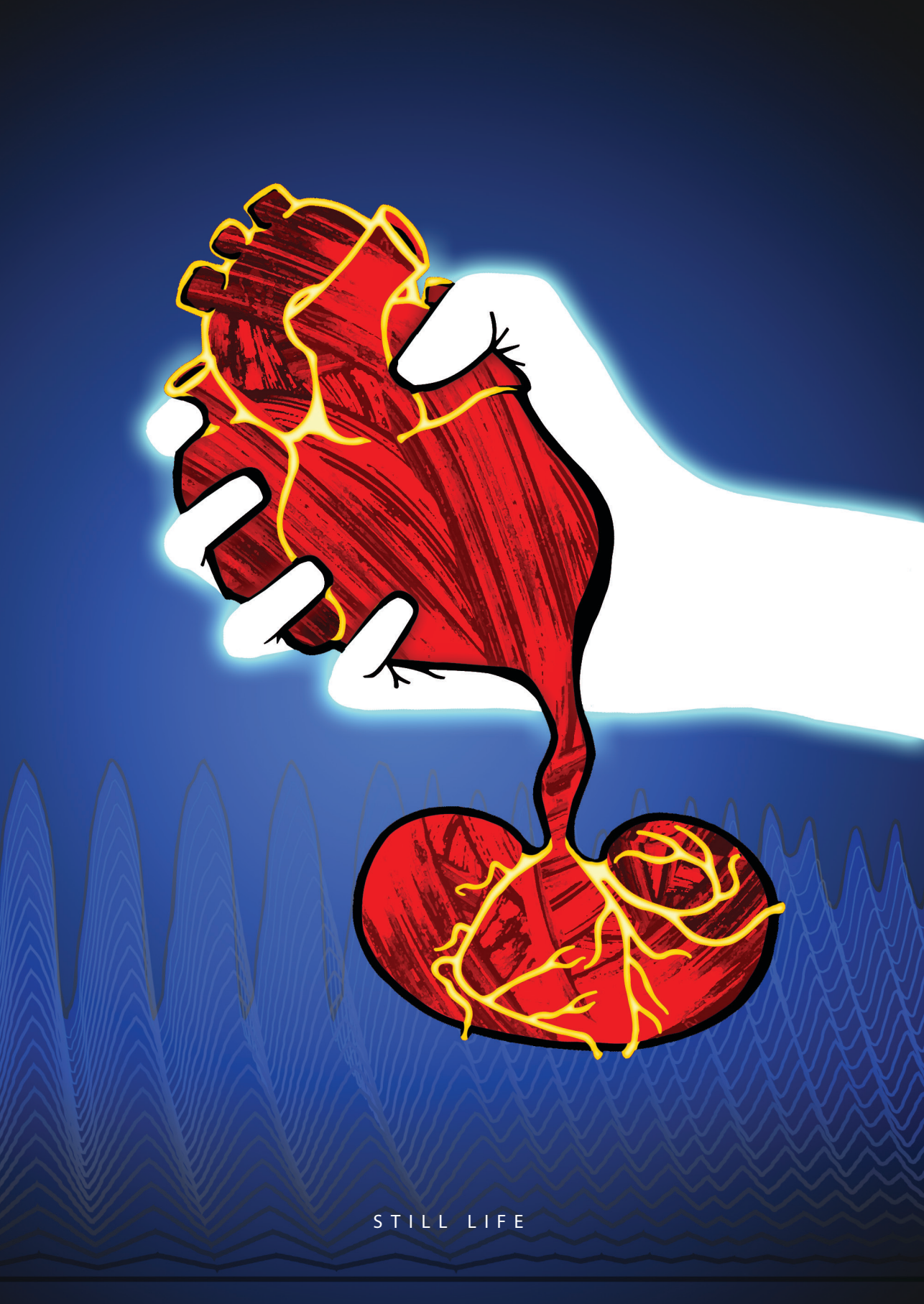
STILL LIFE

Part IV

LESSONS LEARNED FROM CLINICAL PRACTICE

CHAPTER 12

Predictive Value of Right Heart Hemodynamics for Acute Kidney Injury After Heart Transplantation

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ABSTRACT

Background

Acute kidney injury (AKI) frequently occurs after heart transplantation (HTx), but its relation to preoperative right heart hemodynamic (RHH) parameters remains unknown. Therefore, we aimed to determine their predictive properties for postoperative AKI severity within 30 days after HTx.

