Original Article

Risk factors of renal replacement therapy after heart transplantation: a retrospective single-center study

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Background: Acute kidney injury (AKI) and renal replacement therapy (RRT) are common after heart transplantation (HT). The need for RRT has been reported to be one of the most important predictors of a poor prognosis after HT. Therefore, it is important to early identify risk factors of RRT after HT. However, in the heart transplantation setting, the risk factors are less well studied, and some of the conclusions are controversial. This study aimed to identify the clinical predictors of RRT after HT.

Methods: This single-center, retrospective study from January 2010 to June 2021 analyzed risk factors (pre-, intra-, and postoperative characteristics) of 163 patients who underwent HT. The endpoint of the study was RRT within 7 days of HT. Risk factors were analyzed by multivariable logistic regression models.

Results: Fifty-five (33.74%) recipients required RRT within 7 days of HT. Factors independently associated with RRT after HT were as follows: a baseline estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 [odds ratio (OR) =3.123; 95% confidence interval (CI): 1.183–8.244; P=0.022], a dose of intraoperative methylprednisolone >10 mg/kg (OR =3.197; 95% CI: 1.290–7.923; P=0.012), the use of mechanical circulatory support (MCS) during surgery (OR =4.903; 95% CI: 1.628–14.766; P=0.005), a cardiopulmonary bypass (CPB) time ≥5 hours (OR =3.929; 95% CI: 1.222–12.634; P=0.022), and postoperative serum total bilirubin (TBIL) ≥60 umol/L (OR =5.105; 95% CI: 1.868–13.952; P=0.001). Protective factors were higher postoperative serum albumin (OR =0.907; 95% CI: 0.837–0.983; P=0.017) and higher postoperative left ventricular ejection fraction (LVEF) (OR =0.908; 95% CI: 0.838–0.985; P=0.020).

Conclusions: A low preoperative eGFR, a high intraoperative dose of methylprednisolone, a long CPB time, the use of mechanical circulatory support, and a high postoperative TBIL were risk factors for RRT after HT. While a high postoperative serum albumin level and a high left ventricular ejection fraction were protective factors. Understanding these risk factors may help us identify high-risk patients and intervene early.

Keywords: Heart transplantation (HT); acute kidney injury (AKI); renal replacement therapy (RRT)

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Introduction

Heart transplantation (HT) is a successful procedure that increases survival, exercise capacity, and quality of life for patients with end-stage heart failure. Acute kidney injury (AKI) is a frequent complication following HT, with an incidence ranging from 14% to 76% (1-6). Moreover, 10–39% of patients who develop severe AKI after HT receive renal replacement therapy (RRT) as a salvage treatment (5,7-11). Patients with AKI after HT are at risk for adverse clinical outcomes, such as prolonged hospitalization, higher cost, the development of chronic kidney disease (CKD), and an increased risk of death (7,12,13). Therefore, it is necessary to identify risk factors of AKI and RRT in patients who received HT, which may help prevent and early intervene to reduce the occurrence of AKI.

The need for RRT has been reported to be one of the most important predictors of a poor prognosis after HT (14). Previous studies have reported that risk factors for RRT after heart transplantation include history of CKD (15,16), history of hypertension (17), history of diabetes (15,16), liver disease (17), intraoperative cardiopulmonary bypass (CPB) time (16), postoperative ventricular assist device (VAD)/extracorporeal membrane oxygenator (ECMO) therapy (18) and mechanical ventilation (17). Boyle *et al.* (16) showed that increased CPB time was an independent risk factor for RRT after HT, but this conclusion was not confirmed in the studies by Gašparović *et al.* (19). The study conducted by Ivey-Miranda *et al.* revealed that CKD was an independent predictor of RRT after HT (8), but Nadkarni *et al.* cannot get this conclusion in patients who received HT (17). Mostly previous studies were retrospective studies with small sample size, and the conclusions were controversial. Moreover, the patients of these studies were mainly European and American populations, which lacked of data in Asian peoples. Therefore, our study aimed to explore the risk factors of RRT after HT. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-541/rc).

Methods

Patient population

We studied patients who received HT at Guangdong Provincial People's Hospital between January 1st, 2010, and June 1st, 2021. The exclusion criteria were as follows: age younger than 18 years, second heart transplantation, multiorgan transplants, preoperative dialysis, and death within 48 hours of surgery. A total of 163 heart transplant recipients were included in the final analysis (*Figure 1*).

