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Original Article

Acute Kidney Injury After Heart Transplantation: Risk Factors and Clinical Outcomes

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Objective: Acute kidney injury (AKI) requiring renal-replacement therapy (RRT) after heart transplantation (OHT) is common and impairs outcomes. This study aimed to identify independent donor and recipient risk factors associated with RRT after OHT.
Design: A retrospective data analysis.
Setting: Data were collected from clinical routines in a maximum-care university hospital.
Participants: Patients who underwent OHT.
Interventions: The authors retrospectively analyzed data from 264 patients who underwent OHT between 2012 and 2021; 189 patients were eligible and included in the final analysis.
Measurements and Main Results: The mean age was 48.0 ± 12.3 years, and 71.4% of patients were male. Ninety (47.6%) patients were on long-term mechanical circulatory support (lt-MCS). Posttransplant AKI with RRT occurred in 123 (65.1%) patients. In a multivariate analysis, preoperative body mass index >25 kg/m^2 (odds ratio [OR] 4.74, $p < 0.001$), elevated preoperative creatinine levels (OR for each mg/dL increase 3.44, $p = 0.004$), administration of red blood cell units during transplantation procedure (OR 2.31, $p = 0.041$) and ischemia time (OR for each hour increase 1.77, $p = 0.004$) were associated with a higher incidence of RRT. The use of renin-angiotensin-aldosterone system blockers before transplantation was associated with a reduced risk of RRT (OR 0.36, $p = 0.013$). The risk of mortality was 6.9-fold higher in patients who required RRT (hazard ratio 6.9, 95% CI: 2.1-22.6 $p = 0.001$). Previous lt-MCS, as well as donor parameters, were not associated with RRT after OHT.
Conclusions: The implementation of guideline-directed medical therapy, weight reduction, minimizing ischemia time (ie, organ perfusion systems, workflow optimization), and comprehensive patient blood management potentially influences renal function and outcomes after OHT.

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ACUTE KIDNEY INJURY (AKI) after cardiac surgery is a well-recognized complication that occurs in up to 50% of patients, leading to impaired short- and long-term outcomes.[1-3] Factors contributing to the development of AKI include cardiopulmonary bypass flow, renal ischemia, pulsatile reperfusion after cardiopulmonary bypass, oxidative stress, inflammation, hemolysis, macro- and microemboli.[4-7]

Patients undergoing heart transplantation have additional risk factors, including (1) the postoperative use of nephrotoxic calcineurin inhibitors and other drugs, (2) preoperative cardiorenal syndrome, and (3) ischemia or reperfusion injury, leading to right ventricular (RV) failure with reduced renal perfusion pressure.[8-12] Overall, AKI requiring renal-replacement therapy (RRT) is common after heart transplantation.[13-15]

Numerous research efforts have been devoted to investigating AKI after heart transplantation, yet only a limited number of these studies have focused specifically on the Eurotransplant (ET) region. Despite Germany accounting for approximately 60% of all transplants within the ET area, no study specifically has investigated the incidence of AKI after heart transplantation in a German cohort.[13] The transplant centers in Germany will be faced with additional challenges in the near future. The age of both donors and recipients is increasing, and the decline in the number of organ donors in Germany has exacerbated the shortage. This has necessitated the acceptance of marginal donors, with 366 donors utilized in 2011 and 358 in 2021.[16,17] However, as of December 31, 2021, there were still 1,129 patients on the waiting list.[17-19]

The aim of this study was to evaluate independent donor and recipient risk factors for heart transplant-associated severe AKI and to analyze the impact on patient outcomes, taking into consideration various baseline patient and donor characteristics in Germany. These characteristics include, among others, recipient age, waiting times, comorbidities, ischemia time, and the presence of left ventricular assist devices (LVADs).

Methods

Study Design

The authors conducted a retrospective study to identify risk factors and evaluate outcomes in patients with AKI who underwent orthotopic heart transplantation (OHT) at their institution between October 24, 2012, and December 31, 2021. The local ethics committee (EA2/014/022) approved the analysis.

Study Cohort and Data Collection

The study authors retrospectively screened data from 264 patients who underwent OHT at their unit in the investigational period. Fifty-five patients under the age of 18 were excluded. Fourteen patients who underwent combined transplantation and 2 patients who underwent retransplantation were excluded from the study. Three patients died intraoperatively during OHT, and follow-up data were insufficient for further analyses; 1 patient record had to be excluded due to missing data (Fig 1).

Medical records of all participants were reviewed, and electronic data were either extracted from an electronic patient data management system (m.life; medisite GmbH, Hanover, Germany) as CSV-export with the use of a data parser and then collated in Microsoft Excel (Microsoft, Corp, Redmond, WA) or directly filed via Microsoft Access (Microsoft, Corp). All data were collected and managed using REDCap electronic capture tools hosted at the authors' institution (REDCap Consortium, Vanderbilt University, Nashville, TN).

Demographic data and the presence of an LVAD, as well as concomitant diseases, previous cardiac surgery other than LVAD, medication, and blood results before OHT, were collected. Donor parameters (eg, demographics, echocardiography results, and concomitant diseases, as well as transplantation parameters and times) were obtained; postoperative parameters included vital parameters, laboratory results, medication, and ultrasound examination. Postoperative parameters, as well as laboratory results, including cyclosporin (CyA) blood levels, were collected automatically at hours 0, 12, 24, and 72 with an allowed deviation of −2.4, −9.6, −21.6, and −24 hours, respectively. If more results were within the allowed deviation, the closest value to the time point was chosen. Hour 0 was defined as admission to the intensive care unit (ICU). Patients currently undergoing RRT at those specific time points have been excluded from the subgroup analysis conducted at hours 12, 24, 48, 72, and 120 (n = 12, 32, 63, 78, 98, respectively).

