

Cardiovascular Disease Risk Assessment in Kidney Transplant Recipients

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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in kidney transplant recipients (KTR). Risk factors for CVD are prevalent pre- and post-transplantation.

Objective: To identify CVD and to examine related risk factors after six months of kidney transplantation.

Methods: A cross sectional study was conducted in the nephrology unit, Hawler teaching hospital, Erbil, Iraq, from 1st July 2021 to 30th December 2021 on a sample of KTR after six months of transplantation. Recipients' characteristics including; age, gender, body mass index, history of rejection, prior CVD, smoking, hypertension, and diabetes mellitus were recorded. Lab tests were done; serum creatinine, 25(OH) D, C-reactive protein (CRP), parathyroid hormone (PTH), lipid profile, hemoglobin, HbA1C, and urinary protein. The CKD-EPI equation was used to estimate glomerular filtration rate (eGFR). In addition to history and physical exam, diagnosis of cardiac abnormalities were accomplished through electrocardiography and echocardiography studies.

Results: A total of 100 KTR were studied, of them 52% were male, their mean age was 43.8 ± 10.9 years. CVD was detected in 18% of participants, associated with multiple risk factors; older age, previous CVD, smoking, history of rejection, $eGFR < 60 \text{ mL/min/1.73m}^2$, anemia, and proteinuria, all with a highly significant p value (< 0.001), left ventricular hypertrophy (LVH) ($p 0.02$), hypertension ($p 0.01$), high CRP ($p 0.01$), and HbA1C $> 7\%$ ($p 0.03$). Gender, obesity, LDL cholesterol, triglyceride, vitamin D, and high PTH were not significantly related to CVD in KTR.

Conclusion: Cardiovascular diseases are common among KTR, it were significantly associated with increasing age, prior CVD, smoking, history of rejection, low eGFR, hypertension, anemia, high HbA1C, proteinuria, high CRP and LVH.

Keywords: Kidney transplant. Cardiovascular diseases. Acute rejection. Risk factors

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1. INTRODUCTION

Kidney transplant surgery is the preferred option for patients with end-stage renal disease (ESRD) that characterized recently by saving lives, appropriate cost and higher quality of life with good prognosis as compared to long-life dialysis (1). The cardiovascular disease (CVD) represented the commonest complication and a major cause of death with a functioning graft following renal transplant (2, 3), accounting for about 30% of hospitalizations with an associated 4% mortality (4). Although the incidence of CVD death is markedly reduced in the transplant population compared with those on dialysis, it is significantly greater than that of the general population (5). Strategies to address CVD in kidney transplant recipients (KTR) have focused on risk factors modification and medical management of co-morbidities (6). The spectrum of CVD seen in KTR includes coronary artery disease, heart failure, cardiac dysrhythmias, pulmonary hypertension, peripheral artery disease, and cerebrovascular stroke (7). Risk factors for CVD are classified into either traditional (hypertension, diabetes mellitus, dyslipidemia, obesity and smoking) or non-traditional (anemia, left ventricular hypertrophy (LVH), mineral bone diseases, inflammation, oxidative stress, and immunosuppression) which might present before or after the transplant (8, 9, 10). Although CVD risk factors are easily identifiable, however the control of these factors in KTR is often poor, as has shown in FAVORIT study, blood pressure were inadequately controlled in 69% of hypertensive KTR, and 60% of those with dyslipidemia were not treated (10). Heart failure with reduced ejection fraction is prevalent in KTR, it is the leading cause of CVD-related hospitalization (4), while prevalence of heart failure with preserved ejection fraction is not well known (11). The coronary artery disease and dysrhythmias are also prevalent CVD detected in pre and post-kidney transplant patients (2, 12). Over 50% of CVD related deaths in KTR are sudden and presumed to be secondary to dysrhythmia and cardiac arrest (13). Screening echocardiogram is essential for post-transplant patients with heart failure symptoms, previous CVD (11). In Iraq, kidney- transplantation (KT) has begun since 50 years, is still developing with promising results despite of many challenges (14). The scarcity of national literatures assessing the CVD post-transplant urged us to conduct this study that is aimed

to identify the cardiovascular disease and related risk factors after six months of kidney transplantation.

