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CLINICAL STUDY

Significant benefits after renal transplantation in patients with chronic heart failure and chronic kidney disease

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Abstract

Background: Chronic heart failure (CHF) and chronic kidney disease (CKD) are serious medical conditions with significant morbidity and mortality and often coexist. Because of perioperative risks in these patients, they may not be considered a candidate for renal transplantation (RTx).
Material and methods: We compare retrospectively RTx outcomes [graft/patient survival, rejection rates and adverse cardiac events] in study group [low left ventricular ejection fraction (LVEF) $\leq$45% by echocardiogram, $n = 63$] and control group [normal LVEF $\geq$50%, $n = 537$] from a developing country.
Results: The mean EF was 35 ± 5.6 and 57 ± 3% for the study and control groups, respectively ($p < 0.001$). Majority of these patients (98%) showed normalization of LVEF post-transplant. The median EF was 60% at 1–3 months post-transplant. No difference was noted in graft survival, patient survival, rejection rates, serum creatinine and adverse cardiac events of study group at 1.3-year mean follow-up compared to control group. Outcome was not adversely affected by preexisting LV dysfunction. The study and control groups had nearly similar percent of patients with established CAD but significantly more hospitalization for CHF pre RTx in the study group compared with the control group.
Conclusion: RTx may play a role in reversing LV systolic dysfunction. Once thought by many to be a contraindication for renal transplantation, this appears not to be the case. The outcomes between the 2 groups are comparable and transplant is an option for even low EF patients.

Keywords

Chronic heart failure, chronic kidney disease, low ejection fraction, outcome, renal transplantation

History

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Introduction

Chronic heart failure (CHF) and chronic kidney disease (CKD) often coexist. Increasingly, the cardiorenal syndrome, defined as the confluence of cardiac and renal impairment, has been recognized as a known entity in which not only does cardiac and renal dysfunction coexist, but the failure of one system accelerates the decline of the other. Intrinsic renal disease shares many of the same risk factors (e.g. diabetes mellitus and hypertension) as cardiomyopathy. This confluence of cardiac and renal impairment may lead to an endless cycle of progressive concomitant functional decline.[1]

Both decreased glomerular filtration rate (GFR) and increased proteinuria increase the risk of CVD. Early implementation of hemodialysis may halt its progression. Nonconventional hemodialysis, such as frequent hemodialysis, appears to have an advantage over conventional hemodialysis. Because of perioperative risks in these patients, they may not be considered a candidate for renal transplantation (RTx).[2,3]

In one study that used the United States Renal Data System database, long-term survival was evaluated among 310,456 incident hemodialysis patients with a first hospital admission for heart failure, fluid overload, or pulmonary edema.[4] Five-year survival was only 12.5, 20.2, and 21.3 percent for these three groups, respectively. Low left ventricular ejection fraction (LVEF) is associated with higher incidence of cardiovascular death in patients with non-dialysis-dependent CKD and in patients on dialysis.[4–7] The 3-year survival rate after CHF is 17% in patients on dialysis.[7]

Cardiovascular disease (CVD) in CKD is treatable and potentially preventable and CKD appears to be a risk factor for CVD. In order of incidence and frequency systemic hypertension, left ventricular failure, congestive cardiac failure, ischemic heart disease, anaemic heart failure, rhythm disturbances, pericarditis with or without effusion,

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cardiac tamponade, uratemic cardiomyopathy are various cardiovascular complications encountered in patients with chronic renal failure. A patient may present with one or more complications of cardiovascular system. The survival rate and prognosis to a great extent depends on proper management of these complications.[8]

A therapeutic intervention that improves one of these organ systems might interrupt this cycle leading to improved function of the other organ system. To this end, increasing evidence suggests that improving renal function through renal transplantation in patients with CHF does not only interrupt this cycle, but it can also reverse cardiac dysfunction.[1] Use of regular dialysis and renal transplant has changed the death pattern in developed countries but it is still a major problem in developing country.[8] We report our RTx outcomes of ESRD patients with low LVEF compared to normal LVEF in a developing country.