Data were obtained from a computerized database, electronic patient records, and chart review. The data included information on demographics, clinical history, treatment, examinations, and records of renal replacement. This study was approved by Guangdong Provincial People's Hospital Research Ethics Committee (No. KY-Q-2021-083-01). All patients signed a consent form for treatment, and our institutional review board approved the study protocol. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

Definition of variables

The endpoint of the study was RRT within 7 days of HT. Patients were divided into two groups: RRT and non-RRT, according to whether they received RRT in the first week after HT. Indications for dialysis initiation were renal insufficiency and heart failure that could not be corrected by medication. Preoperative laboratory variables were the routine blood test results closest to the surgery time. Postoperative laboratory variables were the results of routine blood tests within 24 hours of surgery. white blood cell count (WBC) and hemoglobin (HGB) were tested by the SYSMEX XN9000 automatic hematological analyzer. serum creatinine, blood urea nitrogen (BUN), serum albumin (ALB), serum total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood glucose, total cholesterol (CHOL) and triacylglycerol (TRIG) were tested by the

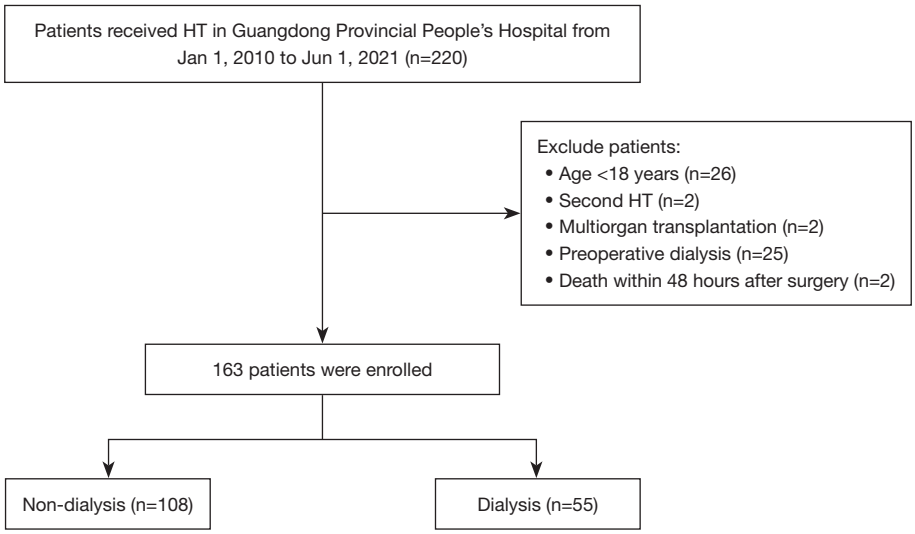

Figure 1 Flow chart of patient selection. HT, heart transplantation.

BECKMAN COULTER AU5800 automatic biochemistry analyzer. N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T (TNT) were tested by ROCHE COBAS E602 automatic chemiluminescence analyzer. Postoperative left ventricular ejection fraction (LVEF) measures were obtained from the cardiac ultrasound results within 7 days of surgery. The Modification of Diet in Renal Disease (MDRD) formula was used to estimate eGFR. Other clinical various such as age, weight, BMI, history of disease and intraoperative data were collected from medical records.

Statistical analysis

The Shapiro-Wilk test was used to verify the normal distribution of continuous variables. Normally distributed continuous variables were expressed as the mean and standard deviation (mean ± SD), while abnormally distributed continuous variables were shown as the median and interquartile range (median, IQR). Comparisons between continuous variables were made using Wilcoxon rank-sum and *t*-tests. Categorical variables were expressed as frequencies and percentages, and compared between RRT and non-RRT when appropriate using a Chi-square or Fisher's exact test. Subsequently, we used a stepwise backward selection to fit a multivariate competing risk regression model: Candidate risk factors were included in the multivariate model according to their statistical significance and clinical relevance. We constructed final models after adjusting for confounders, testing for potential interactions, and ensuring no multi-co-linearity between predictor variables. All reported P values were two-tailed, and $P<0.05$ was considered statistically significant. The statistical analysis was conducted using SPSS for Windows (Version 24.0; IBM Corp., Armonk, NY, USA).

