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Impact of heart disease before kidney transplantation on overall survival and graft function at 12 and 24 months. A single-center observational study.

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Abstract

Introduction: Cardiovascular Disease is considered the leading cause of death in patients with stage 5 chronic kidney disease (CKD), on dialysis and postkidney transplant (KT). There is no optimal pretransplant cardiovascular screening strategy, and most tests are limited to detecting coronary heart disease. The study aimed to measure the impact of pretransplant heart disease on 12- and 24-month overall graft survival.

Methods: A retrospective cohort of patients with TR between 2009 and 2019 recorded cardiovascular history, CKD etiology, cardiac surgeries, echocardiographic, and pretransplant biochemical diagnoses. For outcomes, discharge glomerular filtration rate at 12 and 24 months, number of causes of death, and cardiovascular outcomes at 12 and 24 months were recorded. The variables were analyzed using X^2, T test, and Kaplan–Meier survival.

Results: A total of 326 patients entered the study. 7.7% had a cardiovascular diagnosis before the transplant protocol, 3.6% had a cardiac intervention, 11.4% had LVEF <50%, and valvular disease in 47.7%. Overall survival was 96.9%, and cardiovascular outcomes were 1.5%. At 12 and 24 months 42.4% and 48.3%, respectively, the GFR was <70 ml/min. Overall survival was lower with a history of cardiovascular disease and valvular disease ($P < 0.05$). graft survival was lower for cardiovascular disease ($P < 0.05$) and previous cardiac surgery ($P < 0.05$) and higher for LVEF <40% at 12 ($P<0.05$) and 24 months.

Conclusion: The nonfatal cardiovascular outcome occurred in 1.6%, and the causes of mortality were infectious. Cardiovascular history, cardiac surgery, and pretransplant valvular disease negatively impact overall survival and graft function. Detection of other forms of cardiac disease will lead to a more accurate assessment of posttransplant prognosis regarding graft survival and function.

Keywords:

Chronic kidney disease, heart disease, kidney transplant, mortality, survival.

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Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD). However, the relative contributions of different types of cardiovascular events (CVEs), such as incident heart failure, valvular disease, coronary artery disease, and stroke, are unclear [1].

CKD is an independent risk factor for coronary artery disease, being prevalent in 37% to 58% of asymptomatic patients with end-stage CKD. Even in patients with the best clinical conditions who are selected for kidney transplantation, a high prevalence of traditional risk factors for cardiovascular disease is described: 94.7% of patients have arterial hypertension, 81.1% have dyslipidemia, 23.6% have diabetes, 12.7% have a BMI of 30 or more, and up to 21.3% have a history of coronary artery disease. Myocardial infarction occurs in 9% to 17% of patients on the transplant waiting list, but the rate after kidney transplantation remains at 4% to 11% [2].

The causes of mortality in the 3- to 12-month posttransplant period include age, pretransplant heart failure, the presence of type 2 diabetes, the presence of posttransplant urinary tract infection, treatment for acute rejection, new-onset heart failure, coronary events, and malignancies. Among these factors, the most important is death associated with cardiovascular disease, with an odds ratio (OR) of 4.9 and a cumulative incidence of myocardial infarction at three years posttransplant of 4.2--15.5% [3, 4].

In the immediate posttransplant period of less than 3 months, the predictors of cardiovascular outcome were heart failure (RR=5.4), myocardial infarction before transplant (RR=4.3), postoperative decrease in hemoglobin (RR=3.6), and age at transplant (RR=1.05). Although contradictory, pretransplant evaluation of ischemia with positive noninvasive ischemia tests (positive ergometry or exercise ECG) was not associated with a predictor of cardiovascular outcome [5]. Pretransplant evaluation, in general, does determine variables related to a cardiovascular event: a medical history of cardiovascular disease (HR = 2.06 [1.06–4.03], P = 0.03), echocardiographic left ventricular hypertrophy (HR = 2.04 [1.04–3.98], P = 0.037) and abnormal myocardial perfusion tests (HR = 2.25 [1.09–5.96], P = 0.03). However, pretransplant evaluation allows the diagnosis of only unknown coronary lesions in 8.9% of patients [6].

Left ventricular hypertrophy and systolic and diastolic dysfunction are well-recognized indicators of worse cardiovascular outcomes in dialysis patients, attributed to decreased cardiovascular functional reserve. This outcome is the pathophysiological result of myocyte hypertrophy, reduced myocardial capillarization, nonvascularized interstitial fibrosis, atherosclerosis, and arterial stiffness. These conditions lead to cardiac structural changes in stage 5-D CKD patients.

