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Severe Acute Kidney Injury Postheart Transplantation: Analysis of Risk Factors

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Background. Acute kidney injury (AKI) is a common complication postheart transplantation and is associated with significant morbidity and increased mortality. **Methods.** We conducted a single-center, retrospective, observational cohort study of 109 consecutive patients undergoing heart transplantation between September 2019 and September 2021 to determine major risk factors for, and the incidence of, severe postoperative AKI as defined by Kidney Disease Improving Global Outcomes criteria in the first 48-h posttransplantation and the impact that this has on mortality and dialysis dependence. **Results.** One hundred nine patients were included in our study, 83 of 109 (78%) patients developed AKI, 42 (39%) developed severe AKI, and 37 (35%) required renal replacement therapy in the first-week posttransplantation. We found preoperative estimated glomerular filtration rate (eGFR), postoperative noradrenaline dose, and the need for postoperative mechanical circulatory support to be independent risk factors for the development of severe AKI. Patients who developed severe AKI had a 19% 12-mo mortality compared with 1% for those without. Of those who survived to hospital discharge, 20% of patients in the severe AKI group required dialysis at time of hospital discharge compared with 3% in those without severe AKI. **Conclusion.** Severe AKI is common after heart transplantation. Preoperative kidney function, postoperative vasoplegia with high requirements for vasoactive drugs, and graft dysfunction with the need for mechanical circulatory supports were independently associated with the development of severe AKI in the first-week following heart transplantation. Severe AKI is associated with a significantly increased mortality and dialysis dependence at time of hospital discharge.

http://links.lww.com/TXD/A618

(*Transplantation Direct* 2024;10: e1585; doi: 10.1097/TXD.0000000000001585.)

Heart transplantation is a treatment option available for some patients with end stage cardiac disease that can substantially improve survival and quality of life.[1] This procedure is commonly associated with complications, one of the most concerning of which is the development of acute kidney injury (AKI).

The kidneys are vulnerable organs to injury following heart transplantation due to many factors including preexisting impairment (particularly from cardiorenal interactions and comorbid conditions), susceptibility to low or nonpulsatile flow, venous congestion, and exposure to nephrotoxic drugs.

The reported incidence of AKI following heart transplantation varies between 14% and 83% and reported rates of renal replacement therapy (RRT) range from 5% to 46%.[2–29] The consequences of developing AKI can be severe due to complex cardiorenal interactions and the impact on inflammatory cascades among numerous other effects. It has been shown that severe renal impairment in the early postoperative period is associated with increased early and late mortality, mechanical ventilation duration, length of stay, and healthcare-associated costs.[2–29]

We aimed to investigate the incidence of severe AKI in adult heart transplant recipients in our institution and analyze the

Received 6 October 2023. Revision received 19 December 2023.
Accepted 29 December 2023.
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D.G. did study design, data collection and analysis, and writing of the article. S.A.-S. participated in study design, data collection and analysis, and writing of the article. P.M.D. did writing of the article. P.N. participated in study design and writing of the article.
D.G. and S.A.-S. have contributed equally as first authors.

P.M.D. received reports peer-reviewed research funding from NHMRC and NSW Health. He reports industry supported research funding to his institution from Amgen and Novartis and consultancy fees paid to him from AstraZeneca, Boehringer-Ingelheim, and Novartis. The other authors declare no conflicts of interest.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001585

association of plausible risk factors with the development of severe AKI. In addition, we aimed to assess the impact of severe AKI on outcomes such as early survival, dialysis dependence, duration of mechanical ventilation, intensive care unit (ICU) length of stay, and hospital length of stay.

MATERIALS AND METHODS

We conducted a single-center, retrospective, observational cohort study of consecutive patients who underwent isolated orthotopic heart transplantation between September 2019 and September 2021 at St Vincent's Hospital Sydney. Those who were >18 y old or who were on any form of RRT in the immediate preoperative period were excluded.

We performed a search of multiple local databases developed specifically and maintained for the cardiothoracic transplant program at this center and electronic medical records used in the ICU and broader hospital medical records to collect detailed demographic, baseline clinical, intraoperative, postoperative, and outcome data with a particular focus on risk factors suspected to be associated with the development of AKI.