Methods

From 1984 to 2016, all consecutive HTx recipients (n=595) in our tertiary referral center were included and analyzed for the occurrence of postoperative AKI staged by the Kidney Disease Improving Global Outcome Criteria. The effects of preoperative RHH on postoperative AKI were calculated using logistic regression, and predictive accuracy was assessed using integrated discrimination improvement (IDI), net reclassification improvement (NRI), and area under the receiver operating characteristics curves (AUC).

Results

Postoperative AKI occurred in 430 (72%) patients including 278 (47%) stage-1, 66 (11%) stage-2, and 86 (14%) stage-3. Renal replacement therapy (RRT) was administered in 41 (7%) patients. Patients with higher AKI stages had also higher baseline right atrial pressure (RAP) (median: 7, 7, 8, 11 mmHg, p-trend=0.021), RAP-to-pulmonary capillary wedge pressure (PCWP) ratio (0.37, 0.36, 0.40, 0.47, p-trend=0.009), and lower pulmonary artery pulsatility index (PAPi) values (2.83, 3.17, 2.54, 2.31, p-trend=0.012). Higher RAP and lower PAPi values independently predicted AKI severity (adjusted OR per doubling of RAP 1.16[1.02–1.32], p=0.029; of PAPi 0.85[0.75–0.96], p=0.008). Based on IDI, NRI, and delta AUC, inclusion of these parameters improved the models' predictive accuracy.

Conclusions

Preoperative PAPi and RAP strongly predict the development of AKI early after HTx and can be used as early AKI predictors.

INTRODUCTION

Heart transplantation (HTx) remains the gold standard therapy for patients with end-stage heart failure (HF) improving both their survival and quality of life.[1] Recent advances in immunosuppressive therapy and treatment protocols have significantly improved the long-term outcome in HTx recipients despite the propensity for accepting older donors.[2] However, the short-term outcome during the early postoperative phase has remained complex, affecting both morbidity and mortality.[2,3]

Acute kidney injury (AKI) occurs frequently after HTx ranging from 22 to 76% and carries unfavorable prognosis.[4-7] In addition to anesthesia- and surgery-related factors that can precipitate AKI, postoperatively used nephrotoxic drugs (e.g., CNI) and hemodynamic instability may also lead to AKI.[4]

It is known that the preexisting pulmonary hypertension increases the right ventricular afterload that can lead to the right ventricular failure (RVF).[8] Importantly, RVF can critically diminish renal function by increasing renal venous pressure causing congestive AKI.[9,10] Consequently, the right heart hemodynamic (RHH) parameters have been routinely assessed in all HTx candidates.[11] However, it is unclear how these RHH parameters relate to RVF and, more importantly to AKI early after HTx. Finally, the question remains whether and to what extent is the relationship between preoperative RHH parameters and the occurrence of postoperative AKI explained by the occurrence of RVF along that pathway.

Recently, new composite hemodynamic parameters such as the pulmonary artery pulsatility index (PAPi), the right atrial pressure-to-pulmonary capillary wedge pressure ratio (RAP/PCWP), and diastolic pulmonary gradient (DPG) are considered to be the predictors of RVF.[12-15] However, their relationships with postoperative AKI early after HTx remain unknown.

