

Cardiovascular diseases and risk factors in kidney transplant candidates

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ABSTRACT

Objectives: Cardiovascular diseases and risk factors are associated with adverse cardiac events following kidney transplant. Therefore, pre-transplant evaluation of cardiovascular diseases and risk factors is important for determining the cardiac risk. The objective of this study is to determine the prevalence of cardiovascular diseases and risk factors in kidney transplant candidates.

Methods: This is a single-center and observational study which includes 174 end-stage renal disease patients (male: 55.2% and mean age: 49 ± 13 years) who underwent kidney transplant. Preoperative clinical characteristics, cardiovascular diseases and risk factors of the patients were examined retrospectively.

Results: The study population had multiple cardiovascular risk factors such as hypertension (66.7%), diabetes (28.2%), dyslipidemia (29.9%) and smoking (30.5%) in the evaluation conducted prior to kidney transplant. The most common cardiovascular diseases were detected as congestive heart failure (10.9%) and coronary artery disease (8.6%). The rate of the patients who underwent myocardial revascularization (percutaneous coronary intervention or coronary artery bypass grafting) before kidney transplant was 6.9%. The patients' mean left ventricular mass index was 114 ± 32 g/m², and 55.5% of the study population had left ventricular hypertrophy.

Conclusions: In our study, the prevalence of cardiovascular diseases and risk factors in the patients who underwent kidney transplant was found to be high.

Keywords: cardiovascular disease, kidney transplantation, risk factor

Cardiovascular diseases and cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, left ventricular hypertrophy are commonly seen in patients with end-stage renal disease (ESRD) [1, 2]. The prevalence of coronary artery disease in ESRD patients who received chronic dialysis was found to be 40%, while the prevalence of left ventricular hypertrophy was detected as 75%, and it is known that the risk of cardiovascular morbidity and mortality has considerably increased in these patients [3]. Kidney transplant is the most appropriate treatment strategy for patients with ESRD, and it is as-

sociated with lower cardiovascular mortality rates compared to chronic dialysis therapy [4]. Moreover, cardiovascular diseases are more commonly seen in patients who undergo kidney transplant compared to the general population and continue to be the leading cause of post-transplant mortality and morbidity [5].

Current guidelines recommend a detailed pre-operative cardiovascular evaluation and assessment of the patient's individual risk status in ESRD patients who will undergo kidney transplant [6, 7]. In these patients, evaluation, treatment and control of cardiovascular diseases and risk factors are very important in

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terms of preventing undesired post-transplant cardiac events [8]. However, in Turkish population, information regarding the frequency of cardiovascular diseases and risk factors in ESRD patients who will undergo kidney transplant is limited.

The objective of this study is to determine the frequency of cardiovascular diseases and cardiovascular risk factors in ESRD patients who will undergo kidney transplant.

METHODS

The present study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by Baskent University Institutional Review Board (Project no: 94603339-604.01.02/9412 - KA20/100) on 10/03/2020.

Study Population

One hundred seventy-four ESRD patients, who underwent kidney transplantation at Başkent University Istanbul Health Practice and Research Center Hospital between January 2011 and January 2017, were included in this study. The patients with ESRD under 18 years of age and the patients whose reliable medical archive records could not be reached were not included in the study.

The patients' demographic characteristics, etiologies of chronic renal failure, type and duration of the dialysis treatment applied, cardiovascular diseases and cardiovascular risk factors, medical treatments they received and laboratory analyses obtained during the

cardiological examination performed before the transplant, electrocardiographic and echocardiographic characteristics were retrospectively obtained from hospital's medical records.

