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ORIGINAL ARTICLE

Incidence, risk factor, and prognosis of end-stage renal disease after heart transplantation in Chinese recipients

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Background/Purpose: End-stage renal disease (ESRD) is an important complication arising after heart transplantation. At least 3–10% of recipients reach ESRD within 10 years after transplant. The incidence of ESRD in Chinese recipients has not been reported. Here we sought to assess the incidence, prognosis, and risk factors for ESRD in Chinese recipients.
Methods: We conducted a retrospective analysis of 248 heart recipients who survived >1 year from 1998 through 2007. ESRD was defined as the requirement of maintenance dialysis.
Results: Renal dysfunction was present in 20 patients (8%) prior to transplant. With a follow-up duration of 5.8 ± 3.9 years, 30 patients developed ESRD. The cumulative incidence of ESRD after heart transplantation was 2.1% ± 0.9%, 6.5% ± 1.8%, 16.8% ± 3.3%, and 36.5% ± 9.5% at 2, 5, 10, and 15 years after transplant, respectively. Median onset of ESRD was 6.9 years after transplant. Actuarial survival after dialysis was 74.8% ± 8.3%, 66.6% ± 9.2%, and 43.6% ± 12.6% at 1, 2, and 5 years, respectively. Independent risk factors for ESRD included pretransplant serum creatinine (hazard ratio, 1.84; $p = 0.001$), presence of diabetes prior to transplant (hazard ratio, 2.51; $p = 0.017$), and old age at transplant (hazard ratio, 1.05; $p = 0.008$).
Conclusion: There was a high incidence of ESRD in Chinese heart recipients. Patients with ESRD had poor prognosis after dialysis.

Introduction

Chronic kidney disease and end-stage renal disease (ESRD) are the important complications developing after heart transplantation. They are associated with significant mortality and morbidity.[1–3] The cumulative 5-year risk of

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developing chronic kidney disease is reported to be 11—59%. With longer patient follow-up after heart transplantation, ESRD becomes an increasingly important problem.[1—3] At least 3—10% of heart transplant recipients reach ESRD requiring renal replacement therapy within 10 years after transplant.[3] Risk factors for the development of chronic kidney disease in heart transplant recipients are well established.[4—10] However, our understanding of ESRD and outcomes after dialysis in heart recipients is limited. Only a few studies have focused on heart recipients once they have ESRD.[11—19]

In Asia, the first clinical heart transplantation was performed by Wada in 1968. Because of poor result, no active heart transplant program was performed for almost two decades. In July 1987, the first heart transplantation was started in Taiwan.[20] Although Taiwan is a small island with a population of 23 million, most of the heart transplantations performed in Chinese population has been performed in Taiwan.[20] Taiwan has the highest incidence and prevalence rates of ESRD in the world.[21] ESRD developing after heart transplantation is an emerging problem. We have published a preliminary result previously.[22] However, the cumulative incidence, risk factors, and prognosis of ESRD in Chinese heart transplant recipients have not been reported properly. Here, we sought to assess the incidence, risk factor, and prognosis of ESRD in Chinese heart transplant recipients.

Patients and methods

Patients

We conducted a retrospective cohort study of all consecutive patients who underwent heart transplantation at the National Taiwan University Hospital from June 1989 to July 2007. After excluding 11 patients who underwent simultaneous heart and kidney transplantation and 54 patients who survived <1 year, the remaining 248 patients comprised the study group. This study has been approved by our institutional ethics committee.

Immunosuppression

All patients received triple-drug immunosuppressive therapy according to our previously reported heart transplant protocol.[23] Since 1995, we have used rabbit antithymocyte globulins for induction therapy. Azathioprine (4 mg/kg) was given 1 hour prior to the operation. Solumedrol (1000 mg) was infused upon release of the aortic cross-clamp. Rabbit antithymocyte globulin 1.5—2.5 mg/kg/d was given after transplantation, for 3—5 days. Cyclosporine was started orally within 5 days after transplantation or after the recovery of renal function. Cyclosporine dose was adjusted according to renal function and serum cyclosporine level, which was maintained at the trough level of 300—500 ng/mL during the first 3 months after transplantation and at 200—300 ng/mL 1 year after transplantation. Azathioprine was given at a dose of 1—2 mg/kg/d after transplantation, with the dose being adjusted to maintain a white blood cell count of 4000—6000/mm^3. Prednisone (0.5 mg/kg/d) was started on the 2nd postoperative day and tapered to 0.2 mg/kg/d by the 1st month after transplantation. Tacrolimus (FK-506) and mycophenolate mofetil (Cellcept) were used for recurrent rejection or severe adverse reactions to cyclosporine and azathioprine. Since 2004, we started to use mycophenolate mofetil for primary immunosuppression instead of azathioprine. To reduce nephrotoxicity, cyclosporine dose was decreased to maintain a serum trough level of 250—350 ng/mL during the first 3 months after transplantation and of 150—250 ng/mL 1 year after transplantation.

