


ORIGINAL ARTICLE

Acute kidney injury post-heart transplant: An analysis of peri-operative risk factors

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Funding information

National Institutes of Health T35 NHLBI Training Grant, Grant/Award Number: 5 T35 HL007815

Abstract

Acute kidney injury is a common complication following heart transplantation, and the factors contributing to acute kidney injury are not well understood. We conducted a retrospective cohort study evaluating patients who underwent heart transplantation between 2009 and 2016 at a single institution. The primary endpoint was incidence of acute kidney injury as defined by Kidney Disease Improving Global Outcomes criteria. Secondary endpoints included 30-day hospital readmission, 30-day mortality, and 1-year mortality. A total of 228 heart transplant patients were included in the study for analysis. In total, 145 (64%) developed acute kidney injury, where 43 (30%) were classified as stage I, 28 (19%) as stage II, and 74 (51%) as stage III. Risk factors found to be associated with the presence of acute kidney injury included increased use of vasopressors and inotropes post-transplant. Protective factors included cardiopulmonary bypass time <170 min. Acute kidney injury was found to be associated with increased 30-day and 1-year mortality.

KEYWORDS

acute kidney injury, heart transplantation, inotropes, vasopressors

1 | INTRODUCTION

Outcomes of heart transplantation have improved due to advancements in immunosuppressive agents and overall risk management. However, patients are still at high risk for developing acute kidney injury (AKI) in the early post-operative phase. Up to 76% of heart transplant recipients have been found to meet the criteria for post-operative AKI, and patients with AKI experience longer hospital stays, increased financial burden, and increased in-hospital and 1-year mortality.¹⁻⁴

Conventional risk factors for AKI are multifactorial and may include impaired baseline renal function, co-morbidities (i.e., diabetes/hypertension), arterial hypoperfusion, right-ventricular failure, and

early initiation of calcineurin inhibitor immunosuppression.^{1-3,5-7} Given the high frequency and deleterious outcomes of AKI post-heart transplant, we sought to investigate the multifactorial nature of AKI with the goal of identifying potentially modifiable risk factors.

2 | PATIENTS AND METHODS

2.1 | Study population and data collection

We conducted a retrospective cohort study evaluating patients who underwent orthotopic heart transplantation between 2009 and 2016 at a single institution. Data were obtained from the Society

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of Thoracic Surgeons national database and chart review. General exclusion criteria included age <18 years and death within 24 h. Additionally, combined heart transplants with kidney, liver, or lungs were excluded due to differences in the nature of the surgery. Renal replacement therapy (RRT) preceding transplantation patients, defined as RRT on a routine basis before surgery, were also excluded due to pre-existing poor kidney function. This study was approved by the institutional review board at Washington University in St. Louis School of Medicine.

Vasopressor and inotropic data were collected immediately after, 24 h after, and 48 h after surgery. Central venous pressure (CVP), pulmonary artery pressure (PAP), and cardiac index (CI) data were collected immediately before surgery from the anesthesia record and immediately after surgery, 24 h, and 48 h after surgery from the cardiac intensive care unit cardiac catheter flowsheet. The CVP and PAP collected before surgery were the average of five consecutive values measured during the first 30-min post-induction. The CVP and PAP collected after surgery at each time point were the average of three consecutive values. Tacrolimus, mycophenolate mofetil, and corticosteroids were the mainstay of the immunosuppressant regimen. Tacrolimus and mycophenolate mofetil were started on day 1 and trough levels were typically achieved by day 5-7 (with the target 7–10 ng/ml). For the steroids, patients received 1000 mg in the OR, 250 IV q8 for days 1-2, and then were switched to 60 mg of prednisone daily. Regimens were not changed if AKI was noted.