Material and methods

This was a single-center retrospective study of 600 patients on regular follow-up, who underwent RTx at our institute from 2011 to 2012. Patients with low ejection fraction (EF), defined as $\leq$45% by echocardiogram constituted the study group. Patients with EF $\geq$50% constituted the control group. The aim of this study was to compare short-term graft survival, patient survival, rejection rates and adverse cardiac events between the study group ($n = 63$) and control group ($n = 537$). The adverse cardiac events studied were hospitalization for CHF, cardiac events {acute MI, revascularization [percutaneous coronary artery angiography (PTCA) or coronary artery bypass grafting (CABG)], or cardiac death}.

Written informed consent was obtained from all patients. This study was performed with the approval of our local Hospital Research Ethics Board. All transplants were performed in accordance with the Istanbul convention. A careful history and physical examination, complemented by an electrocardiogram and an echocardiogram, was performed in all patients. Based upon this initial assessment, the patients were subjected to additional studies, such as stress studies and/or coronary angiography in order to obtain cardiac fitness from cardiologist. Low EF assessed by echocardiogram was performed by an experienced cardiologist who was blinded about the study to avoid observer variation in EF after optimum hemodialysis and ultrafiltration. Volume control (dry weight) was achieved by appropriate dose and duration of ultrafiltration/dialysis [minimum three times per week to a single pool Kt/V of approximately 1.2 per 4 hours per session]. Degree of control of hypertension/anemia and compliance with medical therapy for low EF was verified. Beta blockers [carvedilol], diuretics, dietary sodium [<2 gm/day] and fluid [usually 500–750 mL/day] restriction, low dose digoxin and ACE inhibitors (or ARB) were used to treat both heart failure and hypertension. Careful monitoring of serum potassium concentration was employed. All patients meeting criteria for cardiac testing and all patients with low EF underwent screening for cardiac ischemia and treatment as per hospital protocol during the pre-transplant evaluation. Coronary angiogram (CAG) was performed in patients with $\geq$2 risk factors for coronary artery disease (CAD), kidney disease from diabetes, prior history of CAD and not performed in all patients.

CAG was performed in 20 patients (31.7%) in study group and 6 patients had CAD (5 single vessels and 1 multi-vessel). One patient with multi-vessel CAD with diabetes underwent uneventful CABG and 2 patients with single vessel CAD underwent successful balloon angioplasty/stenting. And others were managed with medical therapy.

The absence of ischemia, adequate control of risk factors and absence of dyspnea was the basis for clearing patients with reduced LVEF for transplantation. To avoid the likelihood of a false negative LVEF, echocardiogram was performed at least twice in all patients after optimum hemodialysis and ultrafiltration and control of risk factors. Post RTx, echocardiogram was performed in all patients with low EF at 1–3 months. No patient was smoking after RTx, and all were under optimum treatment of hyperlipidemia, hypertension, anemia or hyperglycemia.

The donor relation were parents ($n = 29$ vs. 221, p value 0.45), spouse ($n = 15$ vs. 131, p value 0.91), children ($n = 1$ vs. 6, p value 0.39), siblings ($n = 6$ vs. 56, p value 0.27), extended family/unrelated ($n = 7$ vs. 51, p value 0.06), deceased ($n = 5$ vs. 72, p value 0.98).

All patients received induction immunosuppressive therapy with methylprednisolone (500 mg intravenously $\times$ 3 days) $\pm$ rabbit-antithymocyte globulin (1.5 mg/kg, single dose) in high immunologic risk patients. Post-transplant immunosuppression consisted of calcineurin inhibitor-based regimen (majority with tacrolimus, 90%). Graft biopsy was performed in cases of acute graft dysfunction, diagnosed as per the modified Banff classification, and treated according to standard guidelines.

Statistical analysis was performed using Statistical Package for the Social Sciences (version 12.0; SPSS Inc., Chicago, IL). Continuous variables were compared using Student T-test. Chi square test of Fisher exact test were used to assess the effect of change in differences in categorical variables. Survivals were examined using Kaplan–Meier analysis and compared using the log-rank test. Given the low number of overall events, multivariate modeling was not performed.