Management

Endomyocardial biopsy was performed weekly in the first month after transplantation, biweekly in the second month, then monthly up to 6 months, and yearly thereafter. For those patients surviving for more than 6 months after transplantation, coronary angiography was performed annually for surveillance of cardiac allograft vasculopathy.

All patients were followed monthly at a special cardiac transplantation clinic. Standard chest roentgenogram, blood tests, electrocardiogram, and physical examinations were routinely performed at regular intervals.

Data were collected by retrospective chart review. Pretransplant data included age, sex, diagnoses of heart disease, body weight, body height, blood pressure, and laboratory data. We estimated glomerular filtration rate (eGFR) using Cockcroft—Gault formula, as suggested by the National Kidney Foundation guidelines. Patients were classified into five risk groups according to their eGFR levels, and the cut points were selected on the basis of published guidelines. Perioperative data included donor age, donor weight, and allograft ischemic time. Post-transplant data included mortality, date and cause of death, date of first dialysis, and major complications. ESRD was defined as the requirement of maintenance dialysis. None of our patients underwent kidney transplantation after heart transplantation because of ESRD. Diagnosis of renal disease was made without renal biopsy, and some patients had more than one etiology of ESRD.

Statistical analysis

Results are expressed as median with a range for continuous variables or as frequencies for categorical variables. Univariate risk factor analysis was performed using chi-square test, Fisher exact test, and Mann—Whitney test. Cox regression was used to identify independent risk factors for ESRD. The cumulative incidence of post-transplant ESRD and actuarial survival curves were plotted according to the Kaplan—Meier method.

Results

Patients

The study cohort included 248 patients (41 women and 207 men). The median age at transplantation was 47.1 (range, 0.5—71) years. Diabetes mellitus was present in 48 patients

(19%) prior to transplantation. The underlying cause of heart failure was ischemic cardiomyopathy in 66 patients (27%), dilated cardiomyopathy in 144 patients (58%), and others in 38 patients. Previous cardiac operation was present in 60 patients (24%). Median pretransplant serum blood urea nitrogen was 23 (range, 1–113.6) mg/dL, serum creatinine 1.1 (range, 0.4–6) mg/dL, and estimated GFR 71.02 (range, 12.42–176) mL/min/1.73 m^2.

End-stage renal disease

Renal dysfunction with serum creatinine >2.0 mg/dL was present in 20 patients (8%) prior to transplant. The cumulative incidence of ESRD after heart transplantation was 0%, 2.1% ± 0.9%, 6.5% ± 1.8%, 16.8% ± 3.3%, and 36.5% ± 9.5% at 1, 2, 5, 10, and 15 years after transplant, respectively. The median onset time of ESRD was 6.9 (range, 1.2–13.9) years after transplant. The actuarial survival rate after dialysis in ESRD patients was 74.8% ± 8.3%, 66.6% ± 9.2%, and 43.6% ± 12.6% at 1, 2, and 5 years, respectively.

Risk factor analysis

Univariate risk factor analysis (Table 1) revealed that old age at transplant; high pretransplant serum levels of blood urea nitrogen, creatinine, and low estimated GFR; and presence of diabetes prior to transplant were associated with the development of ESRD after transplant. Cox regression analysis revealed that the independent risk factors for ESRD included old age at transplant, pretransplant serum creatinine, and presence of diabetes prior to transplant (Table 2). The cut point of age for the prediction of ESRD was performed by receiver operating characteristic (ROC) curve (Fig. 1). The area under curve was 0.698 (95% CI, 0.614–0.782). The cut point of 49.5 years old can predict postoperative ESRD with 70% sensitivity and 60% specificity.