2.2 | Outcomes and definitions

The primary outcome was the incidence of AKI as defined by the Kidney Disease Improving Global Outcomes criteria during the first 7 days after heart transplantation (Table 1).⁸ Secondary outcomes included 30-day mortality, 1-year mortality, and hospital readmission within 30 days of discharge. The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration equation. Patients were grouped according to their eGFR at baseline based on the Kidney Disease Outcomes Quality Initiative guidelines.⁹ Primary graft dysfunction (PGD) was classified according to International Society for Heart and Lung Transplantation guidelines.¹⁰ The vasopressors and inotropes used post-transplant were converted to a vasoactive-inotropic score (VIS) using the equation: $VIS = \text{dopamine (mcg/kg/min)} + \text{dobutamine (mcg/kg/min)} + 100 \times \text{epinephrine (mcg/kg/min)} + 10 \times \text{milrinone}$

$(\text{mcg/kg/min}) + 10,000 \times \text{vasopressin (units/kg/min)} + 100 \times \text{norepinephrine (mcg/kg/min)}$.¹¹

2.3 | Statistical analysis

Continuous parameters were expressed as median and interquartile range and were compared by Mann-Whitney *U* test or Kruskal-Wallis test as appropriate. Categorical parameters were expressed as number and percentage and were compared by chi-square or Fisher's exact test when appropriate. Multivariable logistic regression analysis was performed to identify risk factors associated with the presence of AKI after heart transplantation. We determined the list of the candidate risk factors based on univariable analysis and literature review. We assessed the linearity of continuous variables using restricted cubic spline transformations. If nonlinearity was detected, we categorized continuous variables to enhance their applicability in clinical practice. A bootstrap stepwise variable selection algorithm was used to screen the resulting list of candidate predictors with a 35% threshold set for selection. A more detailed explanation of the regression analysis and list of candidate risk factors can be found in the supplementary material (Appendix S1). Two-tailed *p* value <.05 was considered statistically significant. Statistical analysis was performed using SPSS version 26.0 for Macintosh (IBM SPSS, Inc).

3 | RESULTS

3.1 | Primary outcome - incidence of AKI and baseline characteristics

A total of 245 heart transplants were performed between August 2009 and December 2016 at our institution. The patient selection diagram is shown in Figure 1. Of the 228 patients included in our analysis, 145 (64%) developed AKI, where 43 (30%) were classified as stage I, 28 (19%) as stage II, and 74 (51%) as stage III. Of these patients with AKI, 66 (46%) required RRT in the hospital post-transplant. Demographic and clinical characteristics were stratified by the presence of AKI (No-AKI vs. AKI group, Table 2). Body mass index (BMI), dyslipidemia, and diabetes were statistically different between the two groups, with AKI patients having a higher median BMI (29.4 vs. 27.1 kg/m², *P* = .009) and increased incidence of diabetes (37% vs. 23%, *P* = .032) and dyslipidemia (75% vs. 59%, *P* = .008)

AKI Stage	Serum creatinine
I	≥ 0.3 mg/dl within 48 hr, or 1.5 to 2.0 times baseline within 7 days
II	2.0 to 2.9 times baseline
III	≥3.0 times baseline, or increase to ≥4.0 mg/dl, or initiation of renal replacement therapy

TABLE 1 Definition of AKI by KDIGO criteria

Note: Modified from KDIGO guidelines.⁹ Urine output criteria were not used due to insufficient data.

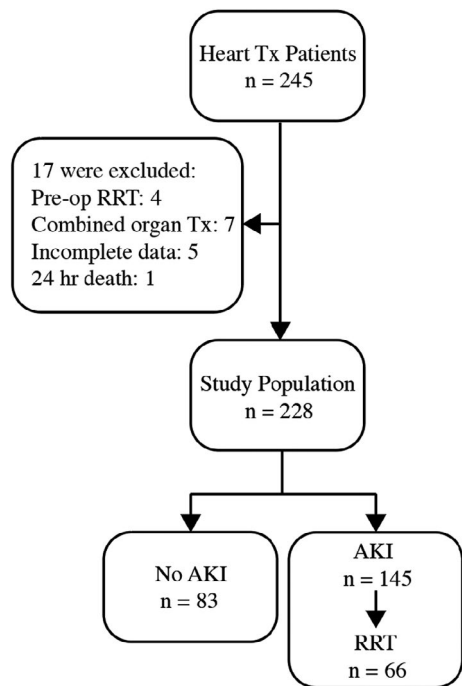


FIGURE 1 Patient selection diagram. RRT, renal replacement therapy; Tx, transplant

compared to the No-AKI group. Three patients were on ECMO prior to transplant.