Results

The baseline demographics of recipients, donors and co-morbidities are listed in Table 1. The basic disease in the 2 groups are shown in Table 2. The mean $\pm$ SD (range) EF (%) was 35 ± 5.6 (25–45) and 57 ± 3 (50–60) for the low EF study and normal EF control groups, respectively ($p < 0.001$). 23.8% (15/63) had EF $\leq$30%. None of the patients ($n = 3$) who had LVEF $\leq$20% developed adverse cardiac outcome post kidney transplantation. All these 3 patients did not have CAD. The study and control groups had nearly similar percent of patients with established CAD by CAG but significantly more hospitalization for CHF pre RTx in the study group compared with the control group.

No significant differences were noted in the cause of ESRD, duration of dialysis (median 6 months), diabetes, hypertension, arrhythmias, between the 2 groups pre RTx. The duration of hemodialysis before transplantation was 7.82 ± 6.96 months (median 6 months) in study group and

Table 1. Demographic of recipients and donors in the study and control group.

Variables	Study group ($n=63$)	Control group ($n=537$)	p Value
Donor age (Yrs) (range)	45.29 ± 10.56 (19–78)	45.62 ± 11.41 (13–76)	0.830
Donor gender (male: female)	20:43	182:355	0.733
Recipient age (Yrs) (range)	31.84 ± 12.18 (8–65)	33.96 ± 11.43 (7–67)	0.167
Recipient gender (male: female)	56:7	434:103	0.117
Mean EF (range) %	35 ± 5.6 (25–45)	57 ± 3 (50–60)	<0.001
CAD by CAG (%)	9.5 ($n=6$)	9.8 ($n=53$)	0.931
CHF hospitalization (%)	31.7 ($n=20$)	4.65 ($n=25$)	<0.001
BPAR (%)	9 (14.2%)	50 (9.3%)	0.55
1 Year serum creatinine	1.38 ± 0.35 (0.92–2)	1.35 ± 0.32 (0.63–2.6)	0.323
Follow-up (Yrs)	1.41 ± 0.62 (0.13–2.4)	1.36 ± 0.58 (0.38–2.4)	0.520
Post RTx arrhythmias	0 ($n=0$)	0.9% ($n=5$)	0.442
NODAT	4.7% ($n=3$)	4.6% ($n=25$)	0.970

Table 2. Basic disease in two groups.

Basic disease	Study group ($n=63$)	Control group ($n=537$)	p Value
CGN	27	232	0.958
DN	9	41	0.071
HT	3	56	0.153
Obstructive uropathy	5	39	0.846
CIN	3	35	0.588
IgA nephropathy	4	16	0.012
Alport syndrome	2	4	0.067
PKD	1	15	0.574
Lupus nephritis	4	5	0.001
Single unit kidney	0	15	0.303
FSGS/MPGN	0	11 + 11	0.252
other	5	57	0.509

CGN: chronic glomerulonephritis; DN: diabetic nephropathy; HT: Hypertension; CIN: chronic interstitial nephritis; PKD: polycystic kidney disease; FSGS: focal segmental glomerulosclerosis; MPGN: membranoproliferative glomerulonephritis.

Table 3. Survival outcome in the study and control group.

	1 Year	2 Years	Event (Expired/graft loss)	Survival (Censored)
Patient Survival (%)				
Study group	98.4	98.4	1.58	98.4
Control group	93.4	92.9	6.33	93.6
Graft Survival (%)				
Study group	97.6	97.6	1.58	98.4
Control group	98.3	97.1	2.04	97.9

By log rank test the p value for patient & graft survivals were 0.132 & 0.754 respectively.

the mean RVERSUSP was 40 ± 10 mm Hg before transplantation. The hemoglobin in study group was 10.9 ± 1.3 gm/dL before transplantation. Median number of the antihypertensive drugs required to control blood pressure was 2 and maximum of 4 drugs.