Definitions

In the pre-transplant evaluation, hypertension was defined as the detection of systolic blood pressure as ≥ 140 mmHg and/or diastolic blood pressure as ≥ 90 mmHg in the consecutive two blood pressure measurements. The patients, who were previously diagnosed with hypertension and/or used antihypertensive drugs, were accepted as hypertensive patients regardless of the value of the measured blood pressure [9]. Diabetes mellitus was accepted as the detection of fasting plasma glucose as ≥ 126 mg/dL or HbA1c value as $\geq 6.5\%$ in the blood glucose measurement. The patients with a previous diagnosis of diabetes mellitus and/or using antidiabetic medication or insulin therapy were accepted as diabetic patients regardless of their blood glucose and HbA1c values [10]. Hyperlipidemia was accepted as the detection of low-density lipoprotein value as ≥ 130 mg/dL or total cholesterol value as ≥ 200 mg/dL or triglyceride value as ≥ 150 mg/dL in blood lipids measurement. The patients, who were previously diagnosed with hyperlipidemia and/or received lipid-lowering medication were accepted as hyperlipidemic patients regardless of their measured lipid values [11]. Occlusive coronary artery disease was defined as the detection of $\geq 50\%$ stenosis in the left main coronary artery and/or $\geq 70\%$ stenosis in the left anterior descending and/or circumflex and/or right coronary arteries in coronary angiography and/or the

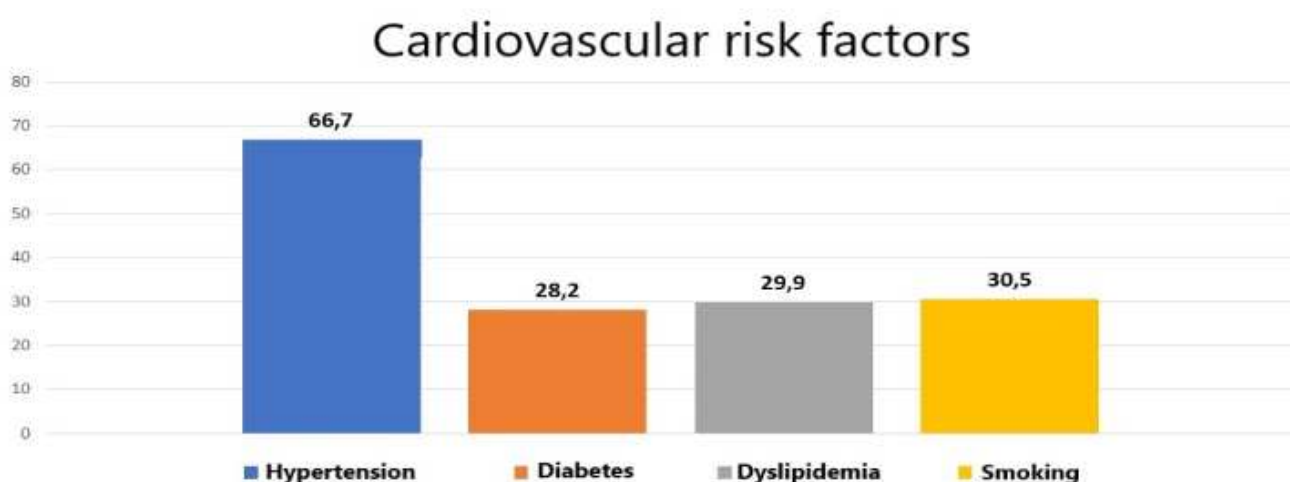


Fig. 1. The figure shows the prevalence distribution of cardiovascular risk factors in the study population.

application of coronary revascularization [12]. Congestive heart failure was defined as the detection of left ventricular ejection fraction as $< 50\%$ together with heart failure symptoms and findings or the detection of natriuretic peptide elevation and/or left ventricular hypertrophy and/or left atrial dilatation and/or left ventricular diastolic dysfunction in the patients with heart failure symptoms and findings and left ventricular ejection fraction as $\geq 50\%$ [13]. Left ventricular mass index was calculated by using the Devereux formula in the light of the echocardiographic data obtained [14]. Left ventricular hypertrophy was defined as the detection of left ventricular mass index as $> 95 \text{ g/m}^2$ in female patients and $> 115 \text{ g/m}^2$ in male patients.