Renal transplantation has not been shown to reduce ventricular mass in serial cardiac magnetic resonance studies. This is probably explained by the fact that renal transplantation requires that the patient be stabilized and have hypervolemia corrected for a considerable period before surgery when regression of hypertrophy induced by hypervolemia has already occurred. The waiting list is between 2 and 3 years in the best cases.

CKD patients receiving renal replacement therapy suffer from multiple cardiac pathologies that are not limited to ischemic heart disease. This is the result of the underlying etiology, usually type 2 diabetes mellitus with arterial hypertension; complications associated with CKD, such as uremia, volume overload, mineral–bone alteration, and inflammatory state; factors resulting from the treatment modality itself; right overload due to the presence of an arteriovenous fistula; and endocarditis associated with vascular access with catheters. The spectrum of heart disease with the most significant impact on the population wishing to undergo a kidney transplant focuses on pulmonary hypertension, valvular heart disease, and ventricular dysfunction [7].

Specific risk factors related to renal transplantation, such as acute rejection episodes, as well as traditional cardiovascular risk factors, appear to increase the risk of cardiovascular events after transplantation. Pretransplant vascular disease is associated with an increased risk of graft failure (HR 2.51; 95% CI: 1.66--3.80). Furthermore, cardiovascular interventions such as endovenous revascularization or cardiovascular surgery in renal transplant recipients have a high rate of severe graft dysfunction or even graft loss. Six to 33% of patients who require cardiovascular surgery after transplantation have severe graft dysfunction, and 3–12% have graft loss.

This study aimed to determine the impact of different spectra of pretransplant heart disease on overall and short-term graft survival (12 and 24 months) in a population that underwent kidney transplant surgery during an eleven-year follow-up period at a national kidney transplant reference center in Mexico City.

Materials and methods

Type of Research

This study is observational and analytical. The source is retrospective.

Scenery

The study was conducted at the nephrology service of the National Institute of Cardiology, “Dr. Ignacio Chávez,” in Mexico City from January 1, 2009, to December 31, 2019.

Universe and sample

The study population corresponds to the anonymized documentary records of the institution's nephrology service patients. Sampling was simply random.

Inclusion criteria

Patients over 18 years of age who underwent a first kidney transplant with a living or cadaveric donor and who had an echocardiographic evaluation before kidney transplantation were included.

Exclusion criteria

Patients without primary imaging data from cardiac evaluations, such as those from electrocardiograms and echocardiograms, were excluded. Patients whose posttransplant records were less than 1 year old and patients who developed neoplastic or autoimmune disease after transplantation were excluded.

Variables

The variables studied are presented in Table 1.

Data sources/measurements

The source was retrospective, and the database of patients included in the institution's nephrology service was reviewed. For the echocardiographic data, reports issued by the cardiology service of the Cardiology Institute were obtained. The surgical and/or hospital discharge notes were reviewed for peri-transplant outcomes. Follow-up notes from the nephrology outpatient clinic and the cardiology service's assessments were reviewed for survival outcomes.

Table 1. Study variables.

Age, sex
Comorbidities: Diabetes Mellitus, arterial hypertension, hyperuricemia, hypothyroidism, atrial fibrillation , cardiovascular disease, lung disease.
Previous cardiac surgery, pacemaker.
Etiology and evolution of chronic kidney disease.
Type and timing of renal replacement therapy and type of vascular access.
ECHO: Ejection fraction, Left ventricular hypertrophy, Diastolic dysfunction.
Valvular disease: tricuspid , aortic, pulmonary, mitral (ECO).
Previous catheterization and number of injured arteries.
Coronary ischemia studies: echo- dobuta , Angiotac.
Survival, glomerular filtration rate, cardiovascular outcome at 1 and 2 years.
Graft failure at 1st and 2nd year.

Biases

The principal investigator always safeguarded the data with a guide and records approved in the research protocol to avoid interviewer, information, and memory biases. Observation and selection biases were avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the period were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their concordance was verified.

Study size

The sample was probabilistic. Through access to the institution's database, 448 patients admitted for kidney transplantation were identified during the study period. With an unknown prevalence of cardiovascular outcomes, the expected frequency was 50.0%, with a confidence limit of 5%. The 99% confidence level was 267 cases. Epi info ™ (CDC, Atlanta, USA, October 2023) was used to calculate the sample size.