Comparison with Western series

Comparison of various studies with respect to patient characteristics and incidence of ESRD after heart

Table 1 Comparison of patient characteristics between heart transplant recipients with and without ESRD after transplant by Fisher exact test and Mann–Whitney *U* test.

Variables	With ESRD (n = 30)	Without ESRD (n = 218)	p
Age at operation (y)	54.2 (27–71)	45.3 (0.5–69)	0.0005
Male sex	28 (93%)	179 (82%)	0.187
Blood type: identical	21 (70%)	152 (70%)	0.999
Underlying heart disease			
Ischemic cardiomyopathy	11 (37%)	55 (25%)	0.191
Dilated cardiomyopathy	14 (47%)	130 (60%)	0.236
Others	5 (6%)	33 (15%)	
Previous cardiac operation	8 (27%)	52 (24%)	0.820
IABP at transplant	2 (7%)	19 (9%)	0.999
ECMO at transplant	0 (0%)	18 (8%)	0.140
Mechanical ventilation	0 (0%)	23 (11%)	0.087
UNOS status I	11 (37%)	87 (40%)	0.843
Presence of diabetes prior to transplant	13 (43%)	35 (16%)	0.001
Pretransplant serum albumin (g/dL)	3.75 (2.3–5)	3.8 (2.2–5.1)	0.5187
Pretransplant serum bilirubin (mg/dL)	1.1 (0.2–34.8)	1.4 (0.1–16.3)	0.4037
Pretransplant serum BUN (mg/dL)	29.5 (14–76)	22.3 (1–113.6)	0.0068
Pretransplant serum creatinine (mg/dL)	1.4 (0.6–6)	1.1 (0.4–4.6)	0.0026
Pretransplant estimated GFR (mL/min/1.73 m^2)	57.7 (12.4–128)	74.75 (17.97–176)	0.004
≥90	1 (3.3%)	55 (25.2%)	
60–89	13 (43.3%)	90 (41.3%)	
30–59	13 (43.3%)	64 (29.4%)	
15–29	2 (6.7%)	9 (4.1%)	
≤14	1 (3.3%)	0 (0%)	
Positive CMV antibody prior to transplant	29 (97%)	197 (90%)	0.489
Positive EBV antibody prior to transplant	30 (100%)	213 (98%)	0.999
Positive HBV surface antigen	3 (10%)	17 (8%)	0.715
Positive HCV antibody prior to transplant	2 (7%)	11 (5%)	0.648
Donor age (y)	27.5 (16–54)	31 (1–60)	0.4527
Donor male sex	23 (77%)	156 (72%)	0.667
Allograft ischemic time (min)	141.5 (48–330)	132 (40–336)	0.7120
Cardiopulmonary bypass time (min)	151.5 (72–293)	143.5 (73–420)	0.340

BUN = blood urea nitrogen; CMV = cytomegalovirus; EBV = Epstein-Barr virus; ECMO = extracorporeal membrane oxygenation; ESRD = end-stage renal disease; HBV = hepatitis B virus; HCV = hepatitis C virus; IABP = intra-aortic balloon pump; UNOS = United Network for Organ Sharing.

Table 2 Independent risk factors for ESRD after transplantation by Cox regression analysis.

Variables	Hazard ratio	Standard error	*p*	95% confidence interval
Age at transplant	1.05	0.02	0.008	1.01—.09
Pretransplant serum creatinine	1.84	0.35	0.001	1.27—.67
Presence of diabetes prior to transplant	2.51	0.97	0.017	1.17—.35

transplantation is given in Table 3. Only those series published in recent 10 years were considered for comparison.[11—19] The crude incidence of ESRD after heart transplantation in Western series ranged from 2% to 8%. The incidence of ESRD in this study was compared to Alam et al's[11] series of Canada and Satchithananda et al's[16] series of United Kingdom because these three groups had similar age at transplant and follow-up duration. In this current series, the crude incidence of ESRD was higher than in Alam et al's series (12.1% vs. 3.9%, $p < 0.001$ by Fisher exact test) and Satchithananda et al's series (12.1% vs. 3.9%, $p = 0.001$ by Fisher exact test). We also had a higher cumulative incidence of ESRD than in Satchithananda et al's series at 5 years (6.5% vs. 3.0%, $p = 0.013$ by Fisher exact test) and 10 years (16.8% vs. 11%, $p = 0.016$ by Fisher exact test) after transplant.