Statistical Analysis

Statistical analyses of the study were performed by using the SPSS software package (SPSS, Inc., Chicago, IL, USA) version 22.0. Continuous variables were expressed as mean \pm standard deviation (mean \pm SD) or median and range, while categorical variables were presented as frequency and percentage (%).

RESULTS

The mean age of 174 patients included in the study was 49.2 ± 13.0 years, while 96 patients (55.2%) were male. The demographic and clinical characteristics of the patients are shown in Table 1. One hundred forty-five (83.3%) ESRD patients were receiving dialysis

treatment. The median dialysis treatment duration before kidney transplant was 24 months. Ten patients (5.7%) had previously undergone kidney transplant. When it was evaluated in terms of ESRD etiology, the most common causes were hypertensive nephropathy (32.2%), diabetic nephropathy (18.4%), glomerulonephritis (17.8%) and polycystic kidney disease (9.2%). The etiology of renal failure was not detected in 18.4% of the patients.

The most common cardiovascular risk factors were hypertension (66.7%), smoking (30.5%), hyperlipidemia (29.9%) and diabetes mellitus (28.2%) (Fig. 1). The most common accompanying cardiovascular diseases in the patients with ESRD were congestive heart failure (10.9%) and obstructive coronary artery disease (8.6%). Only 2 patients had a history of atrial fibrillation, and 1 patient had a history of cerebrovascular disease (Fig. 2). The most common non-cardiac comorbidities were anemia (76.4%), hyperthyroidism or hypothyroidism (9.8%), major depression (9.8%) and chronic obstructive pulmonary disease (3.4%) (Table 1).

Before kidney transplant, 47.7% of the patients were using dihydropyridine group calcium channel blocker, 33.3% beta adrenergic receptor blocker, 26.4% antiaggregant treatment, 14.9% diuretic treatment, 14.4% renin angiotensin system blocker, 14.4% alpha adrenergic receptor blocker and 12.6% statin treatment (Table 2).

In the pre-transplant evaluation of the ESRD patients included in the study, the median serum creatinine value was detected as 7.0 mg/dL (range: 2.1-16.0

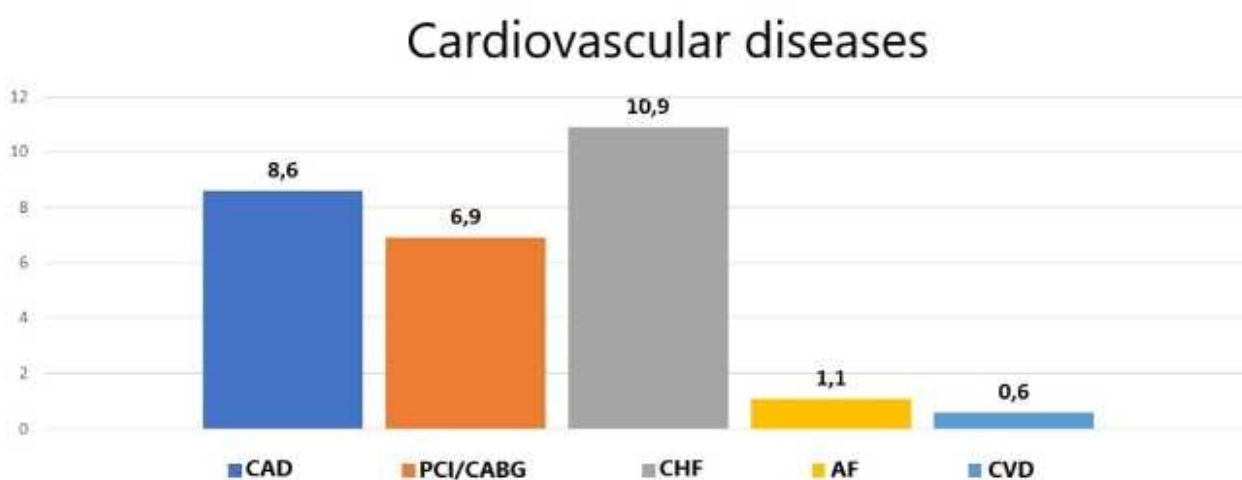


Fig. 2. The figure shows the prevalence distribution of cardiovascular diseases in the study population. (CAD = coronary artery disease, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, CHF = congestive heart failure, AF = atrial fibrillation, CVD = cerebrovascular disease).

