cardiac index; RAP, right atrium pressure; Mean PAP, mean pulmonary artery pressure (PASP + 2 * PADP /3); PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

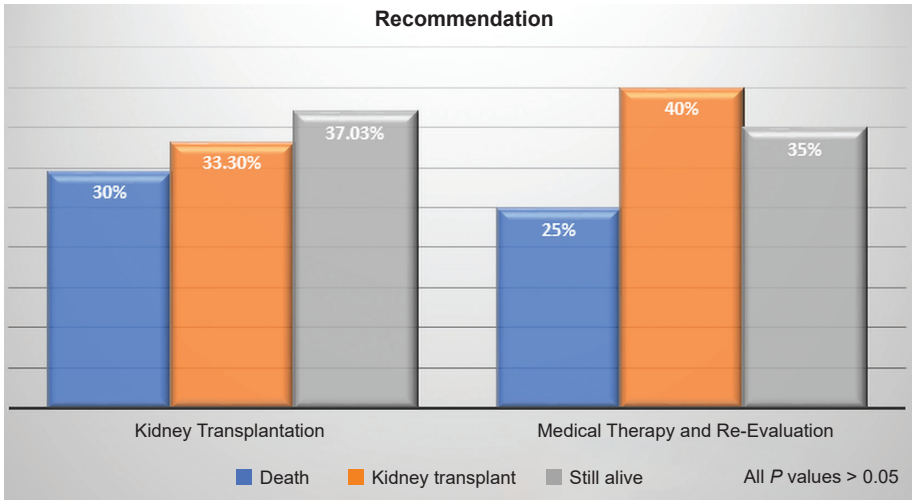

Figure 4. Destiney of Patients in Recommendation Groups (n = 67)

All transplanted patients in group 2 had well controlled heart failure and / or pulmonary hypertension, and the kidney transplant procedure was done with the permission of the heart failure specialist.

Group 4 (Specifically addressing the cardiovascular problem and follow-up): Two patients in group 4 had coronary artery bypass graft surgery (CABG), one of whom had concomitant mitral valve replacement due to severe mitral stenosis, and another had aortic valve replacement due to severe aortic regurgitation; both are alive.

Thirteen patients underwent RHC during COVID-19 pandemic, of whom two patients received a successful transplant and 3 passed away.

Figure 5 shows the frequency of different types of heart failure in kidney transplanted group.

We also asked the transplanted patients to provide a second transthoracic echocardiogram at any time post-transplantation Due to COVID-19 pandemic only 10 patients accepted to perform a new echocardiography. Table 7 shows the comparison of echocardiographic data at baseline and after kidney transplantation.

Figure 6 displays the Kaplan-Meier curve of survival analysis with and without kidney transplantation in individuals who were referred for kidney transplantation, indicating that those who received a kidney transplantation have higher survival rate.

The univariate and multivariate analyses for prediction of all-cause mortality in this group of patients are shown in Table 8. The multivariate analysis model using binary logistic regression showed that older age, lower LVEF and presence of pericardial effusion are independent predictors of mortality. Presence of pericardial effusion was the single most powerful predictor of mortality