Immunosuppressive Regimen

CyA was the immunosuppressive medication administered intravenously during the transplantation procedure and in the initial stage of recovery in the ICU. Perioperatively, CyA was administrated at a dosage of 1.5 mg per kg of body weight over 4 hours, twice daily, with the intention of attaining a targeted trough level ranging from 180-to-200 ng/mL. The 'CyA-first sample' refers to the CyA level measured 24 hours after transplantation. A regimen devoid of calcineurin inhibitors (tacrolimus after oral administration) is not prescribed during the initial 12 months after transplantation at the authors' institution. Antithymocyte globulin (ATG) was given in stabilized patients no earlier than 4 hours after admission to the ICU using a standard starting dose ranging from 1-to-4.5 mg per kg of body weight. ATG was administered in 1-to-3 separate doses. The decision to use ATG was determined by assessing each patient's clinical and laboratory status to meet their individual needs. However, patients who had undergone heart transplantation due to LVAD infection did not receive ATG.

RRT

In line with the Heart Failure Association statement, RRT was initiated primarily due to oliguria, leading to fluid overload and unresponsive to medical treatments such as loop

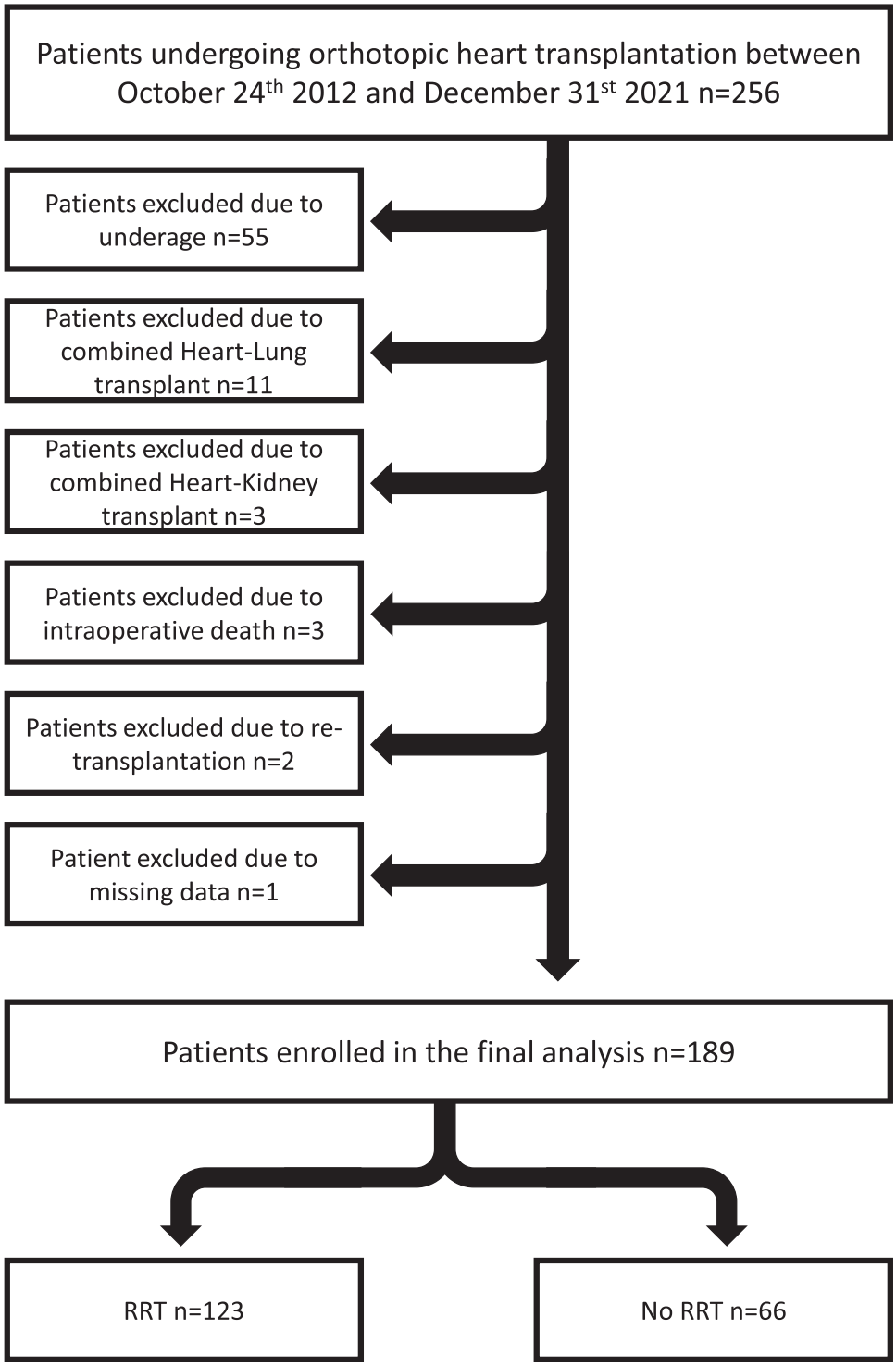

Fig 1. Patient selection. Enrollment scheme for study. RRT, renal-replacement therapy.

diuretics. This overload results in altered RV geometry, characterized by RV dilation, tricuspid insufficiency, and impaired RV function.[20] Patients requiring RRT received vascular access through a double-lumen catheter inserted into either the left or right jugular or femoral vein. The PRISMAFLEX System (Baxter Corporation, Deerfield, IL) was used to administer continuous venovenous hemodiafiltration with a prescribed RRT dose of 3,000 mL per hour. Initially, the blood flow rate was adjusted to the patient's tolerance, starting at 100 mL per minute. Likewise, the ultrafiltration rate was adjusted to the individual patients' needs, starting at 100 mL per hour. Continuous venovenous hemodiafiltration was switched to discontinuous RRT as soon as the patients' hemodynamics were stable.