Table 1. Clinical characteristics of kidney transplant candidates

Variables	n = 174
Age, years	49.2 ± 13.0
Sex, male	96 (55.2)
Dialysis treatment before kidney transplant	145 (83.3)
Dialysis type	
Hemodialysis	126 (72.4)
Peritoneal dialysis	19 (10.9)
Dialysis treatment duration before kidney transplant (months)	24 (1-240)
History of kidney transplantation	10 (5.7)
Donor type	
Living donor	147 (84.5)
Deceased donor	27 (15.5)
End-stage renal disease etiology	
Hypertensive nephropathy	56 (32.2)
Diabetic nephropathy	32 (18.4)
Glomerulonephritis	31 (17.8)
Polycystic kidney disease	16 (9.2)
Connective tissue disease	4 (2.3)
Renovascular disease	3 (1.7)
Unknown	32 (18.4)
Cardiovascular risk factors	
Hypertension	116 (66.7)
Diabetes mellitus	49 (28.2)
Dyslipidemia	52 (29.9)
Smoking	53 (30.5)
Cardiovascular diseases	22 (12.6)
Obstructive coronary artery disease	15 (8.6)
History of myocardial revascularization	12 (6.9)
Heart failure	19 (10.9)
Atrial fibrillation	2 (1.1)
Cerebrovascular disease	1 (0.6)
Other chronic conditions	
Chronic obstructive pulmonary disease	6 (3.4)
Anemia	133 (76.4)
Thyroid disease	17 (9.8)
Depression	17 (9.8)

Data are given as mean ± SD or n (%).

Table 2. Medical treatments, laboratory results, electrocardiographic and echocardiographic data of kidney transplant candidates

Variables	n = 174
Medical treatments	
Renin angiotensin system inhibitors	25 (14.4)
Beta – blockers	58 (33.3)
Diuretics	26 (14.9)
Calcium channel blockers	83 (47.7)
Alpha blockers	25 (14.4)
Statins	22 (12.6)
Antiaggregant/anticoagulants	46 (26.4)
Laboratory data	
Serum creatinine (mg/dL)	7.0 (2.1-16.0)
Fasting blood glucose (mg/dL)	102 (76-552)
HbA1c (%)	5.2 (3.5-9.6)
Low-density lipoprotein cholesterol (mg/dL)	111 ± 40
Hematocrit (%)	30.8 ± 5.4
C-reactive protein (mg/dL)	4.0 (0.2-98)
Thyroid stimulating hormone (mU/L)	1.5 (0.006-8.5)
Parathyroid hormone (pg/dL)	264 (17-2071)
Electrocardiographic data (117 patients)	
Sinus rhythm	115/117 (98.3)
Heart rate (bpm)	79 ± 13
Left bundle branch block	2/117 (1.7)
Non-Left Bundle Branch Block	4/117 (3.4)
Echocardiographic data (164 patients)	
Left ventricular ejection fraction (%)	58 ± 4
Left atrial diameter (mm)	38 ± 6
Mitral E velocity (cm/s)	79 ± 24
Mitral A velocity (cm/s)	76 ± 22
E/A ratio	1.1 ± 0.4
Posterior wall thickness (mm)	11.9 ± 1.7
Interventricular septum thickness (mm)	12.1 ± 1.8
Left ventricular hypertrophy	91/164 (55.5)
Left ventricular mass index (g/m ²)	114 ± 32
Moderate-to-severe mitral regurgitation	25/164 (15.2)
Moderate-to-severe tricuspid regurgitation	16/164 (9.8)
Systolic pulmonary artery pressure (mm Hg)	40 (25-65)

Data are given as mean ± SD or n (%).

mg/dL), the median fasting glucose 102 mg/dL (range: 76-552) and the median HbA1c value 5.2% (range: 3.5%-9.6%). The mean low-density lipoprotein value of the patient population was 111 ± 40 mg/dL, and the mean hematocrit value was $30.8\% \pm 5.4\%$ (Table 2).