Results

In total, 145 patients (88.96%) developed AKI, of which 49 (30.06%) were stage I, 31 (19.02%) were stage II, and 65 (39.88%) were stage III. Overall, 55 (33.74%) recipients required RRT within 7 days of HT.

Patients were divided into two groups based on whether they received RRT within the first week after HT. The baseline demographic, clinical, and laboratory characteristics of the 163 patients are shown in *Table 1*. There was a preponderance of men (n=141, 86.5%). The mean age of the cohort was 47±13 years (range, 18–74 years). Cardiomyopathy was the most common reason for heart transplantation in 85 (52.15%) patients, followed by coronary heart disease in 52 (31.90%) patients. There was no statistically significant difference in age, height, body mass index, history of hypertension, diabetes, pacemaker use, or prior cardiac surgery. Before HT, the baseline laboratory characteristics of WBC, HGB, serum creatinine, BUN, NT-proBNP, TNT, ALB, TBIL, DBIL, ALT, AST, blood glucose, CHOL, TRIG, and LVEF were not statistically different between the RRT and non-RRT patients. Patients who received RRT postoperatively had a higher

Table 1 Demographics and perioperative characteristics of HT recipients

Variables	Non-RRT (n=108)	RRT (n=55)	P value
Demographic data			
Age (y)	46.31±13.11	48.65±13.41	0.285
Male, sex, n (%)	92 (85.2)	49 (89.1)	0.49
Weight (kg)	63.87±13.33	60.80±10.87	0.142
Height (m)	1.68±0.07	1.68±0.06	0.861
BMI (kg/m^2)	22.58±3.80	21.60±3.46	0.109
Comorbidities, n (%)			
Hypertension	14 (13.0)	11 (20.0)	0.238
Diabetes mellitus	20 (18.5)	11 (20.0)	0.82
Chronic kidney disease	2 (1.9)	6 (10.9)	0.011*
Pacemaker use	17 (15.7)	11 (20.0)	0.495
Prior cardiac surgery	43 (39.8)	29 (52.7)	0.116
Etiology, n (%)			0.12
Myocardiopathy	62 (57.4)	23 (41.8)	
Coronary artery disease	31 (28.7)	21 (38.2)	
Valvular disease	14 (13.0)	8 (14.5)	
Other heart disease	1 (0.9)	3 (5.5)	
Preoperative characteristics			
WBC (×10^9/L)	7.88±3.18	7.47±2.83	0.588
HGB (g/L)	136.72±21.80	131.52±22.08	0.187
Serum creatinine (μmol/L)	96.25±34.06	106.70±39.12	0.068
BUN (mmol/L)	9.24±9.97	10.37±5.26	0.37
eGFR (mL/min per 1.73 m^2) <60	19 (17.6)	19 (34.5)	0.016*
NT-proBNP (pg/mL)	2,761 (1,070, 4,204)	2,761 (2,033, 5,829)	0.172
TNT (pg/mL)	32.1 (21.5, 51.2)	32.1 (25.0, 58.8)	0.205
ALB (g/L)	39.53±5.68	37.85±6.32	0.066
TBIL (μmol/L)	21.3 (14.9, 29.1)	23.9 (15.7, 31.7)	0.437
DBIL (μmol/L)	4.8 (3.1, 8.7)	6.5 (3.5, 12.1)	0.154
ALT (U/L)	23 (15, 33)	25 (18, 39)	0.299
AST (U/L)	26 (21, 32)	28 (22, 38)	0.335
Blood glucose (mmol/L)	6.36±2.87	7.17±4.06	0.175
CHOL (mmol/L)	4.13±1.08	4.15±0.78	0.974
TRIG (mmol/L)	1.18±0.53	1.10±0.38	0.325
LVEF pre-HT (%)	25 (20, 33)	24 (21, 32)	0.722