Patients who undergo heart transplantation at our institution receive a standardized immunosuppression protocol (Table S1, SDC, http://links.lww.com/TXD/A617). For defining and staging AKI, we used the Kidney Disease Improving Global Outcomes (KDIGO) guidelines[30] and also collected data to grade AKI based on the RIFLE criteria[31] to analyze definition concordance and to enable comparisons with prior studies. eGFR was calculated using the CKD-EPI formula.[32] Baseline eGFR was based on the most recently documented serum creatinine before transplantation. We used the Inotrope Score (IS) as defined by Kobashigawa et al[33] and Vasopressor Inotrope Score as defined by Gaiea et al.[34]

The primary aim of this study was to determine the incidence of postoperative severe AKI and to identify the risk factors for its development. The primary outcome measure was the incidence of KDIGO stage 3 AKI in the first-week following heart transplantation. Secondary outcome measures were ICU, hospital, 90-d mortality, and 12-mo mortality, dialysis at ICU discharge, 28 d, 90 d, and at hospital discharge, ICU and hospital length of stay, and duration of invasive mechanical ventilation.

For the statistical analysis, we used XLSTAT software by Addinsoft. Demographic and clinical patient data were grouped into those with stage 0–2 AKI and those with stage 3 AKI according to KDIGO criteria. We used Student *t* tests or Mann-Whitney *U* test for continuous variables and Chi-square or Fisher Exact test for categorical variables to detect any associations of data between these groups and the incidence of AKI. We considered a 2-sided *P* value of <0.05 significant, with 95% confidence intervals. A Bonferroni correction was applied to address the risk of type 1 error from multiplicity of testing. The data have been presented as median with interquartile range for continuous variables or as a count with percentile for categorical variables.

We used subject-specific background knowledge to guide variable selection for multivariable logistic regression analysis in view of their redundancy, availability, and chronology for building a multivariable model. We limited the ratio between the number of independent variables and the number of events in the less frequent outcome to 1:10 to minimize the risk of over-fitting the data. Variables were only included if they were not missing for >10% of the cohort and not known to correlate with each other. Multicollinearity was further assessed with calculation of variance inflation factors. Residual diagnostic plots of quantile residuals were inspected for violation of assumptions.[35] We followed the advice of Heinze et al[36] to fit a Firth's penalized-likelihood logistic regression model with profile penalized-likelihood confidence intervals provided by the R package logistf in case of complete separation of individual variables.[37]

Data collection was carried out under The Intensive Care Observation Program and with strict compliance to the ISHLT ethics statement.[38] The Intensive Care Observation Program is a retrospective observational program, which allows sampling of data from existing data already collected as part of routine clinical care and carries ethical approval from the hospital Human Research Ethics Committee.

RESULTS

Between September 2019 and September 2021, 114 isolated orthotopic heart transplantations were performed. Following exclusion of 2 patients aged <18 y and 3 patients who needed RRT preoperatively, data of 109 patients were included for analysis (Figure 1).

Eighty-three (76%) patients developed AKI based on the KDIGO criteria, 30 patients (28%) stage 1, 11 patients (10%) stage 2, and 42 patients (39%) stage 3 AKI. Using the RIFLE AKI criteria 88 patients (81%) developed AKI, 31 patients (28%) developed stage 1 (risk), 15 patients (14%) stage 2 (injury), and 42 patients (39%) stage 3 (failure) AKI.

Patients with severe AKI were older and had a higher BMI, which was predominantly due to differences in weight rather than height. They had a higher rate of ischemic than nonischemic heart disease ($P = 0.04$) as an indication for transplant, had a lower preoperative eGFR, and a higher baseline creatinine. There were no significant differences in preoperative echocardiographic or right heart catheter results (Table 1).

Cardiopulmonary bypass (CPB) time and duration of operation were longer in the severe AKI group. Intraoperative peak lactate concentration was higher and total intraoperative urine output lower in this group (Table 2).