The aim of this study was to determine the predictive properties of the routine and the novel RHH parameters measured at the time of transplantation listing in relation to AKI early after HTx. Preliminary results have been previously reported.[16]

METHODS

Study population

Data of all consecutive HTx in the Erasmus Medical Center, Rotterdam, have been collected prospectively since the first transplantation in June 1984.[2,4] We included all adult (≥18 years) patients transplanted between 1984 and December 2016. Patients

were excluded if age <18 years at the time of transplantation, were on renal replacement therapy (RRT) before transplantation, died within 48 hours or were re-transplanted within 7 days after transplantation (Figure 1). No patients underwent simultaneous heart-kidney transplantation. Patient data were obtained from the hospital database, electronic records and by chart review.

Immunosuppressive protocol

From 1984 to 1999, the immunosuppressive therapy consisted of calcineurin inhibitor (CNI) cyclosporine A and tacrolimus thereafter. In patients who did not receive induction therapy, CNI was initiated peri-operatively or immediately after HTx. The induction therapy was used to delay the starting of CNI, especially in patients with already impaired kidneys and/or postoperative hemodynamic instability, to postpone the CNI nephrotoxicity.[4] The induction therapy consisted of anti-CD3 (1987-1994), anti-IL2 (1987-1994), horse polyclonal anti-thymocyte globulin (1987-2008), and rabbit anti-thymocyte globulin (2008 and thereafter).

Preoperative right heart catheterization parameters

All HTx candidates underwent right heart catheterization during the screening for transplantation listing. If a patient's clinical status deteriorated with suspicion of pulmonary hypertension while on the waiting list, an additional catheterization was performed where the most recent data prior to HTx were used for our analysis. Procedural data were extracted from the catheterization reports and included the following parameters: RAP, PCWP, pulmonary artery (PA) systolic, diastolic and mean pressures, systemic arterial systolic, diastolic and mean pressures, cardiac output, pulmonary vascular resistance, and systemic vascular resistance, PAPi, transpulmonary gradient (TPG), and DPG (Figure 2).[13,15]

Renal function assessment

Serum creatinine was measured as part of routine clinical care at baseline, daily from postoperative day 0 until day 7, and at 1, 3, 6, 9 and 12 months. Baseline creatinine was defined as the most recent outpatient value up to 6 months before transplantation. If unavailable, creatinine values at hospital admission were accepted as the baseline. Estimated glomerular filtration rate (eGFR) was assessed by the CKD-EPI equation[17], and categorization was performed by National Kidney Foundation–Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines.[18]

Follow-up and study endpoints

The primary endpoint was AKI severity as defined by Kidney Disease Improving Global Outcome (KDIGO) criteria during the first month after HTx. AKI stage 1 was defined as serum creatinine increased by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours or by 1.5–1.9 times baseline; AKI stage 2 as serum creatinine increased 2.0–2.9 times from baseline; and AKI stage-3 as serum creatinine increased 3.0 times from baseline or by ≥4.0 mg/dl (≥353.6 μmol/l) or starting RRT.[19] The time interval between HTx and the RRT was recorded within the first month. RRT requirement at 1-year was evaluated in all survivors.

The secondary endpoints were postoperative RVF and 1-year survival. RVF was defined as need of postoperative RVAD or as reported in the medical reports by the attending physicians. Post-discharge survival status was obtained from our hospital's electronic patient file and was completed for all patients.

Statistical analysis

For reasons of uniformity all continuous variables are presented as median (interquartile range, IQR), and categorical variables are presented as numbers and percentages. The distributions of continuous variables were tested for normality by the Kolmogorov-Smirnov test, and if skewed were ^{2}log-transformed. For continuous variables, the linear trend across AKI stages was performed by analysis of variance (ANOVA) or the Kruskal-Wallis test, when appropriate; categorical variables were tested by the χ^2-trend test.