3.2 | Hemodynamics

Pre- and post-operative hemodynamics and VIS were stratified by No-AKI, AKI without RRT, and AKI with RRT (Table 3). There were no significant differences in pre- and post-operative mean arterial pressures (MAP) and cardiac index (CI) at the indicated pre-op, post-op, 24 h, and 48 h timepoints. The CVP was significantly different at the pre-op (16 vs. 18 vs. 19 mmHg, $p = .023$) and 24 h (13 vs. 14 vs. 16 mmHg, $p = .003$) timepoints. The VIS was significantly elevated in the AKI group at all timepoints (post-op: 21 vs. 27 vs. 31, $p < .001$; 24 hr: 12 vs. 16 vs. 21, $p < .001$; and 48 h: 8 vs. 12 vs. 17, $p < .001$). There was a downward trend in VIS over time in both groups, with the highest VIS being immediately post-op. There was a significant difference in intra-op cryoprecipitate used (3 vs. 4 vs. 4 units, $p = .012$). There were no differences among groups of intra-op coagulation factors including factor 7 and prothrombin complex concentrate and pulmonary vasodilators such as nitric oxide and epoprostenol.

3.3 | Operative variables, complications, and outcomes

The operative variables, complications, and outcomes of patients were stratified by No-AKI, AKI without RRT, and AKI with RRT

(Table 4). Differences observed among the groups included cardiopulmonary bypass time, intra-op intra-aortic balloon pump (IABP), intra-op extracorporeal membrane oxygenation (ECMO), reoperation for bleeding, delayed sternal closure, sepsis, pneumonia, PGD, 30-day mortality, 1-year mortality, length of hospital stay, length of intensive care unit (ICU) stay, number of patients requiring RRT after discharge, and eGFR at 1-year post-transplant. Patients with AKI had longer cardiopulmonary bypass times (165 vs. 176 vs. 199 min, $p < .001$), and they had higher incidences intra-op IABP (8% vs. 8% vs. 39%, $p < .001$), intra-op ECMO (1% vs. 4% vs. 18%, $p < .001$), reoperation for bleeding (8% vs. 13% vs. 23%, $p = .043$), delayed sternal closure (30% vs. 40% vs. 71%, $p < .001$), pneumonia (15% vs. 22% vs. 46%, $p < .001$), and sepsis (3% vs. 9% vs. 27%, $p < .001$). Furthermore, AKI patients had longer hospital stays (14 vs. 18 vs. 34 days, $p < .001$). The median ICU stay was also longer in AKI patients (4 vs. 6 vs. 15 days, $p < .001$). The eGFR in AKI patients was noted to be significantly lower 1-year post-transplant (77 vs. 67 vs. 50 ml/min per 1.73 m², $p < .001$). There was also a difference in 30-day mortality (6% vs. 6% vs. 17%, $p = .046$) and 1-year mortality (11% vs. 9% vs. 27%, $p = .003$). Primary graft dysfunction was present in 12 (57%) of the 21 patients who died before 1-year. A total of 11 patients required RRT at the time of discharge, of which, 1 died within 30 days, and the remaining 10 were alive at 1 year. One patient remained on RRT for longer than 1 year, but the others recovered and did not need further RRT.

3.4 | Multivariable analysis

Six independent predictors of AKI were identified: 24 h VIS (98%), diabetes (39%), categorized cardiopulmonary bypass time groups (47%), 24 hr CI (70%), categorized intra-op platelets (56%). The final model is summarized in Table 5. The C-index for the final prediction model was 0.767 and revealed a moderate discrimination capability for the model. As shown in Table 5, the two statistically significant factors were 24 h VIS and the first category of cardiopulmonary bypass times (<170 min). The 24 h VIS had an odds ratio of 1.15 [1.08-1.22] ($p = .001$) per one-unit increase. The first category of cardiopulmonary bypass times (<170 min) had an odds ratio of 0.33 [0.14-0.79] ($P = .011$).