2. PATIENTS AND METHODS

This cross-sectional study was conducted in the Nephrology unit, Hawler Teaching Hospital, Erbil, Iraq from July 1, 2021 to December 31, 2021. The study was approved by the scientific and ethical committee of Kurdistan Board for Medical Specialties in accordance with the Helsinki's declaration guideline for the involvement of humans in research. All participants gave their written and informed consent. A convenient sample of adult KTR underwent live kidney donation were enrolled in the current study. Exclusion criteria were; age <18 years, deceased donor KT, combined kidney-liver transplant, post kidney transplant period of less than six months. Out of 107 patients, 100 of them were included after eligibility to inclusion and exclusion criteria, other dropped because of unwillingness, missing or incomplete data. Each participant, underwent detailed history and comprehensive physical examination. Recipients' demographic characteristics and potential risk factors including; age, gender, body mass index, history of acute rejection episodes, smoking, hypertension, diabetes mellitus and history of CVD were recorded. Lab tests were done; including serum creatinine, 25(OH) D, C-reactive protein (CRP), parathyroid hormone (PTH), lipid profile, hemoglobin (Hb), HBA1C, and urinary protein. The CKD-EPI (epidemiological) equation was used to estimate glomerular filtration rate (eGFR). In addition to history and physical exam, diagnosis of cardiac abnormalities were accomplished through electrocardiography and echocardiography studies. The BMI of patients was divided into >30 Kg/m² and less. The eGFR was categorized into > 60ml/min/1.73m² or less, the proteinuria was diagnosed by dipstick test and confirmed by estimation of protein/creatinine ratio, regarded significant if it is ≥500 mg/g. Vitamin D level was considered low if 25(OH)D less than 20 ng/ml and anemia was diagnosed if Hb level was less than 11.5 g/L, while high CRP was considered high with level of more than 5 mg/L. Triglycerides level of ≥200 mg/dl, LDL of ≥130 mg/dl, PTH > 65 pg/ml, and HbA1c level > 7% were regarded high. Hypertension was defined, as blood pressure level of ≥ 130/80 (15) on two occasion one week apart or the patient already on antihypertensive medications.

Statistical analysis: Results are expressed as numbers and percentages for categorical variables and as a mean (\pm standard deviation) for continuous variables. Chi-squared test and one way ANOVA test were applied for categorical and continuous variables as appropriate to compare proportions. Data were analyzed with the Statistical Package for Social Sciences version 24 (SPSS, IBM company, USA). A p value of <0.05 was considered significant.

3. RESULTS

This study enrolled 100 KTR with a mean age of 43.8 ± 10.9 years, and post-transplant period of 15.7 ± 8.2 months. Their baseline characteristics and investigations are shown in (Table 1)

Table 1. Baseline characteristics and investigations of the study population

Variable	No. (%)	Mean \pm SD
Gender	Male	52 (52.0)
	Female	48 (48.0)
Age (year)	43.8 ± 10.9	-
Post-transplant (month)	-	15.74 ± 8.23
Body mass index (BMI) (kg/m^2)	-	27.87 ± 4.36
Obese ($\text{BMI} \geq 30 \text{ kg}/\text{m}^2$)	25 (25.0)	-
Smoking	14 (14.0)	-
Hypertension	72 (72.0)	-
Diabetes Mellitus	48 (48.0)	-
HbA1C $> 7\%$	44 (44.0)	-
History of acute rejection	10 (10.0)	-
Previous cardiovascular disease	8 (8.0)	-
Left ventricular hypertrophy	56 (56.0)	-
Cardiovascular disease	18 (18.0)	-
Serum creatinine (mg/dl)	-	0.98 ± 0.34
eGFR ($\text{mL}/\text{min}/1.73\text{m}^2$)	-	74.84 ± 22.53
eGFR $< 60 \text{ mL}/\text{min}/1.73\text{m}^2$	15 (15.0)	-
Cholesterol LDL (mg/dl)	-	145.7 ± 23.6
Cholesterol LDL $> 130 \text{ mg}/\text{dl}$	82 (82.0)	-
Triglyceride (mg/dl)	-	223.6 ± 32.9
Triglyceride $> 200 \text{ mg}/\text{dl}$	40 (40.0)	-
Low vitamin D $< 20 \text{ ng}/\text{mL}$	57 (57.0)	-
Parathyroid hormone $> 65 \text{ pg}/\text{mL}$	34 (34.0)	-
Hemoglobin $< 11.5 \text{ g}/\text{dl}$	26 (26.0)	-
C-reactive protein $> 5 \text{ mg}/\text{dl}$	36 (36.0)	-
Proteinuria	38 (38.0)	-