Prior to the transplant, electrocardiographic evaluation data were obtained in 117 of 174 patients included in the study. It was observed that 98.3% of these patients were had normal sinus rhythm, and their mean heart rate was 79 ± 13 beats/minute. Only 2 patients (1.7%) had left bundle branch block and 4 patients (3.4%) had right bundle branch block or intraventricular conduction disturbance. Transthoracic echocardiographic examination was performed in 164 of 174 patients before kidney transplant. The mean left ventricular ejection fraction of the patient population was $58\% \pm 4\%$, while the mean left atrium diameter was 38 ± 6 mm. The mean left ventricular mass index was found as 114 ± 32 g/m², and the left ventricular hypertrophy was detected in 91 patients (55.5%). Moderate and/or severe mitral insufficiency was observed in 15.2% of the patients who underwent echocardiographic examination, and moderate and/or severe tricuspid insufficiency was observed in 9.8% of the patients. The median systolic pulmonary artery pressure of the patients was found as 40 mmHg (range: 25-65 mmHg) (Table 2).

DISCUSSION

In the present study, the prevalence of accompanying cardiovascular diseases and cardiovascular risk factors as well as medications, laboratory data, electrocardiographic and echocardiographic characteristics of the patients with ESRD, who underwent kidney transplant, were determined.

The age of kidney transplant in patients with ESRD varies between 43-50 years, and 58% -61% of these patients consist of male patients [15-19]. The age of the patients included in our study was found as 49 years in accordance with the literature, and 55% of them were male.

In the patients undergoing kidney transplant, long-term dialysis treatment before transplant and transplant from cadaver were found to be associated with an increased incidence of adverse cardiovascular events in the post-transplant period [20, 21]. Previous

studies reveal that the duration of dialysis treatment in the pre-transplant period varies between 18 months and 36 months on average [15, 16, 22, 23]. In our study, the mean dialysis treatment duration before transplant was determined to be 24 months similar to the previous studies. One of the most important differences of our study compared to the literature is the donor-type distribution. Literature data reveal that kidney transplant in patients with ESRD is mostly performed from cadavers rather than living donors. This rate varies between 83% and 92% [15,16]. In our study, differently from the literature, it was found that only 15.5% of the patients underwent kidney transplant from a cadaver, and 84.5% of the patients underwent kidney transplant from a living donor. This situation reveals the inadequacy of organ donation in Turkey and shows that studies that will be conducted countrywide are needed to popularize organ donation.

Our results put forward that the most common cardiovascular risk factor in patients with ESRD who undergo kidney transplant is hypertension. In our study, the prevalence of hypertension was found as 66.7%. While the prevalence of hypertension is between 21% and 26% in the general population, this rate varies between 67% and 86% in patients with ESRD. This is similar to our study data [16, 18, 19, 24].

The prevalence of diabetes mellitus in patients undergoing kidney transplant varies widely from study to study. The study conducted by Fazlzadeh *et al.* evaluated 500 patients who underwent kidney transplant and found the prevalence of diabetes as 7% [18]. On the other hand, in a comprehensive study conducted by Goyal *et al.* [17] where they evaluated 147,431 patients who underwent kidney transplant, the prevalence of diabetes was found to be 24%. The prevalence of diabetes mellitus in our study was 28.2%, and it was higher than other studies where kidney transplant candidates were evaluated [17-19, 24, 25]. According to the assessment results of the European Society of Cardiology 2019 Cardiovascular Diseases Statistics [26], the median prevalence of diabetes mellitus in the general population in the 20-79 age group was 6.8%; this rate was found to be 12.1% in Turkey. Our country is the third country with the highest prevalence of diabetes after Egypt and Lebanon. Similarly, in Turkey, the prevalence of obesity (body mass index ≥ 30 kg/m²) was reported as 25% in males and 39% in females. The high prevalence of diabetes

in our study population may be a result of the increased prevalence of obesity and diabetes in the general population.