On arrival to ICU, patients who developed severe AKI had a lower Cardiac Index, a lower Cardiac Power Output Index, and a higher lactate concentration. Within the first postoperative, 48 h patients with severe AKI had a significantly lower

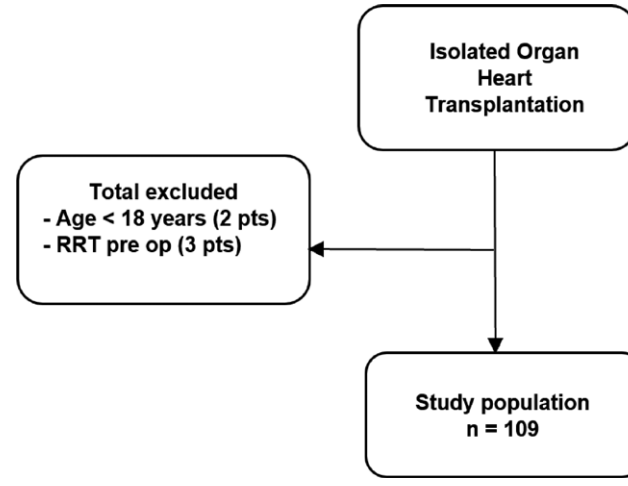

FIGURE 1. Population flow chart.

TABLE 1.

Baseline characteristics and preoperative parameters

Characteristic	Missing data	KDIGO stage			*P*
		All patients (n = 109)	0–2 (n = 67)	3 (n = 42)	KDIGO stage 3 vs 0-2
Demographics					
Male n (%)	0 (0)	86 (79)	52 (78)	34 (81)	0.68
Age (y)	0 (0)	58 (47–65)	55 (46–64)	62 (50–67)	0.02
Weight (kg)	0 (0)	80 (67–91)	75 (66–91)	84 (73–91)	0.12
Height (cm)	0 (0)	174 (165–180)	174 (165–180)	174 (163–180)	0.86
BMI (kg/m^2)	0 (0)	26.6 (23.3–29.4)	25.8 (22.6–28.2)	27.9 (24.8–30.0)	0.02
Clinical baseline					
Indication for HTx	0 (0)				0.13
Ischemic		34 (31)	16 (24)	18 (43)	
Congenital		6 (6)	3 (4)	3 (7)	
Valvular		1 (1)	1(1)	0 (0)	
Other nonischemic		68 (62)	47 (70)	21 (50)	
Frailty Vulnerable/Severe	34 (31)	55 (73)	30 (70)	25 (78)	0.42
Hypertension	0 (0)	23 (21)	14 (21)	9 (21)	0.95
Diabetes	0 (0)	31 (28)	22 (33)	9 (21)	0.20
eGFR (mL/min/1.73m^2)	0 (0)	61 (48–83)	71 (54–86)	54 (44–71)	0.002
Creatinine (µmol/L)	0 (0)	103 (89–133)	98 (87–125)	119 (96–147)	0.02
Cardiac function					
LV EF%	4 (4)	20 (15–30)	20 (15–230	20 (15–26)	0.70
mPAP (mm Hg)	5 (5)	27 (21–34)	27 (21–33)	27 (21–34)	0.90
PCWP (mm Hg)	5 (5)	17 (13–25)	18 (13–26)	17 (14–24)	0.99
TPG (mm Hg)	5 (5)	8 (6–10)	8 (6–10)	8 (6–11)	0.92
PAPi	5 (5)	1.7 (1.3–2.7)	1.9 (1.1–2.8)	1.6 (1.3–2.3)	0.65
CI (L/min/m^2)	16 (15)	2.1 (1.7–2.4)	2.0 (1.7–2.5)	2.2 (1.8–2.3)	0.76

Values are expressed as median (interquartile range) or n (%).
BMI, body mass index; CI, cardiac index; eGFR, estimated glomerular filtration rate; HTx, heart transplant; IHD, ischemic heart disease; LV EF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary gradient.

TABLE 2.