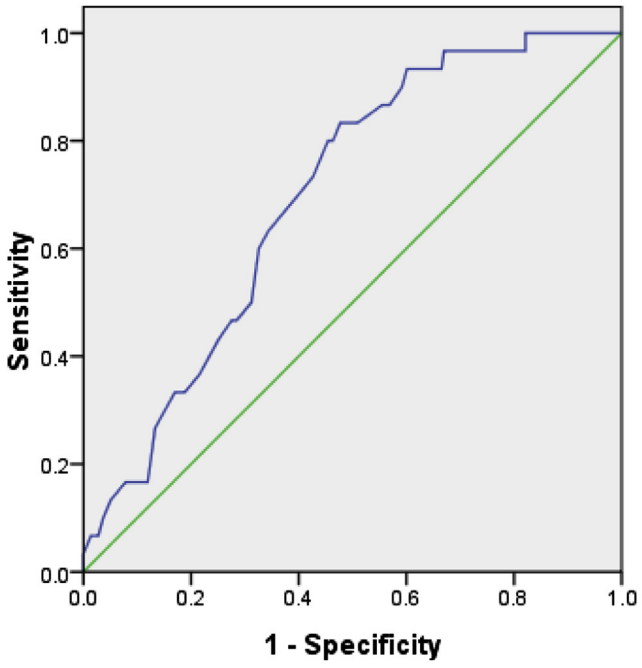
Discussion

End-stage renal disease

A number of studies have reported the incidence, etiology, pathology, and clinical course of chronic renal disease after heart transplantation.[1—10] Many patients have marked deterioration in renal function over the first 6 months to 1 year. ESRD is often a long-term complication, occurring several years after transplant, and a higher cumulative risk of ESRD has been reported in studies with a longer follow-up duration. The current study demonstrated that there was a high incidence of ESRD in Chinese heart transplant recipients. By actuarial analysis, 16.8% of our patient population developed ESRD by the end of the 10-year follow-up. Although the follow-up duration was short, the current cohort of heart transplant patients starting dialysis was larger than the ones of previously published series.[11—19] In our series, the high incidence of ESRD after heart transplantation is probably related to an environmental factor. In Taiwan, nontransplant cases of ESRD requiring dialysis have increased progressively over the last decades. When compared to international data using United States Renal Data System, ESRD incidence in Taiwan ranked first and prevalence ranked second in the world.[21,24] It is considered to be related to the use of Chinese herbal drugs or compound analgesics.[24]

Risk factors

The previously reported risk factors for chronic kidney disease after heart transplantation include pretransplant



Age cut point (y)	Sensitivity (%)	Specificity (%)
29.50	96.67	21.56
35.00	96.67	33.03
39.50	93.33	38.53
41.50	90.00	40.83
43.50	86.67	44.50
45.50	83.33	52.29
46.50	80.00	53.67
49.50	70.00	60.09
50.50	66.67	62.84
53.50	50.00	68.81
55.50	46.67	72.48
57.50	36.67	78.44
60.50	26.67	86.70
62.50	16.67	92.20
64.50	10.00	96.33

Figure 1 ROC curve of age for prediction of end-stage renal disease after heart transplant.

Table 3 Comparison of studies reporting incidence of end-stage renal disease after heart transplantation in Chinese patients (Hsu) and other Western series published after 1998.