Statistical Analysis

Continuous variables are presented as mean with ±SD or median with upper and lower IQR in case of nonnormally distributed data. For binary or ordinal data, absolute and relative frequencies are given. Differences between groups were tested with *t* tests or Mann–Whitney *U* tests (normally or nonnormally distributed continuous data), and chi-square test with Yates continuity parameter for categorical data.

The hazard ratio and associated 95% CI were calculated using a Cox Regression with RRT as a time-dependent covariate. For potential risk factors, an univariate logistic regression was conducted, and odds ratios (ORs) with 95% CI were presented. Prognostic factors for a multivariate logistic regression model were determined using the least absolute shrinkage and selection operator.[21] The authors used a bootstrap resampling procedure to study the stability of their final model and to quantify its optimism. As a measure of predictive performance, the concordance index (C-index) and Somers' D were calculated and corrected from overoptimism by 1,000 bootstrap samples. To judge calibration, the Brier score[22] and the maximal absolute difference in predicted and calibrated probabilities are given. For statistical calculations, R software, Version 4.03 (R Foundation for Statistical Computing, Vienna, Austria)[23] was used.

Results

Patient Characteristics

In total, 189 patients were included in the analysis. The mean age was 48.0 ± 12.3 years, and 135 (71.4%) were male. The majority of patients (91.0%) underwent OHT in high urgent listing status, with dilated cardiomyopathy (67.2%) being the most common diagnosis leading to heart failure, followed by coronary artery disease (21.7%). Additionally, 47.6% of patients were on long-term mechanical circulatory support (lt-MCS), and 55.0% had undergone previous cardiac surgery other than lt-MCS implantation. Chronic kidney disease (CKD), as defined by the Kidney Disease: Improving Global Outcomes, was the most prevalent concomitant disease (79.9%).[24] Before OHT, 70.9% of patients were on angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), or angiotensin receptor-neprilysin inhibitors (ARNI), and 83.1% were on loop diuretics. Further baseline characteristics are presented in Table 1. Reasons for redo surgery can be found in Supplementary Table S1.

Perioperative Characteristics

All patients underwent orthotopic transplantation with bicaval anastomoses. The median ischemic time during the transplantation procedure was 273 minutes (248-308 minutes). The median clamp time was 128 minutes (113-144 minutes]. The median number of red blood cell concentrates (RBCC; 330 mL each) administered during transplantation surgery was 2 RBCCs (1-4 RBCCs). Additional characteristics of the transplantation procedure can be found in Table 1. The median CyA-first sample was 97.5 ng/mL (46-142 ng/mL) and did not show a difference between the RRT and no-RRT groups (97 ng/mL [46-137 ng/mL] *v* 100 ng/mL [49-151 ng/mL], p = 0.345). The distinction between patients not requiring RRT and those who will need RRT in the future course is depicted in Supplementary Figure S2.

Acute Renal Failure

Overall, 123 (65.1%) patients required RRT after OHT. Patients who underwent RRT had higher body mass indices (BMI; 26.9 ± 4.8 *v* 24.3 ± 4.0 kg/m^2, p < 0.001) and were more often suffering from preoperative CKD (87.0% *v* 66.7%, p = 0.001). During transplantation, the donor hearts of patients with postoperative need for RRT had longer ischemic times (284.6 ± 52.2 *v* 258.2 ± 56.5 minutes, p = 0.005), clamp times (131.0 [117.5-148.0] *v* 124.5 [110.0-138.8] minutes, p = 0.018), bypass times (252.0 [222.8-287.5] *v* 228.0 [197.0-259.0] minutes, p = 0.001) and reperfusion times (92.5 [77.0-120.8] minutes *v* 78.0 [59.3-98.0] minutes, p = 0.003). Patients who underwent RRT received more units of RBCCs (2 [1-5] *v* 1 [0-4] RBCC, p = 0.016) and fresh frozen plasma units (FFP; 220 mL each) (5 [0-10] *v* 4 [0-6] FFP, p = 0.008). Additionally, patients in need of second-look surgery required RRT more often after the second procedure (33.3% *v* 16.7%, p = 0.013).

Univariate Risk Factor Analysis

Univariate risk factor analysis showed that obesity was associated with a 3.7-fold increased risk for RRT post-OHT (OR 3.667, 95% CI 1.448-9.285, p = 0.004). Patients suffering from CKD before transplantation had a 3.3-fold higher risk for RRT (95% CI 1.606-6.962, p = 0.001) compared to patients without CKD. For each mg/dL increase of creatinine in serum, the risk for RRT after surgery increased 4-fold (OR 4.015, 95% CI 1.774-9.079, p = 0.003). Ischemic times >270 minutes and bypass times >240 minutes were associated with a 2-fold increased risk (OR 2.101, 95% CI 1.142-3.865, p = 0.017; OR 2.172, 95% CI 1.180-3.999, p = 0.012, respectively) for RRT after OHT. The use of RBCCs, FFPs, and platelet concentrates was associated with an increased risk for each administered unit (RBCC: OR 1.139, 95% CI 1.006-1.290, p = 0.016; FFP: OR 1.089, 95% CI 1.023-1.158, p = 0.008; platelet concentrates: OR 1.443, 95% CI 1.073-1.939, p = 0.001). Need for second-look surgery after OHT was associated with a 2.5-fold higher risk for RRT later during the hospital stay (OR 2.531, 95% CI 1.197-5.350, p = 0.013; Fig 2; Supplementary Table S3).