eGFR estimated glomerular filtration rate, SD: standard deviation

A total of 18 (18%) of participants showed CVD, each of them might had one or more of the following; coronary artery disease, congestive heart failure, dysrhythmia, peripheral artery disease, pulmonary hypertension, and cerebrovascular stroke (Table 2).

The risk for CVD in KTR was significantly associated with increasing age, prior CVD, acute rejection episodes, cigarette smoking, hypertension, poorly controlled diabetes mellitus, LVH, impaired renal function ($eGFR < 60 \text{ mL/min/1.73m}^2$), Anemia, high CRP, and proteinuria. While gender, obesity, dyslipidemia, low vitamin D, and high PTH demonstrated statically non-significant association with CVD. (Table 3)

Table 2. The spectrum of cardiovascular diseases among kidney transplant recipients

	No.	%
Cardiovascular disease	18	18
Coronary artery disease	12	12
Congestive heart failure	9	9
Dysrhythmia	4	4
Peripheral artery disease	2	2
Pulmonary hypertension	1	1
Cerebrovascular stroke	1	1

Table 3. Analysis of factors associated with cardiovascular disease in kidney transplant recipients

Variables	Cardiovascular disease		P. value
	Yes (n = 18)	No (n = 82)	
Age/years (mean \pm SD)	44.7 \pm 10.6	39.4 \pm 16.4	< 0.001
Gender	Male	8 (44.4%)	0.400
	Female	10 (56.6%)	
Obese (BMI \geq 30 kg/m ²)	5 (27.8%)	20 (24.4%)	0.760
Smoking	8 (44.4%)	6 (7.3%)	< 0.001
Hypertension	17 (94.4%)	55 (67.1%)	0.01
Prior cardiovascular disease	6 (33.3%)	2 (2.4%)	<0.001
HbA1C > 7%	12 (66.7%)	32 (39%)	0.03
Cholesterol LDL >130 mg/dl	13 (72.2%)	69 (84.1%)	0.23
Triglyceride > 200mg/dl	8 (44.4%)	32 (39%)	0.67
History of rejection	7 (38.9%)	3 (3.7%)	<0.001
Left ventricular hypertrophy	16 (88.9%)	40 (48.8%)	0.02
eGFR <60 mL/min/1.73m ²	10 (55.6%)	5 (6.1%)	<0.001
25-OH-D <20 ng/mL	12 (66.7%)	45 (54.9%)	0.36
Parathyroid H > 65 pg/mL	9 (50%)	25 (30%)	0.11
Hemoglobin <11.5 g/dl	11 (61.1%)	15 (18.3%)	<0.001
C- reactive protein >5 mg/dl	11 (61.1%)	25 (30.5%)	0.01
Proteinuria	13 (72.2%)	25 (30.5%)	<0.001

eGFR: estimated glomerular filtration rate

4. DISCUSSION

Renal transplantation is considered the optimal form of renal replacement therapy due to increased patient survival and improved quality of life (1, 2). While a successful transplant can reduce CVD risk significantly, however CVD remains one of the leading causes of poor outcome in KTR (13). Higher incidence of cardiac events in post-transplant recipients is related mainly to preexisting cardiac risk factors, surgical procedure and long perioperative duration (16).