Intraoperative parameters

Characteristic	Missing data	KDIGO stage			*P*
		All patients (n = 109)	0–2 (n = 67)	3 (n = 42)	KDIGO stage 3 vs 0–2
Prior sternotomy	0 (0)	57 (52)	31 (46)	26 (62)	0.11
VAD explant	0 (0)	40 (37)	24 (36)	16 (38)	0.81
DCDD donor	0 (0)	36 (33)	20 (30)	16 (38)	0.37
Ischemic time (min)	3 (3)	197 (149–250)	191 (149–235)	225 (152–262)	0.14
Cross clamp time min)	0 (0)	81 (72–95)	79 (71–95)	84 (77–94)	0.07
CPB time (min)	14 (13)	150 (131–183)	143 (126–171)	167 (146–211)	0.002
Operation time (h)	1 (1)	5.6 (4.6–6.4)	5.3 (4.4–6.2)	5.9 (5.4–6.9)	0.01
Peak lactate (mMol/L)	0 (0)	4.0 (2.7–5.7)	3.5 (2.6–4.8)	5.2 (3.2–7.5)	0.001
Total intraoperativeurine output (ml)	21 (19)	400 (290–628)	500 (300–800)	350 (180–500)	0.005
Red blood cell transfusion (units)	0 (0)	1 (0–2)	1 (0–2)	2 (0–4)	0.21
FFP transfusion (units)	0 (0)	2 (2–3)	2 (2–3)	2 (2–3)	0.30
Cryoprecipitate transfusion n(units)	0 (0)	5 (4–8)	5 (4–7)	6 (4–8)	0.15
Platelet transfusion (units)	0 (0)	1 (1–2)	1 (1–2)	1 (1–2)	0.22
PCC administration (units)	0 (0)	1500 (0–2500)	1500 (0–2250)	2000 (0–2500)	0.56

Values are expressed as median (interquartile range) or n (%).
CPB, cardiopulmonary bypass; DCDD, donation after circulatory determination of death; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; VAD, ventricular assist device.

minimum mean arterial pressure and a higher peak lactate. They had significantly higher adrenaline, noradrenaline, and vasopressin dosage requirements, a higher Vasoactive Inotrope Score and a higher IS. Patients with severe AKI were significantly more likely to require mechanical circulatory support and to have more often left and right ventricular impairment on echocardiography. Patients with severe AKI had a lower minimum hemoglobin level and required

TABLE 3.