Multivariate Risk Factor Analysis

Recipient BMI above 25 kg/m^2 (OR 4.75, 95% CI 2.36-9.55, p < 0.001), creatinine before OHT (OR per each mg/dL increase: 3.44, 95% CI 1.48-7.98, p = 0.004), and donor heart ischemia time (OR per each hour increase: 1.77, 95% CI 1.19-2.63, p = 0.004), as well as need for RBCC administration

Table 1
Baseline Characteristics Before Transplantation

	All n = 189	No RRT n = 66	RRT n = 123	p Value
Recipient				
Age at transplantation, mean ± SD, y	48.04 ± 12.25	45.98 ± 12.89	49.13 ± 11.75	0.086
Male sex, n (%)	135 (71.43)	42 (63.64)	93 (75.61)	0.111
Body weight, mean ± SD, kg	81.03 ± 17.91	75.10 ± 15.08	84.22 ± 18.48	< 0.001
BMI, mean ± SD, kg/m^2	26.02 ± 4.69	24.29 ± 3.97	26.94 ± 4.79	< 0.001
Waiting list status (high urgent), n (%)	172 (91.01)	63 (95.45)	109 (88.62)	0.196
Days on waiting list in HU status, median (IQR)	92 (39-171)	87 (36-158)	95 (44-181)	0.441
Days on waiting list total, median (IQR)	200 (87-491)	190 (74-484)	207 (91-502)	0.396
Diagnosis leading to transplantation, n (%)				0.360
DCM	127 (67.2)	44 (66.67)	83 (67.48)	
HCM	6 (3.17)	2 (3.03)	4 (3.25)	
RCM	2 (1.06)	0	2 (1.63)	
ARVC	1 (0.53)	0	1 (0.81)	
CAD	41 (21.69)	17 (25.76)	24 (19.51)	
Other	12 (6.35)	2 (3.03)	10 (8.13)	
LVAD, n (%)	90 (47.62)	30 (45.45)	60 (48.78)	0.589
HVAD, n (%)	66 (34.92)	25 (37.88)	41 (33.33)	
HeartMate II, n (%)	12 (6.35)	2 (3.03)	10 (8.13)	
HeartMate 3, n (%)	12 (6.35)	3 (4.55)	9 (7.32)	
CKD, n (%)	151 (79.89)	44 (66.67)	107 (86.99)	0.001
eGFR <60 mL/min/1.73 m^2, n (%)	87 (46.03)	22 (33.33)	65 (52.85)	0.011
Comorbidity, n (%)				
Diabetes mellitus	31(16.4)	10 (15.15)	21 (17.07)	0.734
Hyperlipoproteinemia	56 (29.63%)	23 (34.85%)	33 (26.83%)	0.222
Former smoker	45 (23.81%)	15 (22.73%)	30 (24.39%)	0.752
Previous cardiac surgery other than LVAD surgery	104 (55.03%)	34 (51.52%)	70 (56.91%)	0.440
Medication				
ACEi, n (%)	51 (26.98)	27 (40.91)	14 (11.38)	0.002
ARB, n (%)	28 (14.81)	11 (16.67)	17 (13.82)	0.649
ARNI, n (%)	55 (29.10)	15 (22.73)	40 (32.52)	0.592
ACEi or ARB or ARNI, n (%)	134 (70.9)	53 (80.3)	81 (65.85)	0.063
ß-blocker, n (%)	120 (63.49)	40 (60.61)	80 (65.04)	0.408
MRA, n (%)	141 (74.60)	49 (74.24)	92 (74.80)	0.712
Loop diuretics, n (%)	157 (83.07)	53 (80.3)	104 (84.55)	0.252
SGLT2-inhibitor, n (%)	10 (5.29)	6 (9.09)	4 (3.25)	0.216
Catecholamines, n (%)	101 (53.44)	33 (50.00)	68 (55.28)	0.487
VIS, median (IQR)	0 (0.0-5.7)	0 (0.0-6.1)	0 (0.0-5.3)	0.463
Antibiotics, n (%), none	97 (51.32)	35 (53.03)	62 (50.41)	0.731
Laboratory values				
Hemoglobin, mean ± SD, g/dL	11.86 ± 1.89	11.51 ± 1.69	12.05 ± 1.96	0.050
GGT, median (IQR), U/L	56 (31-124)	46 (28-103)	68 (31-136)	0.055
BUN, median (IQR), mg/dL	41.4 (32.2-59.4)	37.9 (31.3-47.6)	43.3 (33.9-65.7)	0.014
Creatinine, median (IQR), mg/dL	1.2 (1.0-1.5)	1.1 (0.9-1.3)	1.3 (1.0-1.7)	0.003
Albumin, median (IQR), g/dL	3.8 (3.6-4.1)	3.8 (3.6-4.0)	3.8 (3.6-4.1)	0.829
CRP, median (IQR), mg/dL	0.4 (0.2-1.2)	0.3 (0.1-1.2)	0.5 (0.2-1.1)	0.076
Bilirubin, median (IQR), mg/dL	0.58 (0.39-0.87)	0.57 (0.36-0.90)	0.58 (0.41-0.87)	0.839
Transplantation characteristics				
Ischemic time, median (IQR), min	273 (248-308)	260 (236-289)	280 (251-312)	0.005
Cold ischemic time, median (IQR), min	180 (163-208)	180 (151-189)	186 (170-211)	0.080
Clamp time, median (IQR), min	128 (113-144)	125 (110-139)	131 (118-148)	0.018
Bypass time, median (IQR), min	242 (211-280)	228 (197-259)	252 (223-288)	0.001
Reperfusion time, median (IQR), min	87 (70-114)	78 (60-98)	93 (77-121)	0.003
Immunosuppression induction, n (%), ATG	76 (40.21)	23 (41.79)	48 (39.34)	0.886
Second look surgery, n (%), yes	29 (15.34)	11 (16.67)	18 (14.63)	0.712
RBCC during transplantation, median (IQR), units	2 (1-4)	1 (0-4)	2 (1-5)	0.016
RBCC during transplantation, n (%), yes	154 (81.48)	48 (72.72)	106 (86.18)	0.023
FFP during transplantation, median (IQR)	4 (0-9)	4 (0-6)	5 (0-10)	0.008