The present study demonstrated CVD in 18% of patients. Coronary artery disease and congestive heart failure were the prevalent clinical cardiovascular pattern detected in 12% and 9% of patients respectively. In the current study, the risk factors associated significantly with post-transplant CVD were older age, pre-transplant CVD (8% of patients), smoking (14%), hypertension (72%), HbA1C>7% (44%), history of acute rejection episodes (10%), eGFR< 60ml/min/1.73m² (15%), LVH (56%), high CRP (36%), anemia (26%) and proteinuria (38%).

Traditional and non-traditional CVD risk factors including some unique to the post-transplant state contribute to the higher CVD burden, which has been reported in various studies in 10- 40% of KTR (10, 16, 17, 18). Regarding the clinical pattern of CVD, in agreement to our results several studies demonstrated coronary artery disease in 7 to 14% of patients (19, 20, 21), likewise heart failure post-KT is a major contributor to CVD-related hospitalization (4), Goyal et al. in a large observational study, reported adverse cardiovascular events in 6.5% of the study population, 78% were driven by heart failure (22). In a large population study, pre-transplant atrial fibrillation reported in 6.4% of patients and associated with adverse post-transplant outcomes (12).

The KTR have a high prevalence of preexisting as well as de novo traditional CVD risk factors, such as hypertension (40-90% of patients) (10, 17), diabetes mellitus (40-49%) (4, 10), prevalence of smoking (13%) usually reflects that of the general population (23, 24), dyslipidemia is highly prevalent (LDL cholesterol 82%, Triglyceride 40%) in our patients, similar to other studies (10, 16, 25) and is exacerbated by comorbid conditions such as obesity, diabetes mellitus, proteinuria and immunosuppression (17), KDIGO guidelines suggest treating KTR with a statin regardless of LDL concentration (26).

Our study revealed no statistically significant association between gender, obesity, triglyceride, LDL cholesterol, low vitamin D and high parathyroid hormone with CVD in KTR.

The results of the current study are generally consistent with those in literature. In the study by Weiner D, et al. (27) the factors associated with an increase of CVD in KTR were old age, prior CVD, hypertension, diabetes, smoking, low BMI and low eGFR, while gender, LDL, triglyceride were not significant. The bivariate analysis of the study by Seoane-Pillado MT, et al. (2) shows that patients experiencing a cardiovascular event are generally older, male, smokers, with previous CVD, high blood pressure, left ventricular hypertrophy and diabetes, while proteinuria, anemia, renal impairment and dyslipidemia were not significantly associated with cardiovascular events. A review study by Birdwell KA, et al. (7) highlighted many traditional and non-traditional risk factors for CVD in KTR such as hypertension, diabetes, cigarette smoking, dyslipidemia, obesity, prior CVD, history of acute rejection episodes, LVH, proteinuria, anemia, and high C-reactive protein (inflammatory marker). Hoffman, et al (20) showed an association between multiple risk factors and the occurrence of perioperative cardiovascular complications in KTR. At present, aggressive management of risk factors remains the cornerstone of effective cardiovascular disease prevention (25).

The limitations of this study include being a single center cross sectional involving relatively small number of participants, and covering relatively short post-transplantation period.

5. CONCLUSIONS

Cardiovascular diseases are common among KTR, it were significantly associated with increasing age, prior CVD, smoking, history of rejection, low eGFR, hypertension, anemia, high HbA1C, proteinuria, high CRP and LVH. Being more proactive regarding cardiovascular risk may lead to the better outcomes. Further national longitudinal large sized studies on cardiovascular diseases and related risk factors post-kidney transplant must be encouraged and supported.

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Ethical Clearance:

All ethical issues were approved by the author. Data collection was in accordance with Ethical Principles of Declaration of Helsinki of the world Medical Association, 2013, for ethical principles of research involving human subjects.

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