Parameters on arrival to ICU and in the first 48 h of ICU admission

Characteristic	Missing data	KDIGO stage			*P*
		All patients (n = 109)	0–2 (n = 67)	3 (n = 42)	KDIGO stage 3 vs 0–2
Hemodynamics ICU arrival					
MAP (mm Hg)	0 (0)	71 (64–79)	73 (65–79)	69 (62–76)	0.19
CVP (mm Hg)	0 (0)	11 (8–14)	11 (9–14)	13 (8–14)	0.83
mPAP (mm Hg)	2 (2)	24 (20–28)	25 (20–28)	24 (20–27)	0.84
HR (bpm)	0 (0)	101 (97–111)	101 (97–111)	103 (100–111)	0.39
CI (L/min/m^2)	2 (2)	3.0 (2.3–3.4)	3.1 (2.5–3.5)	2.8 (1.8–3.3)	0.02
PAPi	2 (2)	1.5 (0.9–1.9)	1.5 (1.0–2.0)	1.3 (0.8–1.9)	0.50
CPOi (W/m^2)	2 (2)	0.5 (0.4–0.5)	0.5 (0.4–0.5)	0.4 (0.3–0.5)	0.02
SvO_2 (%)	8 (7)	72 (67–79)	73 (68–78)	70 (62–79)	0.15
Lactate (mMol/L)	0 (0)	4.9 (3.2–7.1)	4.1 (2.8–5.7)	5.6 (4.1–8.5)	0.01
Hb (g/L)	0 (0)	105 (94–115)	105 (97–117)	102 (93–112)	0.25
TTE findings first 48 h					
LV dysfunction any	12 (11)	27 (26)	11 (17)	16 (40)	0.01
LV dysfunction mod–severe	12 (11)	16 (16)	6 (10)	10 (25)	0.03
RV dysfunction any	12 (11)	45 (43)	22 (34)	23 (58)	0.02
RV dysfunction mod–severe	12 (11)	25 (24)	9 (14)	16 (40)	0.003
Mod-to-severe graft dysfunction[a]	12 (11)	29 (28)	11 (17)	18 (45)	0.002
Hemodynamics first 48 h: ICU					
Lowest MAP	0 (0)	59 (54–62)	60 (58–62)	56 (51–60)	0.0003
Highest CVP	0 (0)	22 (19–27)	23 (19–25)	22 (19–29)	0.97
Highest mPAP	2 (2)	32 (29–35)	32 (29–35)	31 (29–35)	0.43
Lowest CI	2 (2)	2.0 (1.8–2.3)	2.1 (1.8–2.3)	1.9 (1.6–2.2)	0.10
Lowest SvO2	5 (5)	54 (49–60)	54 (49–60)	54 (48–60)	0.82
Peak lactate	0 (0)	7.0 (5.6–9.8)	6.5 (5.1–8.6)	8.0 (6.7–10.8)	0.004
Time to lactate <3 (hrs)	0 (0)	14 (11–18)	14 (10–17)	16 (11–20)	0.14
Maximal vasoactive dose 48 h					
Milrinone (µg/kg/min)	0 (0)	0.25 (0.20–0.35)	0.25 (0.19–0.34)	0.26 (0.20–0.37)	0.45
Dobutamine (µg/kg/min)	0 (0)	0 (0–2.51)	0 (0–3.27)	0 (0–0)	0.12
Adrenaline (µg/kg/min)	0 (0)	0.06 (0.05–0.09)	0.05 (0.04–0.07)	0.08 (0.06–0.11)	0.0006
Noradrenaline (µg/kg/min)	0 (0)	0.22 (0.14–0.33)	0.19 (0.14–0.24)	0.30 (0.21–0.44)	0.0002
Vasopressin (unit/kg /h)	0 (0)	0.02 (0–0.03)	0 (0–0.03)	0.03 (0.00–0.03)	<0.0001
VIS	0 (0)	31.7 (21.3–44.3)	28.2 (19.7–34.6)	41.7 (31.1–60.8)	<0.0001
IS	0 (0)	31.1 (21.2–41.2)	28.3 (20.7–33.9)	38.8 (30.2–58.4)	<0.0001
Mechanical Circulatory Support					
VA-ECMO or IABP use in 48 h	0 (0)	11 (10)	0 (0)	11 (26)	<0.0001
Transfusions first 48 h					
Lowest Hb	0 (0)	79 (74–87)	80 (75–90)	76 (72–81)	0.03
RBC transfusion	0 (0)	0 (0–1)	0 (0–0)	1 (0–2)	<0.0001
Fresh frozen Plasma transfusion	0 (0)	0 (0–0)	0 (0–0)	0 (0–0)	0.002
Cryoprecipitate transfusion	0 (0)	0 (0–0)	0 (0–0)	0 (0–0)	0.001
Platelet transfusion	0 (0)	0 (0–0)	0 (0–0)	0 (0–0)	0.06

Values are expressed as median (interquartile range) or n (%).

[a]Primary Graft Dysfunction defined by Kobashigawa et al.[33]

CI, cardiac index; CPOi, cardiac power output index; CVP, central venous pressure; Hb, hemoglobin; IABP, intra-aortic balloon pump; IS, Inotrope Score; MAP, mean arterial pressure; PAPi, pulmonary artery pulsatility index; SvO_2, mixed venous oxygen saturation; VA-ECMO, veno-arterial extra corporeal membrane oxygenation; VIS, Vasoactive Inotrope Score.

significantly more blood product transfusions within the first 48 h (Table 3). No patients reached therapeutic or toxic calcineurin inhibitor levels in the 48-h timeframe.

A Bonferroni correction was applied to the comparison of 66 parameters, setting a significant *P* value of <0.0008. With this correction, in the first 48 h of ICU, the severe AKI group had significantly higher doses of noradrenaline, adrenaline and vasopressin, higher red blood cell transfusion, and lower MAP.