Quantitative variables

Quantitative variables, such as ejection fraction, progression time, and survival, were obtained from scale measurements. Categorical data, such as sex or the presence or absence of comorbidities, are presented as proportions.

Statistical analysis

Descriptive statistics were used for numerical variables, including central tendency and dispersion measures, means or medians, and standard deviations or interquartile ranges (IQRs). Categorical variables are presented as absolute and relative frequencies, and percentages and confidence intervals were used for proportions of the primary outcome. ANOVA, Student's t-test, and chi-square tests were used when appropriate, and survival analysis was performed via the Kaplan–Meier method. Statistical significance was considered at $P < 0.05$. *The* Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.)

Results

Study participants

A total of 326 patients who underwent kidney transplantation for the first time were included in the study. A total of 122 cases were eliminated because they did not meet the entry criteria.

Characteristics of the study groups

Among the 326 patients, 62% were men, and 38% were women. The average age was 31.12 ± 12.03 years. The average body mass index (BMI) was 23.5 kg/m^2. A total of 177 patients (54%) were diagnosed with systemic arterial hypertension (SAH), 11.3% (37) with hyperuricemia, 5.8% (19) with diabetes mellitus and 4.9% (16) with hypothyroidism. Undetermined etiology accounted for 66.6%, followed by focal segmental glomerulosclerosis in 5.8%, type 2 diabetes in 5.5%, systemic lupus erythematosus in 3.4%, uroglobulin abnormalities with membranous proliferative glomerulonephritis in 3.1%, and ANCA vasculitis in 2.1%.

The duration of chronic kidney disease evolution was 41.3 ± 36.7 months, of which 88.3% (288) were already on replacement therapy, 51.5% (168) on hemodialysis and 36.8% on peritoneal dialysis. The duration of replacement therapy was 23.07 months. Regarding the type of vascular access of patients on hemodialysis, 71.4% (120) had some catheter, and 28.6% (48) had an arteriovenous fistula.

Cardiac history before kidney transplantation

For 25 patients, 7.7% (95% CI 4.8%-10.6%) had a cardiac history before the start of the transplant protocol: 9 with ischemic heart disease (IHD), 4 with cerebrovascular events (CVEs), 2 with primary pulmonary hypertension (PAH), 3 with atrial fibrillation (AF) and 3 with obstructive sleep apnea (OSA). A total of 3.6% (12) had some cardiac intervention, of which four patients had valve replacement, 3 had

closure of the patent foramen ovale, 2 had revascularization, and four were pacemakers.

Cardiological evaluation before kidney transplantation

Among the total population, 300 patients underwent an echocardiogram study before kidney transplantation, of which the mean LVEF was 57.6% 9.5 (minimum 12 and maximum 80%). The mean TAPSE was 21.21 ± 3.09 (minimum 9 and maximum 33), and the mean PSAP was 33.09 ±10.68 (minimum 14 and maximum 81). Valvular disease was found in 47.7% of the patients, with the most frequently affected being the tricuspid valve in 36.6%, the mitral valve in 31.3%, the aortic valve in 11.3%, and the pulmonary valve in 11.3%. 2.3% had a patent foramen ovale, 44.7% had concentric hypertrophy, 1% had eccentric hypertrophy, and 47.5% had diastolic dysfunction. In major studies, 47.7% had a patent foramen ovale, 44.7% had concentric hypertrophy, 1% had eccentric hypertrophy, 47.5% had diastolic dysfunction screening, 5.2% underwent dobutamine echocardiography, 2.5% cardiac MRI, 7.1% nuclear medicine, and 4% coronary angiography.

a) Left systolic dysfunction: A total of 11.4% (34) had an LVEF less than 50% before surgery, of which 29 (9.7%) had an LVEF in the range of 30–49%, and five patients had an LVEF <30%.

b) Right systolic dysfunction: A total of 6.4% (16) of patients presented a TAPSE < 18 mmHg.

c) Pulmonary hypertension: Echocardiographic diagnosis for PAH or PASP >35 mmHg was present in 27.7% (78) of the study population.

d) Diastolic dysfunction: 47.5% were classified as having some degree of diastolic dysfunction, of which 29.8% were Grade 1, 15.7% were Grade 2, and 2% were Grade 3.

Pretransplant clinical analysis

Pretransplant clinical analyses are presented in Table 2.