Patient and graft survival is shown in Table 3 and Figures 1 and 2. No difference was noted in graft survival, patient survival, biopsy proven acute rejection (BPAR), new onset diabetes after transplant (NODAT) and adverse cardiac events of low LVEF study group at 1.3-year mean follow-up compared to normal EF control group

Post RTx, the use of cardiac and immunosuppressive medications were not significantly different. No significant difference was observed in hospitalization for CHF in the

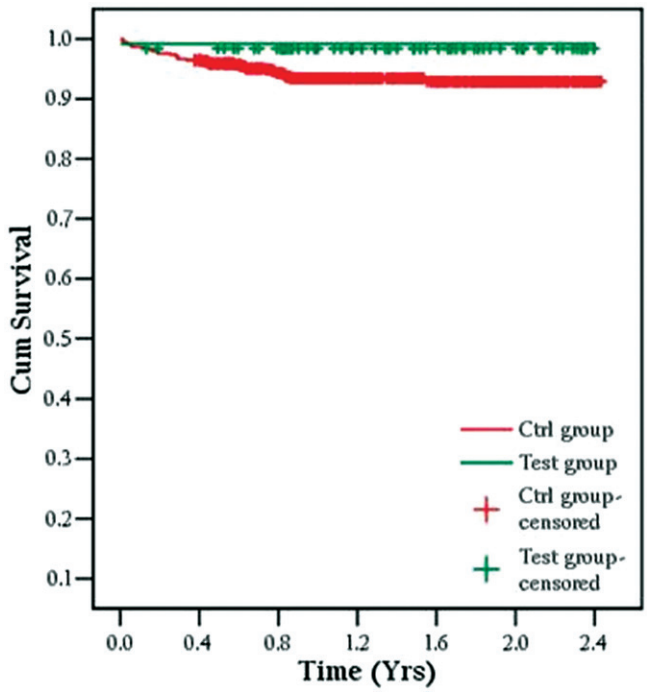

Figure 1. Kaplan–Meier curve for patient survival in low and normal LVEF groups.

first year post RTx in study group compared with control group (1.5% vs. 1.8%; $p=0.87$). Improvement and even normalization was observed as early as 1 week after RTx. The median EF was 60% at 1–3 months post transplant. The most frequent echocardiographic finding in study group was left ventricular hypertrophy (LVH), for which the incidence decreased from 88% ($n=56$) before transplantation to 38% ($n=24$) at 12 months after transplantation ($p=0.125$). Only 1 patient (1.5%) with CAD had not normalized the EF at 3 months after RTx in the study group. This patient had post-transplant congestive cardiac failure and a rejection episode and his creatinine was 2 mg/dL.

Discussion

Our study shows that patient and graft survival are not adversely affected by preexisting left ventricular (LV) dysfunction. Majority of these patients (98%) showed normalization of EF post-transplant. There was no difference in

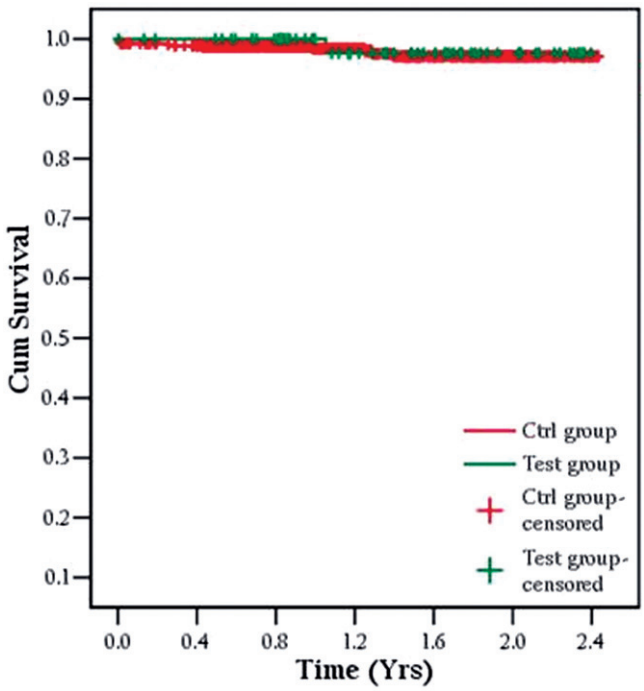

Figure 2. Kaplan–Meier curve for graft survival in low and normal LVEF groups.

the rate of adverse cardiac events between the 2 groups post RTx. This is likely due to a thorough evaluation of all patients for ischemia followed by treatment before transplantation. The mortality rate in our study group was not significantly higher than the control group and that is likely related to the normalization of LVEF that occurred in the majority (98%) of our study group patients. The serum creatinine was also similar between the groups at last follow-up. There is possibility of irreversible myocardial dysfunction with long-term dialysis.