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Non-RRT (n=108)	RRT (n=55)	P value
Intraoperative characteristics			
MCS, n (%)	10 (9.3)	18 (32.7)	<0.001*
Surgery time (min)	382 (332, 424)	425 (373,510)	<0.001*
CPB duration (min)	233 (209, 268)	251 (210, 308)	0.033*
ACC time (min)	126 (110,142)	124 (110, 143)	0.851
Blood loss (mL)	300 (300, 400)	400 (300, 525)	0.003*
Urine volume (mL)	500 (300, 1,000)	500 (300, 1,000)	0.532
RBC transfusion (units)	0 (0, 2)	0 (0, 4)	0.004*
Plasma transfusion (mL)	0 (0, 600)	0 (0, 600)	0.737
Platelet transfusion (units)	1 (1, 2)	1 (1, 2)	0.782
Methylprednisolone (mg/kg)	10.73±7.59	14.05±6.93	0.007*
CPB-hematocrit (%)	26.86±4.00	25.42±4.88	0.045*
CPB-maximum lactic acid (mmol/L)	4.81±2.83	6.04±3.76	0.035*
Cold ischemia time (min)	204 (185, 230)	207 (200, 242)	0.053
CPB-ultrafiltration volume (mL)	2,600 (2,000, 4,000)	2,600 (1,800, 4,500)	0.901
Postoperative characteristics			
WBC ($\times 10^9$/L)	15.74±6.14	15.52±5.23	0.884
HGB (g/L)	106.26±15.62	104.11±16.66	0.581
ALB (g/L)	42.38±5.31	38.77±6.17	<0.001*
BUN (mmol/L)	10.42±3.30	12.37±4.05	0.008*
TBIL (μmol/L)	43.35 (28.1, 54.9)	48.1 (35.4, 69.1)	0.018*
DBIL (umol/L)	17.15 (9.8, 24.2)	22.70 (13.4, 39.5)	0.001*
ALT (U/L)	29 (23, 38)	38 (26, 53)	0.014*
AST (U/L)	132 (102, 164)	143 (113, 187)	0.039*
Blood glucose (mmol/L)	13.51±5.00	14.22±4.52	0.372
UA (μmol/L)	520.28±157.63	545.59±222.67	0.484
LVEF post-HT (%)	62.91±5.83	58.96±11.18	0.017*

Normally distributed numerical variables are presented as the mean ± standard deviation (M ± SD), nonnormally distributed numerical variables are presented as the median (25thpercentile, 75thpercentile), categorical variables are expressed as frequencies (percentages). *P<0.05. HT, heart transplantation; RRT, renal replacement therapy; BMI, body mass index; WBC, white blood cell; HGB, hemoglobin; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; TNT, troponin T; ALB, serum albumin; TBIL, serum total bilirubin; ALT, alanine aminotransferase; AST aspartate aminotransferase; CHOL, total cholesterol, TRIG, triacylglycerol; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; MCS, mechanical circulatory support (which included IABP, intra-aortic balloon pump; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenator); CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; RBC, red blood cell; UA, uric acid.

Table 2 Multivariate analysis of characteristics associated with RRT after HT

Variables	P value	OR	95% CI
Preoperative-eGFR <60 mL/min per 1.73 m^2	0.022*	3.123	1.183–8.244
Intraoperative-methylprednisolone >10 mg/kg	0.012*	3.197	1.290–7.923
Intraoperative-MCS	0.005*	4.903	1.628–14.766
CPB duration ≥5 hours	0.022*	3.929	1.222–12.634
postoperative-ALB (g/L)	0.017*	0.907	0.837–0.983
Postoperative-TBIL ≥60 μmol/L	0.001*	5.105	1.868–13.952
Postoperative-LVEF (%)	0.020*	0.908	0.838–0.985

*P<0.05. HT, heart transplantation; RRT, renal replacement therapy; OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; MCS, mechanical circulatory support (which included IABP, intra-aortic balloon pump; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenator); CPB, cardiopulmonary bypass; ALB, serum albumin; TBIL, serum total bilirubin; LVEF, left ventricular ejection fraction.

incidence of CKD (10.9% *vs.* 1.9%; P=0.011) and preoperative eGFR <60 mL/min per 1.73 m^2 (34.5% *vs.* 17.6%; P=0.016) than non-RRT patients.

Intraoperatively, the RRT group had a longer surgery time (P<0.001), a longer cardiopulmonary bypass (CPB) time (P=0.033), more blood loss (P=0.003), less hematocrit (P=0.045), a higher frequency of mechanical circulatory support (MCS) [including intra-aortic balloon pump (IABP), extracorporeal membrane oxygenator (ECMO), and ventricular assist device (VAD)] (P<0.001), a higher dose of intraoperative methylprednisolone (P=0.007), more red blood cell (RBC) transfusions (P=0.004), and higher lactic acid levels (P=0.035). However, there were no differences between the two groups in cold ischemia time, aortic cross-clamping (ACC) time, urine volume, plasma transfusion, platelet transfusion, or ultrafiltration volume.