NOTE. Data are presented as mean ± SD, median (first quartile-third quartile), or frequencies (percentages).
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ARVC, arrhythmogenic right ventricular cardiomyopathy; ASAT, aspartate aminotransferase; ATG, antithymocyte globulin; BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; FFP, fresh frozen plasma; GGT, gamma-glutamyltransferase; HCM, hypertrophic cardiomyopathy; HU, high urgency; HVAD, HeartWare ventricular assist device; LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonist; RBCC, red blood cell concentrate; RCM, restrictive cardiomyopathy; RRT, renal-replacement therapy; SGLT2, sodium/glucose cotransporter 2; VIS, vasoactive-inotropic score

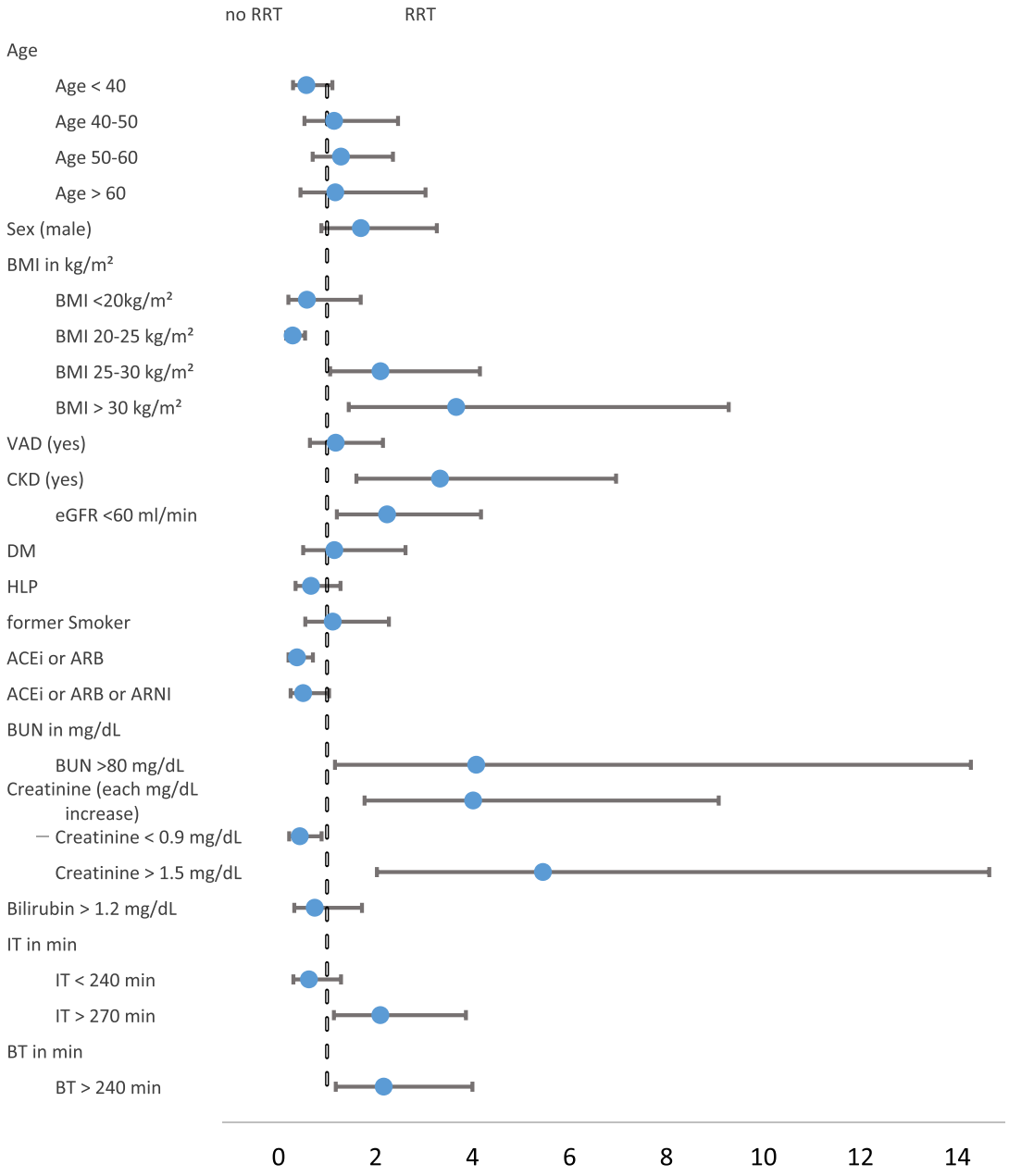

Fig 2. Univariate risk factor analysis. Forest plot of potential risk factors for acute kidney injury requiring renal-replacement therapy. Univariate risk factor analysis with odds ratios favoring renal-replacement therapy. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; BT, bypass time; BUN, blood urea nitrogen; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HLP, hyperlipoprotenemia; IT, ischemic time; RRT: renal-replacement therapy.