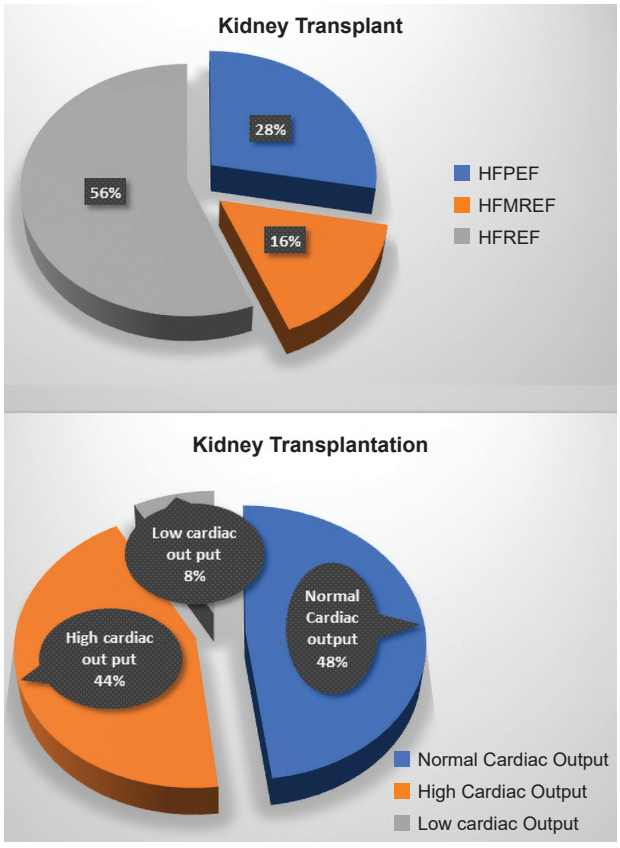

Figure 5. Frequency of the Heart Failure Types in Kidney Transplanted Group (n = 25)

Table 7. Comparison of Echocardiographic Data Pre- and After Kidney Transplantation (n = 10)

	Before Kidney Transplant (n = 10)	After Kidney Transplant (n = 10)	*P*
LVEF, % [mean (SD)]	27 (12)	45 (7)	< .05
LVEDVI, mL/m^2 [median (IQR)]	106 (102 to 110)	64 (38 to 91)	> .05
TAPSE, mm [median (IQR)]	16 (15 to 17)	19 (18 to 21)	> .05
RVSm, m/s [median (IQR)]	8.5 (7 to 10)	10.2 (9.5 to 11)	< .05
TRG, mmHg [median (IQR)]	27 (25 to 30)	19 (15 to 23)	> .05

Abbreviations: LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-systolic volume index; LVOTVTI, left ventricular outflow tract velocity time integral; RVsm, right ventricle peak systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TRG, tricuspid regurgitation gradient.

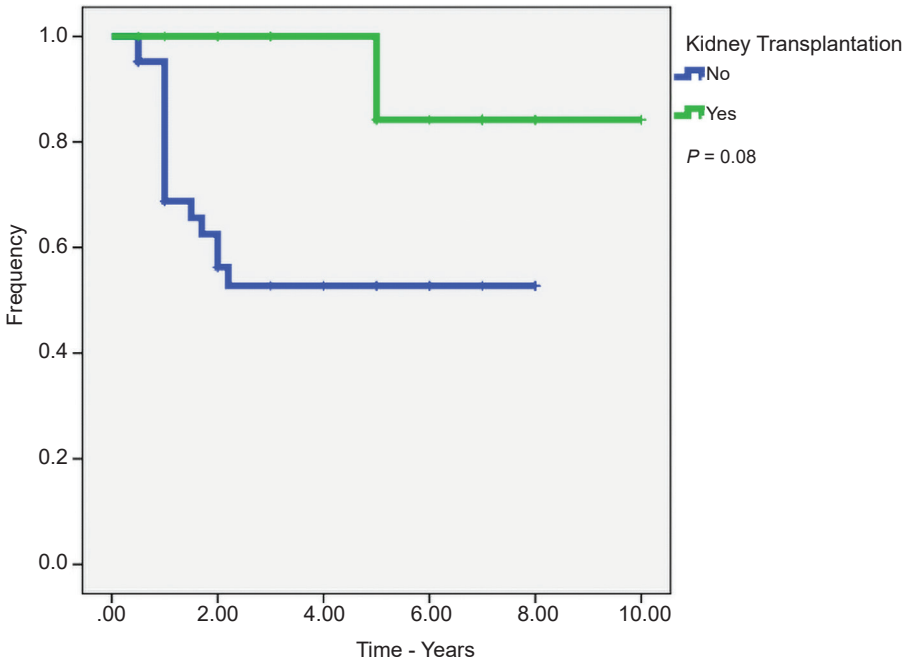

Figure 6. Kaplan-Meier Curve of Survival Analysis With and Without Kidney Transplantation

in subjects who were on waiting list for kidney transplantation [β = 1.8, *P* = .04, OR (95% CI) = 6.5 (1.08 to 39.8)].