4 | DISCUSSION

In this study, we sought to identify risk factors for AKI following heart transplantation. We focused on surgical variables and hemodynamics at pre-, peri-, and multiple post-operative time points to understand their relationship to AKI following heart transplantation. AKI of some degree occurred in 64% of patients and was found to be associated with hemodynamic derangements such as elevated CVP and a higher requirement of inotropic and vasopressor support. These findings provide insight into the importance of right-sided filling pressures and pressor requirements as risk factors for AKI

	No-AKI (n = 83)	AKI (n = 145)	p
Age - yr	57 (48-63)	56 (48-63)	.742
BMI - kg/m ²	27.1 (23.6-30.6)	29.4 (25.8-32.8)	.009
Baseline creatinine - mg/dL	1.2 (0.9-1.5)	1.2 (1.0-1.5)	.320
Male sex	56 (68)	102 (70)	.805
Race			.392
White	65 (79)	110 (75)	-
Black	17 (21)	33 (23)	-
Other	0 (0)	3 (2)	-
Cardiac disease			.384
Nonischemic	50 (61)	93 (64)	-
Ischemic	25 (31)	47 (32)	-
Other	7 (9)	6 (4)	-
Hypertension	54 (66)	102 (70)	.532
Coronary artery disease	24 (29)	50 (34)	.441
Peripheral artery disease	10 (12)	11 (8)	.243
Dyslipidemia	48 (59)	110 (75)	.008
Diabetes	19 (23)	54 (37)	.032
Baseline eGFR - mL/min per 1.73 m ²			.597
≥90	18 (22)	22 (15)	-
60-89	31 (38)	62 (43)	-
30-59	31 (38)	57 (39)	-
15-29	2 (2)	5 (3)	-
Class NYHA			.396
Class I or II	10 (12)	24 (17)	-
Class III or IV	71 (88)	121 (83)	-
Previous cardiac surgery	63 (77)	117 (80)	.557
Previous VAD	52 (63)	95 (65)	.802
Pre-op IABP	1 (1)	5 (3)	.318
Pre-op inotropes	26 (32)	51 (35)	.621

TABLE 2 Demographics stratified by presence of AKI

Note: Continuous variables are presented as median and interquartile range. Categorical variables are presented as number and percentage. Bold values are statistically significant ($P < .05$); Patients were classified under pre-op inotropes if they received inotropes within 48 h prior to transplant.

Abbreviations: BMI, body mass index; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; NYHA, New York Heart Association; VAD, ventricular assist device.

and are supported by other studies that have found increased post-operative CVP and inotrope use to be associated with impaired renal function.^{6,7,12,13}

4.1 | Impact of high dose vasoactive-inotropic agents

The results of this study showed that VIS was much higher in patients who developed AKI. The CI and MAP in the AKI groups were similar to those in the No-AKI group throughout the pre-operative and post-operative phases of care. This may indicate adequate systemic perfusion was maintained, but the higher dose of

vasopressors needed to maintain the MAP in patients with AKI may have limited renal blood flow. Some medications included in the VIS, such as epinephrine, have a direct pathophysiological relationship with renal perfusion and can cause constriction of the afferent arteriole at higher doses. Further research is needed on vasoactive-inotropic agents and their role in renal perfusion and AKI.

4.2 | Outcomes in patients with AKI

In agreement with many other studies that revealed a link between AKI and poor short and long-term prognoses,^{1,14} our findings showed increased 30-day and 1-year mortality in patients with AKI.

TABLE 3 Pre/Post-operative hemodynamics and clinical characteristics stratified by AKI category

	No-AKI (n = 83)	AKI - No RRT (n = 79)	AKI - RRT (n = 66)	p
MAP - mmHg				
Pre-op	86 (75-96)	85 (77-95)	87 (77-95)	.852
Post-op	82 (75-90)	81 (73-88)	78 (69-87)	.126
Cardiac index - L/min/m²				
Pre-op	2.1 (1.7-2.6)	2.0 (1.6-2.4)	1.9 (1.6-2.4)	.260
Post-op	2.8 (2.4-3.2)	2.7 (2.4-3.0)	2.5 (2.2-3.1)	.436
24 hr	2.7 (2.4-3.2)	2.7 (2.5-3.2)	2.8 (2.5-3.2)	.705
48 hr	3.2 (2.7-3.5)	3.0 (2.6-3.3)	2.9 (2.4-3.4)	.338
Central venous pressure - mmHg				
Pre-op	16 (11-21)	18 (14-23)	19 (15-23)	.023
Post-op	14 (10-17)	15 (12-19)	15 (11-20)	.136
24 hr	13 (10-16)	14 (11-18)	16 (12-19)	.003
48 hr	15 (11-18)	15 (13-18)	16 (12-20)	.101
MPAP - mmHg				
Pre-op	23 (18-30)	26 (22-31)	26 (20-32)	.111
Post-op	23 (19-27)	24 (20-27)	22 (20-27)	.327
24 hr	19 (18-23)	21 (18-26)	22 (19-24)	.145
48 hr	21 (18-24)	21 (18-24)	23 (19-27)	.049
Vasoactive-inotropic score				
Post-op	21 (14-32)	27 (17-38)	31 (22-46)	.001
24 hr	12 (8-16)	16 (10-24)	21 (13-35)	<.001
48 hr	8 (5-11)	12 (7-17)	17 (10-25)	<.001
Intra-op transfusions - units				
pRBC	7 (4-9)	7 (3-11)	7 (4-11)	.613
Platelets	2 (2-3)	2 (2-3)	2 (2-4)	.207
Cryo	3 (1-4)	4 (1-4)	4 (2-4)	.012
FFP	6 (3-10)	6 (3-7)	6 (3-9)	.427
Intra-op coagulation factors	28 (34)	32 (41)	26 (39)	.637
Intra-op pulmonary vasodilators	35 (42)	35 (44)	31 (47)	.842