during transplantation procedure (OR 2.31, 95% CI 1.03-5.17, p = 0.041), are independent risk factors for RRT after surgery. On the other hand, preoperative treatment with an ACEi, ARB, or ARNI before transplantation (OR 0.358, 95% CI 0.16-0.80, p = 0.013) was found to be an independent protective factor against the need for RRT after surgery. The model showed an adequate fit (likelihood ratio chi-square 53.8, degrees of freedom 6, $p < 0.001$) and good discriminative ability with a C-index of 0.806 and Somers' D of 0.61. An internal validation with 500 bootstrap replicates resulted in a corrected C-index of 0.797 and a Somers' D of 0.59. As an index of unreliability, the maximal absolute difference in predicted and calibrated probabilities was measured as 0.027. A Brier score of 0.167 before correcting for overoptimism and 0.177 after correction revealed good model calibration. The findings of the multivariate risk factor analysis are shown in Fig 3 and Table 2.

Postoperative Outcomes

Patients who underwent RRT required longer mechanical ventilation times (9 [3-23] *v* 3 days [2-5], $p < 0.001$) as well as inotropic support (10 [7- 16] *v* 7 days [5-11], $p < 0.001$) and had a longer stay in the ICU (16 [10-40] *v* 8 days [6-12], p

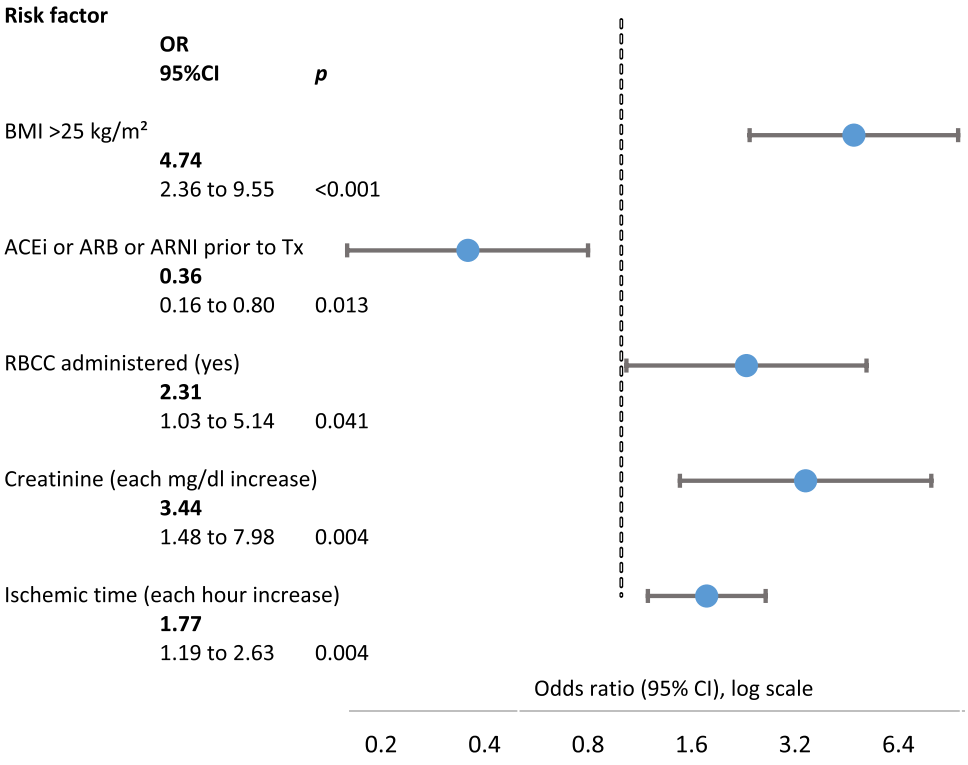

Fig 3. Multivariate analysis of risk factors – forest plot of independent risk factors for acute kidney injury (AKI) requiring renal replacement therapy (RRT). ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, ARNI: angiotensin receptor-neprilysin inhibitor, BMI: body mass index, RBCC: red blood cell concentrate administered during transplantation procedure, creatinine and ischemic time, RRT: renal-replacement therapy

Table 2
Outcomes

	All n = 189	No RRT n = 66	RRT n = 123	p Value
Inotropic support, median (IQR), d	98 (6-15)	7 (5-11)	10 (7-16)	< 0.001
Mechanical ventilation, median (IQR), d	5 (2-17)	3 (2-5)	9 (3-23)	< 0.001
ICU stay, median (IQR), d	12 (8-27)	8 (6-12)	16 (10-40)	< 0.001
Hospital stay, median (IQR), d	48 (35-76)	40 (30-55)	55 (38-84)	< 0.001
eGFR in mL/min/1.73 m^2 at discharge, n (%)				0.021
>90	12 (6.35)	5 (7.58)	7 (5.69)	
60-89	36 (19.05)	14 (21.21)	22 (17.89)	
45-59	25 (13.23)	11 (16.67)	14 (11.38)	
30-44	34 (17.99)	10 (15.15)	24 (19.51)	
15-29	15 (7.94)	1 (1.52)	14 (11.38)	
<15	2 (1.06)	0	2 (1.63)	
RRT, n (%)	19 (10.05)	0	19 (15.45)	

NOTE. Data are presented as median (first quartile-third quartile) or frequencies (percentages).
Abbreviations: eGFR, estimated glomerular filtration rate; ICU, intensive care unit; RRT, renal-replacement therapy.