After excluding the patients who died after kidney transplantation (3 patients) a multivariate analysis, revealed that the presence of pericardial effusion was an independent predictor of mortality [β = 1.29, *P* = .05, OR (95% CI) = 3.6 (0.9 to 13)].

DISCUSSION

In the present study, we assessed various hemodynamic profiles of ESKD patients who were candidates of kidney transplantation and were referred to our heart failure clinic due to reduced left ventricular ejection fraction or pulmonary hypertension. The majority of the participants had HFREF, and pulmonary hypertension, particularly of post capillary type. However, after optimizing their heart failure medications and controlling their blood pressure and volume overload, around one third of them were able to receive a successful kidney transplant, despite their significant cardiac problems.

Unfortunately, approximately one third of the patients died within almost a year after the index RHC, which confirms that this group of patients has very high mortality rate. Older age, smaller body surface area, lower LVEF and the presence of pericardial effusion were independent predictors of mortality in this study. There are similarities and differences between our study and the earlier investigations regarding mortality predictors, which may be attributable to the diverse study populations. However, the presence of congestive heart failure symptoms and reduced LVEF has been suggested in most of the studies.[23-25]

There are also inconsistent results from several studies regarding the prognostic value

Table 8. The Univariate and Multivariate Analyses for Predictor of All-cause Mortality in Patients Who Were Referred for Determination the Possibility of Kidney Transplantation (n = 69)

Characteristics	Univariate Analysis			Multi Variate Analysis		
	β	*P*	OR (95% CI)	β	*P*	OR (95% CI)
Age, y	0.026	> .05	1.02 (0.97 to 1.08)	0.11	< .05	1.1 (1.02 to 1.23)
Sex, male	1.24	< .05	0.28 (0.09 to 0.91)			
Body Surface Area	-4	< .001	54 (2.5 to 1163)	6.35	< .05	57 (2.4 to 133)
Dialysis Duration	0.2	> .05	0.8 (0.6 to 1)			
Presence of CAD	0.04	> .05	0.9 (0.5 to 1.8)			
Coronary Revascularization	0.5	> .05	0.1 (0.4 to 2.1)			
Diabetes Mellitus	0.5	> .05	1.6 (0.4 to 6.5)			
Hypertension	0.5	> .05	0.6 (0.1 to 2.4)			
NYHA Class	0.2	> .05	1.26 (0.63 to 2.50)			
Ascites	1.04	> .05	2.80 (0.93 to 8.65)			
Peripheral Edema	0.66	> .05	1.94 (0.64 to 5.80)			
LVEF	-0.015	> .05	0.98 (0.95 to 1.02)	-0.77	< .05	0.92 (0.86 to 0.99)
LVEDVI	0.004	> .05	1 (0.98 to 1.02)			
TAPSE	0.05	> .05	0.94 (0.81 to 1.1)			
RV Sm	0.03	> .05	1.03 (0.80 to 1.32)			
TRG	0.02	> .05	1.02 (0.98 to 1.06)			
Pericardial Effusion	1.64	< .001	5.17 (1.81 to 14.7)	2.8	< .001	16.5 (3 to 90)
Cardiac Output	0.3	> .05	0.96 (0.85 to 1.09)			
Cardiac Index, L/min /m^2	0.107	> .05	0.9 (0.7 to 1.1)			
PVR	0.27	> .05	1.3 (0.9 to 1.9)			
SVR	0.023	> .05	0.97 (0.5 to 1.09)			
Right Atrial Pressure, mmHg	0.006	> .05	1.006 (0.91 to 1.1)			
PCWP, mmHg	0.01	> .05	1.01 (0.94 to 1.08)			
Mean Pulmonary Artery Pressure, mmHg	0.038	> .05	1.03 (0.98 to 1.09)			
Kidney Transplantation	-1.6	< .05	0.2 (0.05 to 0.77)			

Abbreviations: LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-systolic volume index; RVsm, right ventricle peak systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TRG, tricuspid regurgitation gradient; IVC, inferior vena cava; RAP, right atrium pressure; RV, right ventricle; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; PCWP, pulmonary capillary wedge pressure; RAP, right atrium pressure.