Ordinal logistic regression analysis was performed to relate perioperative data to postoperative AKI severity (i.e., deterioration to any level of AKI). Covariates that were univariably associated with AKI severity (exploratory $p<0.10$) were entered into a multivariable model, applying proportional odds ordinal regression with full likelihood ratio method. All analyses were performed in the total cohort, and subsequently in the subgroup of patients with RAP≥6 mmHg (previously determined as the cut-off for the opening of the collapsed vein).[20,21] A multiplicative interaction between dichotomized RAP and PAPi was also explored.

We assessed predictive accuracy for the most severe AKI (stage 3) before and after adding significant hemodynamic parameters ($p<0.05$) into the clinical model using delta between the areas under the two receiver operating characteristic curves (ROC-AUC), integrated discrimination improvement (IDI), and net reclassification improvement (NRI).[22,23] Clinical variables found to be univariably associated with AKI stage 3 (exploratory $p<0.10$) were entered into a multivariable model using stepwise backward likelihood ratio method. Only clinical predictors with $p<0.05$ in the

multivariable model were used to assess the models' predictive accuracy.

Binary logistic regression analysis was applied to assess the association between RRT administration within 30 days after HTx and chronic RRT dependency at first year, and to relate preoperative data to the onset of RVF.

For 1-year survival, we performed the log-rank test and estimated event-time distributions across AKI stages and temporal RRT requirements using the Kaplan–Meier method. Cox regression analysis was performed to assess hazard ratios with 95% confidence intervals for 1-year survival.

All analyses were performed with a complete dataset using SPSS software (SPSS 20.0; IBMCorp., Armonk, NY) and R-statistical software using packages 'pROC', "Hmisc", and "effects".[22,24,25] All tests were two-tailed, and p-values <0.05 were considered statistically significant.

RESULTS

Incidence and temporal trends of postoperative AKI

From 1984 to 2016, 682 patients underwent HTx at the Erasmus MC, of which 595 patients were included in this study (Figure 1). Of 595 patients, 430 (72%) developed AKI, including 278 (47%) stage 1, 66 (11%) stage 2, and 86 (14%) stage 3 AKI. Of those who developed AKI stage 3, 41 (7%) required RRT which lasted for a median of 7 days (IQR: 5–13) and had a 3.3-times (95%CI: 1.6–6.6, p=0.001) higher crude risk of chronic RRT in the first year than those who did not require such treatment. Figure S1 displays the time distribution for the occurrence of AKI with the highest peaks for all three stages on the seventh day.

We found a tendency towards a higher incidence of overall AKI noticeable in recent years. This tendency was accompanied by a trend in a lower baseline eGFR (median eGFR per six 5-year intervals: 69, 67, 67, 56, 69, 56 years, p-trend <0.001), an increasing incidence of diabetes (0, 3, 10, 9, 13, 13%, p-trend <0.001), and older donors (24, 28, 35, 38, 45, 46 years, p-trend <0.001). We also found a tendency towards a higher incidence of AKI stage 3, but only when defined as a requirement for RRT (Figure S2).

Demographic and perioperative data

Table 1 shows baseline characteristics and perioperative data stratified by AKI stages. Patients who had a higher AKI stage also had a higher baseline BMI (median: 22.6, 23.2, 22.9, 24.2 kg/m^2, p-trend<0.001), a lower baseline eGFR (71, 60, 67, 56 ml/min/1.73 m^2, p-trend<0.001), and more frequent diabetes (4, 7, 8,

13%, p-trend=0.015). They also received a heart from older donors (31, 34, 37, 39 years, p-trend<0.001) with more frequently female gender (46, 46, 58, 59%, p-trend=0.019) and postoperatively were more frequently diagnosed with RVF (7, 5, 12, 28%, p-trend<0.001). These patients had a longer hospital stay (20, 24, 24, 37 days, p-trend<0.001) and were less likely to have received induction therapy (90, 80, 71, 67%, p-trend<0.001). A trend was also seen in higher in-hospital mortality with higher AKI stages (2, 5, 14, 9%, p-trend=0.003).