RRT was required in 37 patients in the first 7 d (34% of all patients, 88% of the severe AKI group). By hospital discharge, 2 of the 67 stage 0–2 AKI survivors and 7 of the 35 severe AKI survivors were dialysis dependent. Twenty-two percent of survivors in the severe AKI group were dialysis dependent at 90-d posttransplantation. Overall hospital mortality was 6.4%, 0% in the stage 0–2 AKI and 17% in the severe AKI group. Ninety-day mortality was 5% overall, 0% in the stage 0–2 AKI, and 12% in the severe AKI group. Twelve-month mortality was 8% overall, 1% in the stage 0–2 AKI group, and 22% in the severe AKI group. Median ICU length of stay, hospital length of stay, and median mechanical ventilation time were longer in the severe AKI group (Table 4).

TABLE 4.
Patient outcomes

Characteristic	Missing data	KDIGO stage			*P* Value
		All patients (n = 109)	0–2 (n = 67)	3 (n = 42)	KDIGO stage 3 vs 0–2
Renal Outcomes					
RRT use first 48 h	0 (0)	28 (26)	0 (0)	28 (67)	
RRT in ICU	0 (0)	36 (33)	0 (0)	36 (86)	
RRT in first 7 d	0 (0)	37 (34)	0 (0)	37 (88)	
Dialysis at ICU d/c alive	0 (0)	28 (26)	0 (0)	28 (72)	
Dialysis >28 d alive	0 (0)	17 (16)	2 (3)	17 (44)	
Dialysis >90-d alive	0 (0)	8 (7)	1 (1)	8 (22)	
Dialysis at Hosp d/c alive	0 (0)	7 (6)	2 (3)	7 (20)	
Other Secondary Outcomes					
Ventilation (h)	0 (0)	36 (18–114)	21 (16–37)	135 (62–323)	<0.0001
ICU length of stay (h)	0 (0)	116 (77–217)	90 (68–120)	234 (148–482)	<0.0001
Hospital length of stay (d)	0 (0)	27 (16–47)	20 (14–35)	43 (26–96)	<0.0001
ICU mortality	0 (0)	3 (3)	0 (0)	3 (7)	0.05
90-d mortality	0 (0)	5 (5)	0 (0)	5 (12)	0.01
Hospital mortality	0 (0)	7 (6)	0 (0)	7 (17)	0.001
12-mo mortality	0 (0)	9 (8)	1 (1)	8 (19)	0.01

Values are expressed as median (interquartile range) or n (%).
D/C, discharge; RRT, renal replacement therapy.

TABLE 5.
Multivariable logistic regression analysis

Factor	OR	95% CI	*P*
Preoperative eGFR (per 10 mL/min/1.73m^2)	0.72	0. 55–0.93	0.01
Red Blood Cell transfusion ICU (per unit)	1.53	0. 80–2.87	0.16
Noradrenaline dose (per 0.1mcg/kg/min)	1.55	1. 16–2.16	0.002
Mechanical circulatory Support	27.74	2. 30–4119.3	0.01

eGFR, estimated glomerular filtration rate.

eGFR, noradrenaline dose, and the need for mechanical circulatory support were all independently associated with the risk of developing severe AKI in a multiple regression analysis (Table 5).

DISCUSSION

Severe AKI in the first-week postprocedure was common in heart transplant recipients in our center. We found a complex interplay between several factors, where an at-risk population has a homeostatic disturbance during transplantation, which results in a phenotype of either graft dysfunction, significant vasoplegia, or a combination of both, leading to the development of severe AKI. Among numerous risk factors preoperative eGFR, noradrenaline dose, and the need for mechanical circulatory support were independently associated with its development. Early severe AKI was associated with an increased rate of hospital death, dialysis dependence at time of hospital discharge, and increased ventilation duration, ICU, and hospital length of stay.

To define AKI in our study, we used the KDIGO criteria,[30] which was created to standardize and unify AKIN and RIFLE definitions with the advantage of improving the sensitivity of both.[39] Studies which report on AKI following heart transplantation adopt variably either RIFLE,[6,27,28,40] AKIN,[10,41,42] or KDIGO[3,4,7,8,11,12,15,16,21–24] criteria with the latter showing the highest sensitivity.[26] We did not find a difference in the classification rate for severe AKI between the KDIGO and the RIFLE criteria.