of pericardial effusion, both its presence and magnitude.[26,27] In contrary to other studies, we found that pericardial effusion was a predictor of mortality. This finding could be explained by a number of factors. First of all, the majority of our selected patients were those with reduced LVEF, who had significant right ventricular failure, pulmonary hypertension and remarkable volume overload. Right ventricular failure is implicated in the pathogenesis of pericardial effusion and the presence of pericardial effusion in the setting of RV failure, for any reason, is an alarming sign.[28] On the other hand, this finding would indicate inadequate hemodialysis in our study population, and the relationship between the adequacy of renal replacement therapy and the patients' outcome is a well-established issue.[29]

Furthermore, we were unable to find any correlation between the hemodynamic measures and outcome in different study subgroups, which could be due to small sample size or the registry-based design of the study or lack of a control group.

We found that implementing an ideal guideline directed medical therapy for heart failure, as well as controlling blood pressure and volume overloads, would be beneficial in these subjects and would optimally prepare them for kidney transplantation with satisfactory results, regardless of impaired cardiac function, significant hemodynamic abnormalities, or the duration of hemodialysis.

The pathogenesis of cardiovascular dysfunction in end stage kidney disease may be multifactorial. The traditional comorbidities such as diabetes mellitus, hypertension, smoking, etc., as well as uremic toxins, endothelial dysfunction, pressure / volume overload, increased cardiac output would be all involved in its pathogenesis. Furthermore, this type of cardiovascular dysfunction may be existing since early stages of the disease, due to the combination of myocardial disorders, coronary

artery disease or pulmonary hypertension and their related complications.[7,9,11,14,15]

Harnett *et al.*, showed that about one third of ESKD patients had volume overload and congestive heart failure (CHF) at the onset of their renal replacement therapy. They also showed that almost 25% of their study population, who did not have initially symptoms of HF, subsequently developed congestive heart failure, during their course on dialysis. They suggested that reduced LV ejection fraction accompanied with older age, anemia, hypoalbuminemia and hypertension are the main risk factors for the development of congestive symptoms. The median survival of the subjects with CHF was significantly lower than those without congestion in this study (36 vs. 62 months).[30]

Despite the high prevalence of cardiovascular complications in ESKD, and challenges with kidney transplant plans in this group that exclude many of these patients, previous investigations and our study results show that kidney transplantation in ESKD patients with different forms of cardiovascular problems, has significantly improved.[23,31-35]

It has also been shown that a low preoperative LVEF, the presence of pulmonary hypertension and prolonged term of dialysis are strong predictors of poor outcome and therefore it is recommended to schedule kidney transplantation as soon as the diagnosis of these problems is made. [13,25,31,32,35]

Although we were not able to properly monitor the heart failure therapies in this trial, it is recommended that all patients receive heart failure treatments based on guidelines. It has been suggested that the main approach for improvement of cardiovascular disorders in this subset of patients may be the elimination of the offending cause, such as uremic toxins, volume and pressure overload and etc. [31] The role of heart failure therapies in the improvement of cardiac performance in post-transplant patients is not yet established and further studies are needed to shed light on this issue.

STRENGHTS AND LIMITATIONS OF THE STUDY

The current study used a registry-based cohort and the strengths and limitations of this type of studies could be taken into account.

The strength of the study would be the availability of concurrent echocardiographic data and the acquisition and analysis of the hemodynamic data by experienced medical professionals. However, small sample size and selection bias, resulting in a non-uniform study population among those who were referred to heart failure clinic, are the main limitation of this study.

In addition, we faced the COVID-19 pandemic, which substantially affected sample referral and recruitment, catheterization, kidney transplant, and patient outcomes.

In conclusion, although ESKD patients with cardiovascular problems, particularly those with HFREF and/or pulmonary hypertension, are more likely to experience cardiac and surgical complications after kidney transplantation, they will have significant improvement in terms of their cardiac performance parameters following kidney transplantation. For a better outcome in these patients, we recommend initiating heart failure specific medications with strict and advised management.

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