The presence of accompanying cardiovascular disease in patients with ESRD is one of the strongest predictors of adverse cardiovascular events in the post-transplant period. According to the results of a study conducted by Aalten *et al.* [15] where 2187 patients, who underwent kidney transplant, were evaluated, the presence of cardiovascular disease before transplant increased the risk of undesired cardiovascular events in the post-transplant period by 76%. This result was confirmed by other observational studies evaluating kidney transplant patients [16, 22]. The study results show that the prevalence of cardiovascular disease varies between 7% and 16% in ESRD patients undergoing kidney transplant [15, 16, 22]. In our study, it was found that 8.6% of the patients had obstructive coronary artery disease, and 10.9% had congestive heart failure, in accordance with the current data.

In this patient group, another important cardiovascular risk factor is smoking. Studies reveal that active smoking or the history of smoking is associated with the development of cardiovascular complications in the post-transplant period [19, 22, 23]. Gonçalves *et al.* [19] reported that the 7-year all-cause mortality risk was higher than 10% in kidney transplant individuals who were smoking actively or who smoked in the past. Similarly, Chuang *et al.* [23] found that pre-transplant smoking increased the risk of developing acute coronary syndrome 3.5 times more in the early period of the first 2 years after the transplantation. In studies involving kidney transplant patients, the smoking rate was quite high and ranged from 25% to 50% [16, 19, 22]. In our country, the prevalence of smoking in the general population aged 15 years and above varies between 40-45% in males and 10-15% in females [26]. Our study shows that approximately one third of the patients who undergo kidney transplant actively smoke or have a history of smoking. In our study, the prevalence of smoking was found to be 30.5% among patients, and this rate almost coincides with the rates in the general population. This situation shows that the efforts and campaigns across the country to provide support for smoking cessation are still insufficient. More widespread and aggressive strategies are needed across the country in order to achieve a reduction in

terms of smoking.

The presence of left ventricular hypertrophy is a risk factor for the development of cardiovascular diseases [9]. The presence of left ventricular hypertrophy in the patients with ESRD is associated with the development of ischemic heart disease, congestive heart failure and ventricular arrhythmia [27]. The prevalence of left ventricular hypertrophy in patients undergoing kidney transplant ranges from 45% to 75%. This significant difference revealed in different studies is due to the lack of a standard approach in the diagnostic methods and estimation values used to detect left ventricular hypertrophy. In our study, the prevalence of left ventricular hypertrophy was found as 55.5%.

Limitations

The most important limitations of our study are its retrospective design and the inclusion of the patients from a single center. The relatively limited number of the patients included in the study reduces the statistical power of the study. Retrospective data were based on the documentation of medical history, clinical examination and treatments during the preoperative cardiac examination, and follow-up data after renal transplantation were not obtained. Thus, the rehospitalization and mortality rates of the patients after transplantation are unknown. Because of these limitations, the results of this study should be interpreted carefully.

CONCLUSION

Our study reveals that the prevalence of cardiovascular disease and cardiovascular risk factors is high in ESRD patients undergoing kidney transplant. Therefore, pre-operative cardiovascular risk assessment is important in terms of minimizing the risk of adverse events in the post-transplant period in ESRD patients who are kidney transplant candidates.

Authors' Contribution

Study Conception: UK; Study Design: UK; Supervision: UK; Funding: UK; Materials: UK; Data Collection and/or Processing: UK; Statistical Analysis and/or Data Interpretation: UK; Literature Review: UK; Manuscript Preparation: UK and Critical Review: UK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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