Reported rates of AKI postcardiac transplantation vary between 14%[6] and 83%[4] with rates of severe AKI between 6%[6,24] and 46%[3,16] in the recent literature. At a rate of 78% for AKI and 39% for severe AKI, our study had quite high incidences. RRT was commenced within 1 wk of transplantation in 35% of our cohort putting it at the higher end of the spectrum along with numerous other studies.[3,11,16,27,28] The significant heterogeneity in AKI rates that exists between studies has a number of possible explanations including variations in study sample sizes, adoption of different definitions, timepoints used for the assessment of renal function, recipient selection criteria, indications for initiating RRT, and the highly variable process of heart transplantation itself (donor selection, retrieval processes, surgical factors, immunosuppression regimes, and postoperative practices).

Regarding the timing of AKI, 28 patients (67% of all stage 3 AKI) were on RRT within 48 h. One RRT patient in the stage 3 AKI group had creatinine rise above the threshold of 354.6 µMol/L within 48 h (this patient never received RRT). Thus, 29 patients out of 42 (69%) were diagnosed with severe AKI within 48 h. Twenty-four (83%) of the stage 3 AKI patients had a urine output of <0. 3 mL/kg/h for >24 h. Therefore, severe AKI occurred commonly early and was most often associated with persistent oliguria resulting in the need for RRT.

In our cohort, older age was associated with the development of severe AKI, which was also found by others.[10,11,17,20,23,28] With regards to our population, the median age of our transplant recipients was 58 y, this is older than the average recipient age of 55 y from international registry data,[43] which may have contributed to the our overall high incidence of kidney injury in our study population.

We found an association between BMI and the development of severe AKI. Obesity has consistently been associated with the development of AKI following cardiac surgery in general[44–46] and specifically after heart transplantation surgery.[3,7,9,12,14,17]

Similar to other studies, severe AKI was associated with both operation time and CPB time.[3,5,8,15,16,27] Mechanisms explaining the association between CPB time and AKI and include perioperative renal ischemia-reperfusion injury, hemolysis and pigment nephropathy, oxidative stress, and systemic inflammation associated with CPB.[47–49] Interestingly, in contrast to the finding of some studies,[13,18,19] we did not find an association between LVAD explant and the development of severe AKI in our cohort, which had a mean LVAD duration of 9.3 mo SD 7.0 mo.

We did not find an association between donation after circulatory death (DCD) and development of severe AKI. Previous studies from our institution have reported rates of delayed graft function and need for mechanical circulatory support in the DCD population in the range of 22% to 35%,[50,51] which we anticipated would lead to a significant association with the development of severe AKI. All of our DCD heart transplants were preserved with Transmedics OCS. Out of the 36 DCD donor heart recipients in our study, only 2 (6%) patients went on to require VA-ECMO and 1 (3%) patient required IABP in the postoperative period perhaps demonstrating improvements in organ retrieval, management of ischemia-reperfusion, and optimization of ex situ cardiac perfusion.

Our cohort had a very low rate of postoperative bleeding with only 3 patients requiring emergency return to theater for bleeding and a very low number of total transfusions being given. The severe AKI group received 78% of the 80 units of packed red blood cells, 87% of the 31 units of fresh frozen plasma, 95% of the 41 units of cryoprecipitate, and 77% of the 13 units of platelets. Most of these blood products were administered to a small number of patients in the severe AKI group. Others have found an association between transfusion and AKI postheart transplantation.[3,9,27] Karkouti summarizes a large number of observational studies investigating the association of blood transfusion with AKI in cardiac surgery patients and summates that each unit of blood transfusion is independently associated with a 10% to 20% risk of AKI.[52]

We found preoperative eGFR to be an independent risk factor for the development of severe AKI, this has been frequently shown by others.[2,5,7,12,13,17–19,22,23,26] Our results highlight the importance of routine examination of preoperative renal function and incorporating these results into risk stratification models to aid the selection process, communicating risks to patients and to implement protective strategies in the perioperative period. From our receiver operator characteristic curve, we found that an eGFR of 55 mL/min/1.73m^2 had a 55% sensitivity and 75% specificity for the development of severe AKI (Figure S1, SDC, http://links.lww.com/TXD/A617).