Postoperatively, there were significant differences in BUN (P=0.008), ALB (P<0.001), TBIL (P=0.018), DBIL (P=0.001), ALT (P=0.014) and AST (P=0.039) within 24 hours of surgery, and LVEF (P=0.017) within 7 days of surgery.

Candidate risk factors including baseline eGFR, dose of intraoperative methylprednisolone, the use of MCS, CPB time, postoperative TBIL, postoperative ALB and postoperative LVEF were included in the multivariate model analysis. The multivariable model for RRT is summarized in *Table 2*. Logistic regression analysis revealed that the risk factors independently associated with RRT after HT were a baseline eGFR <60 mL/min per 1.73 m^2 [odds ratio (OR) =3.123; 95% confidence interval (CI) : 1.183–8.244; P=0.022], a dose of intraoperative methylprednisolone >10 mg/kg (OR =3.197; 95% CI: 1.290–7.923; P=0.012), the use of mechanical circulatory support (MCS) during surgery (OR =4.903; 95% CI: 1.628–14.766; P=0.005), a CPB time ≥5 hours (OR =3.929; 95% CI: 1.222–12.634; P=0.022), and TBIL ≥60 μmol/L (OR =5.105; 95% CI: 1.868–13.952; P=0.001). Protective factors were higher postoperative serum albumin (OR =0.907; 95% CI: 0.837–0.983; P=0.017) and higher postoperative LVEF (OR =0.908; 95% CI: 0.838–0.985; P=0.020).

Discussion

AKI is one of the most common complications after heart transplantation. In our study, the incidence of AKI within one week of HT was as high as 88.96%. Overall, 55 (33.74%) recipients required RRT in the first week. Candidates for heart transplantation are usually in end-stage heart failure, which leads to systolic insufficiency and overload of the heart. In this situation, it is impossible to avoid using a large number of diuretics, which further reduces renal perfusion pressure and results in renal insufficiency and ischemia. Many patients have impaired renal function before HT. A multicenter study in Taiwan showed that CKD before transplantation is associated with an increased risk of early dialysis after transplantation (20). Our research shows that preoperative eGFR <60 mL/min per 1.73 m^2 is an independent risk factor for RRT within one week of transplantation (OR 3.123; 95 % CI: 1.183–8.244; P=0.022). Our results are consistent with a previous study by Ivey-Miranda *et al.* (8), who reported a 3-fold increased risk of RRT after HT in CKD patients.

Immunosuppressive protocols for HT have received much attention. Previous studies have focused on the nephrotoxicity of immunosuppressants, especially calcineurin inhibitors (CNIs) (2,4). Few researchers have paid attention to the relationship between the dosage of glucocorticoids and postoperative acute kidney injury (AKI). The recommended dosage from the guidelines for intraoperative glucocorticoid is 10 mg/kg of methylprednisolone (21). However, the dosage of methylprednisolone used in many centers far exceeds the recommended dose. In a single-center study in Argentina, the dose of methylprednisolone used in heart transplant patients was 15 mg/kg (22). This was also the case in another study of heart transplants in children used 15 mg/kg of methylprednisolone intraoperatively (13). In other studies, patients received 500–1,000 mg intravenous methylprednisolone during HT surgery (22,23). Our study reveals that an intraoperative methylprednisolone dosage >10 mg/kg is an independent risk factor for requiring RRT treatment within one week of HT (OR 3.197; 95% CI: 1.290–7.923; P=0.012). As a primary drug in immunosuppressive programs, glucocorticoid is difficult to replace in clinical use. But high-dose glucocorticoid shock therapy causes water-sodium retention that increases the burden on the heart and decreases the patient's immunity, thus increasing the chance of post-surgery infection. Furthermore, it can hinder tissue repair and delay wound healing. The clinical effects of glucocorticoid are dose-dependent, and its immune suppression ability and side effects are closely related to dosage (24-26). However, the mechanism of glucocorticoid damage to the kidney needs further research.