Note: Continuous variables are presented as median and interquartile range. Categorical variables are presented as number and percentage. Bold values are statistically significant ($p < .05$).

Abbreviations: FFP, fresh frozen plasma; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; pRBC, packed red blood cells.

Furthermore, 57% of the patients who expired before 1-year had PGD, indicating a close relationship between development of PGD and AKI. In a sub-analysis included in the supplementary material, Appendix S2 carries out the same analysis as Table 4 but excludes PGD patients from the population. The exclusion of PGD patients results in no difference in 30-day and 1-year mortality among the No-AKI and AKI groups. Thus, AKI in the absence of PGD may not be as detrimental to short- and long-term outcomes. Further research into the development of PGD and its relationship to AKI is warranted given these findings.

There were no differences in the intra-op pRBC, FFP, platelets, or cell saver volumes between the No-AKI and AKI groups, suggesting

that intra-operative bleeding was not an overt cause of AKI. The eGFR was found to be lower in the AKI without RRT and AKI with RRT groups than the No-AKI group 1 year after transplant which may indicate a lasting effect on kidney function in these patients.

In our study, we found that 29% of patients ($n = 66$) were ultimately placed on RRT. This is higher than other institutions where the average is around 10%.¹⁵ Our mortality outcomes are similar to other institutions, so an explanation for the increased number of patients on RRT may be physician propensity to start RRT when increasing creatinine and diminishing urine output are observed despite a reasonable hemodynamical condition. Further research into criteria for RRT initiation at our institution is needed.

	No-AKI (n = 83)	AKI - No RRT (n = 79)	AKI - RRT (n = 66)	p
Cross clamp time - min	126 (98-159)	127 (104-154)	126 (113-142)	.974
Cardiopulmonary bypass time - min	165 (147-188)	176 (153-210)	199 (177-235)	<.001
Donor heart ischemic time - min	146 (126-189)	149 (125-244)	143 (123-160)	.346
Cell saver - ml	560 (350-1040)	740 (450-1170)	820 (500-1450)	.093
Intra-op IABP	7 (8)	6 (8)	26 (39)	<.001
Intra-op ECMO	1 (1)	3 (4)	12 (18)	<.001
Reoperation for bleeding	5 (8)	9 (13)	15 (23)	.043
Delayed sternal closure	22 (30)	29 (40)	47 (71)	<.001
Sepsis	2 (3)	6 (9)	18 (27)	<.001
Pneumonia	10 (15)	15 (22)	30 (46)	<.001
Primary Graft Dysfunction	7 (8)	11 (14)	21 (32)	.001
Outcomes				
30-day mortality	5 (6)	5 (6)	11 (17)	.046
1-year mortality	9 (11)	7 (9)	18 (27)	.003
30-day readmission	11 (13)	6 (8)	8 (12)	.478
Discharged on RRT	0 (0)	0 (0)	11 (17)	<.001
Total hospital stay - days	14 (11-17)	18 (15-28)	34 (25-48)	<.001
Total ICU stay - days	4 (3-6)	6 (5-10)	15 (9-20)	<.001
1-year GFR	76 (60-96)	67 (52-85)	50 (36-69)	<.001

Note: Continuous variables are presented as median and interquartile range. Categorical variables are presented as number and percentage. Bold values are statistically significant ($p < .05$).