The dose of noradrenaline as well as that of vasopressin and adrenaline in the early postoperative phase was associated with the later development of severe AKI. We did not find any other studies independently associating noradrenaline dose with the development of AKI; however, there have previously been association found between adrenaline and AKI postheart transplantation.[3] Similarly, the Vasopressor Inotrope Score score has previously been shown to be an independent risk factor for the development of AKI.[16,25] The dosage of noradrenaline likely reflects the severity of vasoplegia, which is a commonly encountered complication for patients who have undergone heart transplantation.[53] From our receiver operator characteristic curve, we found a cutoff of 0.25 μg/kg/min had a 64% sensitivity and 78% specificity for the development of severe AKI (Figure S2, SDC, http://links.lww.com/TXD/A617).

AKI is very common in patients on mechanical circulatory support.[54] Consistent with this, we found that mechanical circulatory support in the first 48-h postheart transplantation was independently associated with the development of severe AKI, which has be reported by others.[9,21] All patients in our study who required mechanical circulatory support developed severe AKI and more than half of the severe AKI group had moderate-to-severe graft dysfunction or required mechanical support.

The high odds ratio and extreme confidence intervals for mechanical circulatory support in our multivariable analysis, due to it exhibiting complete separation,[37] has the potential to confound the results of our model. For this reason, we conducted a sensitivity analysis by fitting a logistic regression model excluding the MCS variable. The area under the curve of model predictions exhibited a small decrease, which is anticipated upon the removal of a covariate from a model (Figures S1 and S2, SDC, http://links.lww.com/TXD/A617). Notably, the RBC variable emerged as significant in the absence of MCS (Table S2, SDC, http://links.lww.com/TXD/A617), which could be attributed to a confounding association with the MCS variable. The other variables in the model without MCS have similar values to the full model.

Patients with severe AKI in our study had a mortality rate similar or lower to that reported by a number of other studies.[3,6,7,9,12,13,15–17,23,27] The association of severe AKI and mortality highlights the significance of developing this complication. Mechanical ventilation duration was 6 times longer in the severe AKI group reflecting the complexity of this patient group and possibly also the interactions between renal impairment and respiratory function. Increased ICU length of stay and time of mechanical ventilation highlight the resource implications of patients who develop severe AKI.

It is acknowledged that there are several limitations to our study. Being a single-center study, the clinical management of patients in our institution may vary to that of other centers, limiting generalizability. We collected data on risk factors during the first 48 h, it is acknowledged that other factors between 48 h and 7 d may also contribute to the development of severe AKI, in particular calcineurin inhibitor levels, which may reach supratherapeutic levels by this time point (a recognized risk for AKI development). The study is retrospective and as such susceptible to missing data, the quantity of missing data is outline in Tables 1 to 4, the multivariable logistic regression did not include variables with missing data. The small total number of patients limited the number of independent variables for building a multivariable model. The authors of this study did not have access to donor medical records, which limited exploring the impact of donor factors on the development of severe AKI. Finally, for our data collection, we recorded if a patient required RRT; however, the indication for the commencement was often not recorded, it is possible that different indications for commencing RRT are associated with disparate outcomes.

In conclusion, this retrospective single-center study found that severe AKI is very common in heart transplant recipients. Severe AKI has significant implications on patient centered outcomes, in particular, an increased hospital mortality and dependence on dialysis at the time of hospital discharge.

Preoperative kidney function, postoperative vasoplegia with high requirements for vasoactive drugs and graft dysfunction with the need for mechanical circulatory supports were independently associated with the development of acute severe AKI in the first-week following orthotopic heart transplantation.

ACKNOWLEDGMENTS

We wish to thank the following people:

-Sandra Lopez Yern for assistance with data collection for this study.

-Coralie Williams, Stats Central (University New South Wales), for assistance with statistical calculations.

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