Table 2. Pretransplant clinical analysis.

	Average	Standard deviation
Cholesterol total (mg/dl)	170	38.57
Acid Uric (mg/dl)	6.4	2.00
Triglycerides (mg/dl)	160	88.0
Glucose (mg/dl)	93.6	17.9
Creatinine (mg/dl)	11.6	21.3
Nitrogen urea (BUN) (mg/dl)	61.6	10.20
Hemoglobin (g/dl)	10.1	10.20

Functionality of the graft at hospital discharge

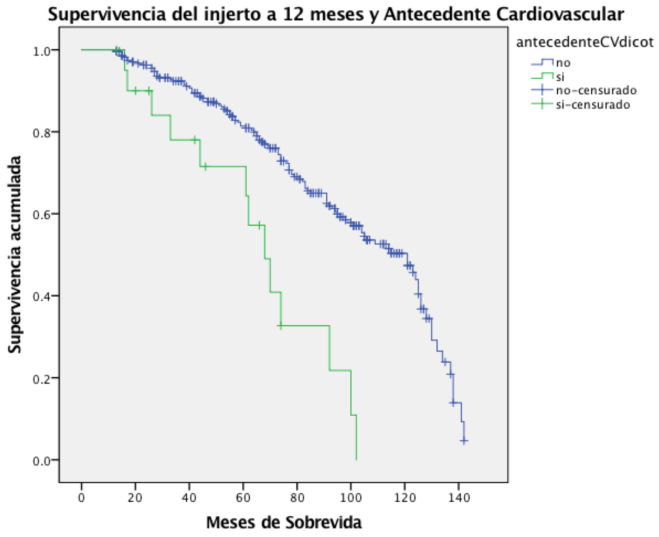
The median glomerular filtration rate at discharge from the hospital was 77.10 ml/min (IQR 25/75), with a mean of 75.54 ml/min (51.6--103 ml/min). In the first year, 29 individuals were lost to follow-up, and 11 were lost to follow-up at 2 years.

Survival analysis

Survival, cause of death, and graft function at 12 months. During the first year, ten deaths occurred, corresponding to 3.4% of the total population. Cardiovascular outcomes occurred in 5 patients (1.5%), 4 with heart failure, and one with a cerebrovascular event. The causes of death in 100% of the patients were infectious. The median GFR was 73.9 ml/min (SD + 24.9). Graft failure in the first year was established as a GFR < 70 ml/min, for which 42.4% (126) were in this classification. The four statuses for graft function at 12 months were as follows: 1) normal (eGFR > 80 ml/min), 2) mild failure (eGFR 79--47 ml/min), 3) moderate failure (eGFR 46--14 ml/min), and 4) advanced failure (eGFR < 14 ml/min). Overall survival at 12 months was significantly ($P < 0.001$) lower in those with a history of cardiovascular disease and those who had the valvular disease at the pretransplant evaluation. This was not the case for the groups with cardiac surgery, a reduced LVEF (<50), diastolic dysfunction, or right systolic failure.

Survival, cause of death, and graft function at 24 months. At 24 months, there was only one death (0.3%) from infectious causes and 0 cardiovascular outcomes. The median GFR was 73.9 ml/min (SD + 24.9). Graft failure was established in 48.3% (138) of patients in the second year. The four statuses for graft function at 12 months were as follows: 1) normal (eGFR > 80 ml/min), 2) mild failure (eGFR 79--45 ml/min), 3) moderate failure (eGFR 44--10 ml/min), and 4) advanced failure (eGFR < 10 ml/min). Graft survival at 12 months was significantly lower ($P < 0.001$) in those with a history of cardiovascular disease ($P < 0.001$) and those with cardiac surgery ($P < 0.001$) and a significantly lower LVEF (< 40 mmHg) ($P = 0.015$). At 24 months, an LVEF < 40% pretransplant was significantly associated with lower graft survival. This was not the case for the groups with valvular disease, diastolic dysfunction, pulmonary hypertension (PASP > 35 mmHg), or right systolic failure, $P = 0.001$ (global comparisons) (Figure 1).

Figure 1. Graft survival graph at 12 months.



The etiology of renal disease, ERPA, membranoproliferative, hypoplasia, and ANCA were related to any cardiovascular history (P <0.001). Patients who had a reduced LVEF (<50%) had lower criteria for graft failure at 24 months than patients who had a preserved LVEF (P =0.026). The LVEF in men was lower than in women (P =0.058). Patients who presented LVEF < 40% were more likely to have heart failure events at 12 months (0.7% vs. 11.8% P =0.001), with a higher percentage of diastolic dysfunction; however, the outcome for graft survival at one year was more significant (P =0.026).