< 0.001) as well as in the hospital (55 [38-84] *v* 40 days [30-55], p < 0.001). Patients discharged with ongoing need for RRT were 10.1% of all patients and 15.5% of patients who underwent RRT. Additional results are shown in Table 2. The risk of mortality after OHT was 6.9-fold higher for patients requiring RRT after transplantation (hazard ratio 6.9, 95% CI 2.1-22.6, p = 0.001). One-year survival is displayed in Fig 4.

Discussion

The objective of this study was to identify independent factors that contribute to the risk of AKI requiring RRT after OHT and the impact of RRT on the outcome in an ET cohort. Through multivariate analysis, the study authors identified factors such as BMI exceeding 25 kg/m^2, RBCC administration during the OHT procedure, pretransplant creatinine levels, and

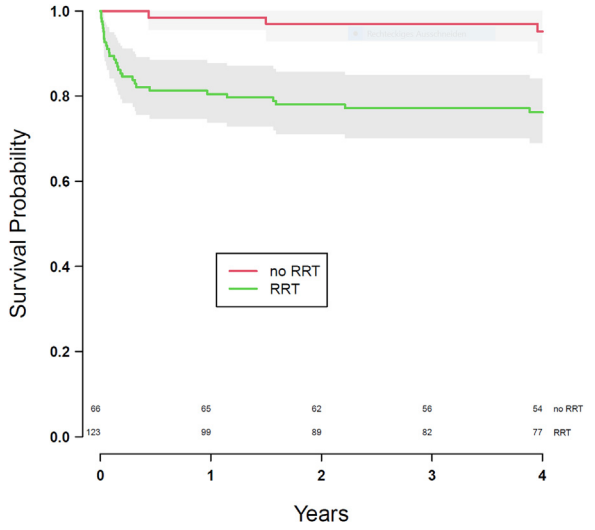

Fig 4. Survival probability after transplantation procedure, Kaplan Meyer curve. The survival curve for patients without renal- replacement therapy (RRT) is shown in red; survival for patients with RRT is shown in green. The 95% confidence interval is shown in grey.

donor organ ischemia time as independent risk factors for the development of RRT after OHT. A novel finding of this study was that treatment with an ACEi, ARB, or ARNI was protective. RRT after OHT was associated with an impaired survival rate at 1 year. AKI after OHT is of broad interest.[13] However, only a few studies were conducted within the ET area.[25-30]

It is important to note the severe shortage of donor organs in Germany, which is notably more acute than in many regions worldwide, especially compared to the United States. The scarcity in Germany leads to accepting more marginal donors, making the authors' study distinct and not directly comparable to research in the United States or other areas beyond the ET area.[16]

Fortrie et al. explored the AKI risk after OHT and its impact on 1-year survival within the ET. It included patients who underwent transplantation from 1984 to 2012; 531 patients participated, and only 25 needed RRT posttransplantation. Compared to the authors' cohort here, the patients had less inotropic support (34.7%) and fewer LVADs (Fortrie et al. [2.7%] *v* Welz et al. [47.6%]). Additionally, 44% were classified as elective cases, accounting for 44% of the total. Furthermore, their ischemic time was shorter, with a mean of 165 minutes (145-198 minutes). Even though the analysis was performed within the ET, the baseline characteristics differed greatly from the cohort presented in the authors' work.

It is essential to take into account the variations in national transplantation regulations, as well as the differences in geographic coverage and the transplant era. These factors could potentially result in disparities in donor and recipient selection criteria, as well as differences in logistical aspects of transplantation processes, all of which have been shown to be risk factors for AKI and, therefore, affect the incidences of severe AKI.

The relationship between BMI and OHT outcomes has been investigated widely. Turker et al. reported a link between BMI and AKI post-OHT, classified by RIFLE criteria.[31] Their study showed that 44.3% of AKI patients required RRT. Their population exhibited BMI differences (18.6 kg/m^2 ± 4.3 kg/m^2 in non-AKI, 24.7 kg/m^2 ± 6.7 kg/m^2 in AKI) compared to the authors' cohort here. Chouari et al. highlighted a potential risk with a BMI over 40 kg/m^2, affecting 1-year survival.[9] Yet, this may not directly apply to current ET cohorts, in which a BMI exceeding 35 kg/m^2 excludes patients due to poorer prognosis and organ scarcity, although it is not an absolute contraindication.[11] The authors' study, though limited to patients more than 30 kg/m^2, lacked statistical power for significant stratification. Nonetheless, their data suggested that even a BMI higher than 25 kg/m^2 could influence post-OHT outcomes.

The second independent risk factor for RRT was CKD. Elevated pre-OHT blood urea nitrogen and creatinine levels were strongly linked to an increased risk of RRT post-OHT. In a cohort undergoing transplantation between 1993 and 2004, Boyle et al. emphasized the significance of preoperative creatinine levels as an independent risk factor for post-OHT RRT in 756 US patients. They reported a 5.8% RRT requirement after OHT, similar creatinine levels to the authors' cohort here (1.2 [1.0-1.5] mg/dL) but shorter ischemic and bypass times and lower body weight (176.0 [136.0-207.0] minutes, 116.0 [100.0-138.5] minutes, 74.0 [65.5-85.0] kg, respectively).[8] Although their study revealed significantly lower post-OHT RRT rates compared to the authors, their patients had a lower-risk profile. Considering the different eras of investigation, the authors' hypothesis was that despite advancements in renoprotective treatments, preoperative creatinine levels remain a significant risk factor. This study underscored the importance of assessing creatinine and considering CKD in evaluating AKI risk before surgery for all patients.