Abbreviations: ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; ICU, intensive care unit; RRT, renal replacement therapy.

4.3 | Risk factor analyses for AKI

Risk factors associated with AKI not already discussed were BMI, diabetes, and dyslipidemia. BMI and diabetes have already been established as risk factors for AKI,^{1,16,17} but the association of dyslipidemia with the incidence of AKI has not been widely reported. Despite the increased incidence of dyslipidemia in the AKI population, there were no differences in the presence of CAD or PAD. The relationship between AKI and dyslipidemia is unclear. We also found in our multivariable model that the patients with shorter cardiopulmonary bypass times (< 170 min) were found to have a decreased risk of developing AKI. Sepsis, pneumonia, intra-op IABP, intra-op ECMO, reoperation for bleeding, and delayed sternal closure were all found to be more common in the AKI groups indicating a sicker population.

Central venous pressure is a modifiable risk factor and thus an attractive parameter to target, but elevated CVP was not found to be an independent risk factor in our multivariable model despite our novel

TABLE 4 Operative variables, complications, and outcomes stratified by AKI category

investigation of both pre- and post-operative pressures. Despite this finding, CVP may still prove useful as an indicator of venous congestion and should still be optimized. To this end, venous congestion can be optimized pre-operatively using a combination of inotropes, vasodilators, and diuretics. This pre-transplant volume optimization may become more feasible with the current allocation system for which many patients stay in the hospital for their IABP management and other supportive treatments for higher status. Additionally, analysis of the current allocation system versus the previous system and its effect on AKI is of great interest for future studies now that sicker patients (i.e., ECMO support) are given higher priority.

4.4 | Limitations

This was a retrospective, single-center study. As such, this study was not able to establish causality between any of the variables and AKI,

TABLE 5 Multivariable logistic regression model predicting the presence of AKI

Variable	Odds Ratio	p	Selection Proportion (n = 5000)
Diabetes	1.93 [0.94-3.98]	.075	39%
24 h VIS	1.15 [1.08-1.22]	.001	98%
24 h CI	1.58 [0.96-2.58]	.072	70%
Intra-op Platelets		.280	56%
≤3	1.56 [0.70-3.46]	-	-
>3	1.00	-	-
Cardiopulmonary bypass time (min)		-	47%
<170	0.33 [0.14-0.79]	.011	-
170 < X < 200	0.70 [0.23-2.21]	.679	-
≥200	1.00	-	-

Note: Bold values are statistically significant ($p < .05$).

Abbreviations: CI, cardiac index; VIS, vasoactive-inotropic score.

and the single-center nature may limit applicability of our findings to patients at different centers. However, the detailed chart review allowed for a granular characterization of each patient's hemodynamics and the shorter 7-year collection period mitigated many effects of the evolving nature of heart transplantation procedures. Additionally, our heart transplant population itself was unique due to a large percentage having LVADs pre-transplant. The percentage of patients in the AKI and No-AKI categories with LVAD was not significantly different, but it should be noted that having an LVAD brings specific disadvantages for transplant patients such as longer cardiopulmonary bypass times and a higher likelihood of bleeding related complications.

5 | CONCLUSIONS

Acute kidney injury is a common complication following heart transplantation, and risk factors such as high use of vasopressors and inotropes were found to be strongly associated with the development of AKI. Furthermore, it was found that cardiopulmonary bypass times less than 170 minutes were protective and lead to a decreased incidence of AKI. A high VIS was found to be an independent risk factor for AKI, and the choice and dose of vasopressors and inotropes may play a role in the incidence of AKI post-heart transplantation.

ACKNOWLEDGEMENTS

We thank Marci Damiano, RN, MSN for contributing to the study design and interpretation of results.

CONFLICT OF INTEREST

Brandon Jocher is supported by the National Institutes of Health T35 NHLBI training grant. Dr Schilling is a member of the speaker's bureau for CareDx.

DATA AVAILABILITY STATEMENT

Data available upon request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Jocher BM, Schilling JD, Fischer I, et al. Acute kidney injury post-heart transplant: An analysis of peri-operative risk factors. *Clin Transplant*. 2021;35:e14296. <https://doi.org/10.1111/ctr.14296>