Previous studies have shown that the longer the duration of CPB, the higher the incidence of AKI (10,16). In our study, the risk of severe AKI and the need to initiate dialysis were 3.929 times higher in patients who received HT with a CPB ≥5 hours than in patients who received HT with a CPB <5 hours. The possible mechanisms for this include changes in renal hemodynamics (blood dilution, hypothermia, and non-pulsatile blood flow) and turbulence and hemolysis caused by closed roller pumps, leading to the production of reactive oxygen species and systemic inflammation. Although cardiopulmonary bypass can replace the heartbeat to supply blood, it can easily lead to renal insufficiency and renal ischemia. The establishment of the CPB circuit will also increase the production of reactive oxygen species and inflammatory factors and induce acute tubular necrosis. In addition, hyperbilirubinemia after cardiac surgery with CPB is frequently observed and associated with worse outcomes (27). A large prospective study found a positive association between hyperbilirubinemia and the incidence of AKI after CPB (28). In a single-center retrospective study of cardiac surgery with CPB, the incidence of AKI was 80.5% in patients with severe hyperbilirubinemia after surgery, of which 18.1% required RRT (29). Our study reveals that a postoperative TBIL ≥60 umol/L is an independent risk factor for requiring RRT after HT (OR =5.105; 95% CI: 1.868–13.952; P=0.001). Though the exact cause of this liver dysfunction is unknown, it may be secondary to liver hypoperfusion, hemolysis or a systemic inflammatory response to CPB (27).

MCS is increasingly used in patients with refractory cardiogenic shock after cardiac surgery. MCS is also used in heart transplantation in patients with difficult CPB withdrawal and severe postoperative heart failure. In our study, MCS included ECMO, IABP, and VAD. AKI occurs commonly in patients requiring MCS. Previous studies have shown that the incidence of AKI is as high as 70–85% in patients who received ECMO (30,31), while the incidence of AKI requiring RRT after LVAD implantation is approximately 10–30% (32-34). The pathophysiology of MCS-associated AKI is complex, multifactorial, time-dependent, and potentially synergistic. Current studies suggest that it is primarily associated with systemic inflammatory responses, renal major or microcirculation disorders, and ischemia—reperfusion injury, hemolysis, and oxidative stress. Our study has shown that the application of MCS during HT surgery is an independent risk factor leading to RRT (OR 4.903; 95% CI: 1.628–14.766; P=0.005).

Serum albumin can promote interstitial fluid to effectively reabsorb and increase renal blood flow to compensate for renal ischemia. Albumin has an antioxidant effect, eliminating and suppressing the production of reactive oxygen species and reducing the necrosis of renal tubular cells (35). In addition, serum albumin also plays a role in the synthesis and repair of polysaccharide coatings, maintains the integrity of the cell barrier, and reduces plasma extravasation (36), thus playing an essential role in protecting the kidneys. Our research shows that high serum albumin levels are protective factors for RRT after heart transplantation (OR 0.907; 95% CI: 0.837–0.983; P=0.017). LVEF refers to stroke output as a percentage of ventricular end-diastolic volume with normal range from 50% to 70%, and it is an index of left ventricular contractility. High LVEF after heart transplantation is a protective risk factor for AKI (OR 0.908; 95% CI: 0.838–0.985; P=0.020). Better contractility of the heart means

better blood flow to the organ and less kidney damage due to organ ischemia. Conversely, a decrease in contractility of the heart can lead to reduced stroke volume, decreased effective circulating blood volume, and insufficient renal perfusion. It can also activate the renin-angiotensin-aldosterone system (RAAS) and cause renal vasoconstriction, thereby causing ischemia and hypoxia that affects kidney functioning.

However, our study has some limitations that should be noted. First, this study was a retrospective, single-center study with the inherent drawbacks of such designs. Furthermore, the small sample size may have prevented the detection of small effects and the accuracy of the multivariate analysis. To further improve our model's validity and predictive power, a larger sample size is recommended, and the interference of numerous confounding factors should be eliminated through multi-factor correction.

Conclusions

AKI requiring RRT is common after HT. This study demonstrated that the risk factors for RRT after HT include a low preoperative eGFR, a high intraoperative dose of methylprednisolone, a long CPB time, the use of mechanical circulatory support, and a high postoperative TBIL. Protective factors were higher postoperative serum albumin and higher postoperative LVEF. Understanding possible risk factors can help us identify high-risk patients and intervene early, which, in turn, may improve survival.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-541/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-541/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-541/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by Guangdong Provincial People's Hospital Research Ethics Committee (No. KY-Q-2021-083-01). All patients signed a consent form for treatment, and our institutional review board approved the study protocol. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

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