Discussion

In the present study, 7.7% of patients (95% CI 4.8%-10.6%) had a cardiac history before the transplant protocol, of which 3.6% had undergone some type of intervention, such as valve replacement, foramen ovale closure, or pacemaker. Compared with those in other studies, the population in this cohort was younger, with a mean age of 31.12 (SD ± 12.03) years and fewer cases of type 2 diabetes [8].

Almost half of the patients (47.7%) were identified to have some valvular disease, and 27.7% were found to have a PSAP > 35 mmHg, which is slightly higher than that reported in a meta-analysis (overall prevalence of PAH of 23%) of the association between PAH and CVD [9, 10]. Five patients had an LVEF < 30%, which was significantly reduced.

The mortality rate was 3.4% per year, which is very similar to that reported by Ramanathan V in his cohort of 210,327 transplants (3.2%). However, the leading cause of mortality in this cohort was of cardiovascular origin (24.7%), followed by infectious causes (15.2%), whereas in our results, 100% corresponded to infectious causes, with no cardiovascular outcomes [11]. It can be assumed that the null cardiovascular outcome in the first year is associated with a young population with fewer cardiovascular risk factors.

Overall survival at 12 months was reduced in those with a history of cardiovascular disease and valvular disease, representing a significant drop in the diagnosis of pretransplant pulmonary hypertension, a fact that is corroborated because a higher risk of mortality from all causes is already known in chronic kidney disease [12].

Survival analysis demonstrated significantly decreased 12-month graft survival in those with a history of cardiovascular disease or prior cardiac surgery. Similar estimates were reported in a recently published cohort this year, where the factor associated with decreased overall graft survival (adjusted HR [95% CI]) was cerebrovascular disease (1.70 [1.10–2.63], P = 0.02) [13]. Cerebrovascular events were not analyzed separately in the present study.

However, paradoxically, a significantly reduced LVEF (<40 mmHg) before transplantation was associated with decreased graft dysfunction. This last result contrasts with the independent associations of posttransplant heart failure with increased mortality and graft loss. However, this was described in those who developed de novo HF [14]. Nevertheless, based on our findings, this group with an LVEF < 40% by 12 months has recovered cardiac function because they were possibly under-dialyzed, which, when taken to transplant, could positively impact survival.

One of the strengths of this study was the relatively large cohort with complete studies and pretransplant cardiological assessment studies that included all kidney transplant recipients, with few missing data at follow-up. However, it also has several limitations, the most important of which is that it may underestimate the outcomes, leading to confusion since the population was relatively young and had few traditional risk factors for cardiovascular outcomes. This is why we did not find associated mortality, which would be a line of future research.

Conclusions

Although kidney transplantation reduces the risk of cardiovascular disease compared with remaining on dialysis, kidney transplant recipients experience an increased risk of pretransplant cardiovascular disease outcomes, including death, and the impact on short-term graft survival is more striking in this study. These results provide novel information for both our hospital and the country to demonstrate that improving the management of risk factors and cardiac disease before kidney transplantation can improve graft outcomes and overall survival in the first and second years. Therefore, multidisciplinary clinical care focusing on the treatment and follow-up of cardiac disease before and after kidney transplantation should be extended to become a routine practice in any transplant center.

Abbreviations

CKD: Chronic kidney disease.
LVEF: Left ventricular ejection fraction.
PAH: Pulmonary artery hypertension.
PASP: Pulmonary artery systolic pressure.
The tricuspid annular plane systolic excursion (TAPSE) is a measurement that assesses the function of the right ventricle of the heart.
GFR: Glomerular filtration rate.

Additional information

No supplementary materials have been declared.

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Authors' contributions

Karina Ordaz López: Conceptualization, methodology, research, writing – original draft.
Francisco Eugenio Rodríguez Castellanos: Conceptualization, project administration, supervision, validation, visualization, writing, review, and editing.
All the authors read and approved the final version of the manuscript.

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Availability of data or materials

Not applicable.

Statements

Ethics committee approval and consent to participate

The "Ignacio Chávez" National Institute of Cardiology Ethics Committee approved the research protocol.

Consent for publication

Does not apply when specific images, X-rays, or photographs of patients are not published.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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