RTx has been shown in several studies to decrease cardiovascular mortality as well as the risk for developing CHF compared with long-term dialysis therapy. Studies have also addressed the effect of kidney transplantation in patients with LV dysfunction.

Melchor et al.[9] followed prospectively 29 CKD patients with a LVEF <50% on dialysis who underwent RTx. The mean LVEF before transplantation was 37.8%. At 1 month post-transplantation, mean LVEF improved to 52% ($p = 0.01$) and it increased to 58.2% at 12 months ($p = 0.01$ compared to pre-transplantation). In addition, echocardiography demonstrated that 69% of patients had a normal study at 12 months, with LVH seen in only 14%.

Another study by Wali et al.[10] examined 138 patients with CKD and LV dysfunction (LVEF ≤40%) with clinical symptoms of CHF referred for RTx. At the time of surgery, 10% patients had an LVEF <20%, 49% from 20% to 30% and 41% from 30% to 40%. Approximately 57% of patients were noted to be in NYHA functional class IV, while 2.5% and 40.5% of patients were in class II and class III, respectively. The mean LVEF increased from 31.6% to 47.2% at 6 months ($p = 0.001$) and to 52.2% at 12 months ($p = 0.002$). The LVEF improved in 69% of patients to >50% and 16% increased to >40% but less than 50%.

With the United States Renal Data System database, 29,597 patients who received RTx between 1996 and 2000 were studied by Abbott et al.[11] Reduced eGFR (<44.8 mL/min per 1.73 m^2, compared with >69.7 mL/min per 1.73 m^2) at the end of the first 1 year after RTx was independently associated with increased risk of adverse cardiac events. Preservation of renal function after RTx may reduce the rates of hospitalized heart disease, and renal transplant recipients with reduced eGFR should be considered at high risk of developing cardiovascular disease.

Ferreira et al.[12] prospectively studied 24 ESRD patients by ambulatory blood pressure monitoring and echocardiography before and after RTx. Patients were also analyzed according to their renal function after transplantation. They observed significant decreases in left ventricular mass and left ventricular mass index in the group of patients who had adequate renal function, as compared with no changes in patients who did not. Correction of the uremic state by RTx leads to complete resolution of systolic dysfunction, regression of LVH, and improvement of left ventricular dilatation. In fact the reduction of LVH was dependent on adequate renal function and on a decrease in the systolic pressure levels.

One study, however, found worse outcomes in patients with low EF. Siedlecki et al.[13] found that patients with LVEF ≤45% were at considerably higher risk for cardiac complications and all-cause mortality after transplantation, during a mean follow-up of 3 years after transplantation. The group with low EF had significantly more risk factors (males, smokers, left ventricular hypertrophy, previous left heart catheterization, and higher exposure to dialysis) that could be responsible for the worse outcomes noted. It is not clear if a significant number of patients had ischemic cardiomyopathy that did not improve post RTx that resulted in worse survival. No post RTx LVEF assessments were available in this study. Patients with low EF should not be excluded from transplantation, given favorable outcomes.[14]

CKD is an independent cardiovascular risk state. Ejection fraction declined during the transition period from advanced CKD to ESRD. Risk factors for new onset CHF include hypertension, anemia, hypoalbuminemia, elevated serum phosphate, elevated serum calcium, baseline systolic dysfunction, less frequent visits to a nephrologist before onset of ESRD, ischemic heart disease, older age.[15–18] The above factors may have contributed to low LVEF in our patients. Fifty-seven patients were presumed to have low LVEF due to uremia. A prospective study devoid of confounding factors to determine the independent effects of RTx on reversal of LV systolic dysfunction is warranted.

In summary, this study demonstrates that RTx is associated with a substantial improvement in LVEF in CKD patients with systolic dysfunction. Even patients with severely decreased cardiac function might be able to successfully undergo surgery and derive a significant benefit after RTx. Once thought by many to be a contraindication for RTx, this appears not to be the case. Majority of our ESRD patients presented late in stage 5 and many with complications of cardiovascular disease. In such scenario outcome of this study will be more useful.

Conclusion

We suggest that RTx should be considered for CKD patients with LV systolic dysfunction. The outcomes between the two groups are comparable and transplant is an option for even low EF patients

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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