The use of RBCC during the transplantation procedure and adverse events, including an increased risk of mortality after OHT, has been described earlier by Zheng et al.[32] This association may serve as an indicator of intraoperative surgical complications, high-risk recipients, or systemic inflammatory response syndrome, leading to a more complex postoperative clinical course. The patients included in the authors' analysis had an increased vulnerability due to VAD (and listing for chronic infections of central components) or a history of previous cardiac surgery, leading to a higher risk of intraoperative bleeding and subsequently receiving more RBCC. This highlights the importance of preoperative patient blood management.[33] In the context of OHT aftercare, this also reduces the risk of immunizations.

The study authors identified ischemic times as an independent AKI risk factor. Wang et al. extensively studied ischemic time in a United Kingdom OHT cohort.[34] Notably, their baseline ischemic time (3.3 ± 1.1 hours) was shorter than in the authors' ET cohort, likely due to differences in organ allocation systems. ET's larger geographic coverage may lead to longer transport times and, subsequently, longer ischemia times. Wang et al. correlated LVAD presence with post-OHT RRT but with a notably smaller LVAD patient population (7.3%) compared to the authors' cohort (47.6%). Moreover, their study lacked details on LVAD-associated complications or

bridge-to-transplant protocols guiding high-urgency heart transplantation acceptances. The authors' data here were derived mainly from patients who required LVADs with HeartWare ventricular assist devices (Medtronic PLC, Dublin, Ireland). The high rates of pump thrombosis associated with this type of LVAD were the primary reason for heart transplantation, contrasting with current-era pumps like the HeartMate 3 (Abbott Laboratories, Abbott Park, IL).[35] With significantly improved hemocompatibility of magnetically levitated pumps, OHT in the presence of an LVAD is typically performed for central LVAD-related infections. Consequently, the previous administration of continuous antibiotic treatment with nephrotoxic side effects in these patients may emerge as a potential risk factor for RRT after OHT. Further research is needed to explore the impact of LVAD-associated infections on the risk of requiring RRT after OHT in this evolving cohort.

The authors' analysis suggested that ACE inhibitors, ARBs, or ARNIs may offer a protective effect against RRT, potentially leading to improved long-term survival. Berger et al. investigated the impact of ACE inhibitors pre-OHT on long-term survival, highlighting potential selection biases in which sicker patients might have been excluded from receiving ramipril in their specific case, a concern also applicable to the authors' cohort.[36]

Additionally, despite retrospective cohort data, there is a lack of evidence from randomized trials supporting this protective effect for modern heart failure therapy in LVAD patients, a significant segment in the authors' cohort.[37] Patients who require LVADs might receive less guideline-directed medical therapy (GDMT). The authors' findings did not reveal differences between patients with LVADs and those without LVADs in outcomes or likelihood of receiving ACE inhibitors, ARBs, or ARNIs. Considering the advancements in medical heart failure treatment, such as sodium-glucose cotransporter-2 inhibitors, the potential impact of full GDMT medication on transplant outcomes requires continuous investigation.[38]

Although the RRT rates in the authors' cohort were higher than in other studies, the overall outcome of the RRT group was better than reported by others. For example, Gasparovic et al. reported RRT in 17% of patients post-OHT who had a 3-month mortality as high as 63% compared to 4% for those without RRT.[26] In general, a possible confounder when comparing the rates of RRT in the current body of literature is the retrospective nature of the analyses. Possibly, the authors' institution had a less-aggressive medical approach and was more liberal in the early implementation of RRT. However, the overall survival rate of their cohort (regardless of kidney function) was comparable to the ones reported by American registries of European transplant centers.[39-42]

Limitations

The retrospective study design was associated with several limitations. These include a lack of control over the data collection process because the data were collected from existing records, as well as the risk of selection bias and being underpowered because the study was conducted at a single center with a relatively small sample size of 189 patients, limiting its generalizability to the broader population of OHT performed in the ET region. Furthermore, the ability to establish causality was limited due to the retrospective study design and lack of controls. The criteria for determining the need for RRT after OHT were not explicitly defined, leading to potential variability in the underlying factors.

Conclusion

BMI exceeding 25 kg/m^2, transfusion of RBCCs during the OHT procedure, elevated creatinine levels (for each mg/mL increase) before OHT, and ischemia time are independent risk factors for RRT after OHT and, subsequently, lead to decreased long-term survival. Treatment with ACEi, ARB, or ARNI, on the other hand, is an independent protective factor against RRT after OHT.

Adopting a comprehensive patient blood management approach, meticulous recipient selection based on preoperative BMI, and implementing systematic exercise training or medically-assisted therapy for weight loss in individuals with a BMI >25 kg/m^2 appear to be promising strategies in preventing AKI after OHT. In addition, GDMT, optimized workflows, transport procedures, and organ perfusion systems to minimize ischemic time during transplantation might further improve OHT outcomes. Further research is needed to investigate the potential risks associated with LVADs before OHT and their clinical relevance, especially as thrombotic events are an increasingly rare indication for OHT.

Declaration of competing interest

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CRediT authorship contribution statement

Friedrich Welz: Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Felix Schoenrath:** Writing – review & editing, Supervision, Conceptualization. **Aljona Friedrich:** Investigation. **Alexa Wloch:** Investigation. **Julia Stein:** Visualization, Validation, Software, Formal analysis. **Felix Hennig:** Conceptualization. **Sascha C. Ott:** Writing – review & editing. **Benjamin O'Brien:** Writing – review & editing. **Volkmar Falk:** Writing – review & editing, Supervision. **Christoph Knosalla:** Writing – review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.jvca.2024.01.024.

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