Lead author	Hsu	Hornberger	van Gelder	Frimat	Satchithananda	Rubel	Senechal	Alam
Year of publication	This study	1998	1998	1998	2002	2004	2004	2007
Country	Taiwan	USA	Netherlands	France	UK	USA	France	Canada
Data source	Hospital	Medicare	Hospital	Hospital	Hospital	Hospital	Hospital	Registry
Patient number	248	1963	304	241	697	370	1211	2709
Age (y)	44.2 ± 16.4	54.5 ± 9.8	NA	52.8	47 ± 10.5	49.1 ± 11.1	NA	45.5 ± 16.3
Male	83%	85%	NA	NA	86%	78%	NA	79.5%
DCM	58%	NA	NA	44%	43%	49%	NA	40.4%
Follow-up (y)	5.8 ± 3.9	NA	6.6	NA	5.25	1—10	13.3	5.6 ± 4.9
Crude incidence (%)	12.1	2	8	6.6	5.8	5.7	2.7	3.9
Cumulative incidence								
1 y	0%	0.37%	NA	NA	NA	NA	NA	NA
5 y	6.5%	1.5%	NA	NA	3%	NA	NA	NA
10 y	16.8%	NA	NA	NA	11%	20.3%	NA	NA

DCM = dilated cardiomyopathy; NA = not available.

renal dysfunction, postoperative acute renal failure, recipient age, presence of diabetes mellitus, hypertension, dyslipidemia, smoking, hepatitis C infection, and treatment with calcineurin inhibitors.[4] However, there is little information on risk factors for ESRD after heart transplantation. It has been reported that preoperative renal dysfunction, high mean cyclosporine trough level in the first 6 months, and presence of diabetes mellitus are significant predictors of ESRD after heart transplantation. However, in other studies, these risk factors have not been proved to be associated with the development of ESRD after heart transplantation.[11—19] Here, we further demonstrated that pretransplant serum creatinine, presence of diabetes prior to transplant, and age at transplant were the major risk factors. These risk factors were similar to those for chronic kidney disease reported in our previous study of Chinese heart transplant recipients.[22] Low dose of cyclosporine or tacrolimus and new immunosuppressive agents such as mammalian targets of rapamycin inhibitors should be considered in recipients with old age, diabetes mellitus, and impaired renal function prior to transplant.[25]

Survival

In our study, the major cause of mortality for patients who survived <1 year were sepsis (12/54), rejection (26/54), and primary graft failure (7/54). We separate the patients into two groups with preoperative eGFR 60 mL/min/1.73 m^2 to compare the impact of chronic kidney disease (CKD) on the mortality in the first year after heart transplantation. The 1-year mortality rate was 12.6% for patients with preoperative eGFR >60 mL/min/1.73 m^2, and 25.2% for patients with preoperative eGFR <60 mL/min/1.73 m^2 ($p = 0.005$ by independent t test).

ESRD is associated with a high mortality in the general population. Survival rate of heart transplant recipients with ESRD is at least as poor, and likely worse.[11—19] Increased cardiac-related deaths seemed to account for the decreased survival in heart transplant recipients starting dialysis. Without renal transplantation, the reported survival rate at 1, 3, and 5 years after first dialysis was 60—70%, 40—50%, and 10—20%, respectively,[11] or even worse.[18] In this study, we also found that heart transplantation was associated with a poor outcome in Chinese heart transplant recipients starting dialysis. Survival of heart transplant recipients after dialysis of our cohort was consistent with that of heart transplant recipients in previously published studies.[11—19] It is much inferior to the cumulative survival rates for all dialysis patients in Taiwan after initiation of dialysis, that is, 85.1%, 74.6%, and 53.7% at 1, 2, and 5 years after dialysis, respectively.[24]

Study limitations

The major limitations of our study are small case number and short follow-up duration. However, despite a high incidence of ESRD in Chinese heart transplant recipients, a cohort of 30 cases of ERSD patients after transplant represents one of the largest previously reported series in a single center. The high incidence of ESRD in our patients enabled us to identify the significant risk factors clearly.

Newer immunosuppressive drugs, such as mammalian target of rapamycin (mTOR) inhibitors, are less nephrotoxic when compared with calcineurin inhibitors. In combination with or replacing calcineurin inhibitors, these have been proved to delay renal functional deterioration in solid organ transplantation.[26,27] The outcome of heart transplant patients with CKD may also be different. In this cohort, mTOR inhibitors were not used, and we applied mTOR inhibitors in heart transplant after 2007. Multicenter studies are still ongoing, and their outcomes will be compared in the future.

Conclusion

There was a high incidence of ESRD in Chinese heart transplant recipients. Patients with ESRD had poor prognosis after dialysis. Pretransplant serum creatinine, presence of diabetes prior to transplant, and old age at transplant were the major risk factors.

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