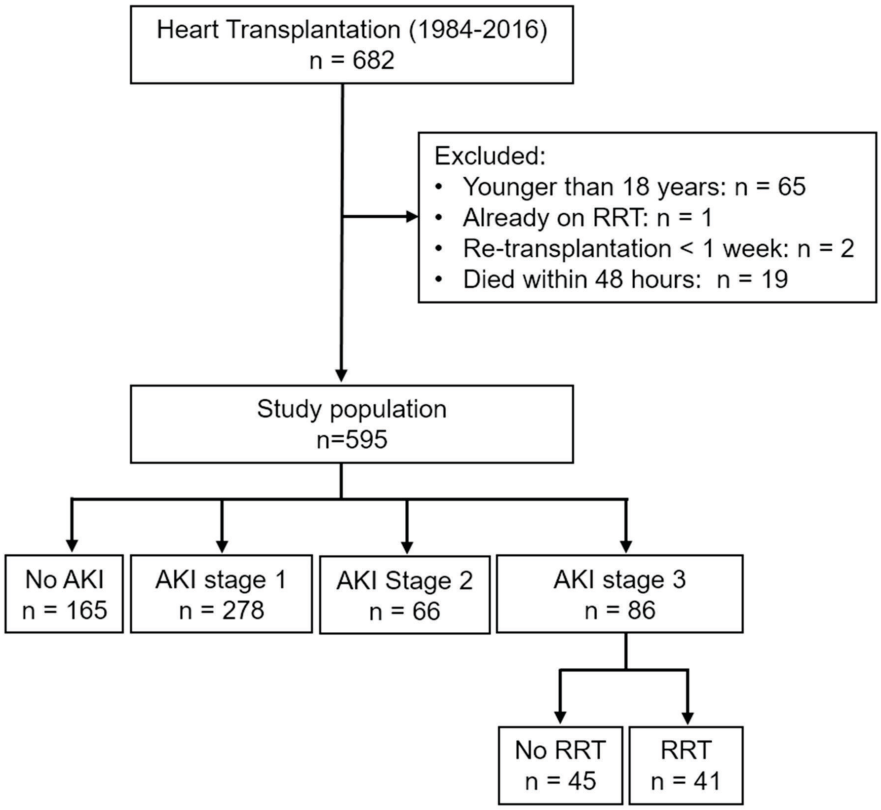

FIGURE 1 Flowchart of study population according to postoperative AKI severity. AKI, acute kidney injury; RRT, renal replacement therapy.

TABLE 1 Baseline characteristics and perioperative data according to postoperative AKI stages.

n (%)	No AKI 165 (28)	AKI Stage 1 278 (48)	AKI Stage 2 66 (11)	AKI Stage 3 86 (14)	p-value
Demographics					
Age, yrs.	51 (45–56)	51 (43–57)	51 (43–57)	48 (41–55)	0.23
Male sex	127 (77)	208 (75)	49 (74)	67 (78)	0.95
BMI, kg/m^2	22.6 (20.1–24.5)	23.2 (21.0–25.2)	22.9 (20.8–25.8)	24.2 (22.1–26.8)	<0.001*
Renal function					
eGFR, ml/min/1.73m^2	71 (58–88)	60 (47–79)	67 (60–79)	56 (43–70)	<0.001*
eGFR ≥90	38 (23)	37 (13)	11 (17)	2 (2)	<0.001*
eGFR 60–89	79 (48)	103 (37)	40 (60)	33 (38)	
eGFR <60	48 (29)	138 (50)	15 (23)	51 (60)	
eGFR 45–59	31 (19)	81 (29)	11 (17)	27(32)	
eGFR <45	17 (10)	57 (21)	4 (6)	24 (28)	
Medical history					
Prior cardiac surgery	45 (27)	89 (32)	15 (23)	25 (29)	0.90
Diabetes mellitus	7 (4)	19 (7)	5 (8)	11 (13)	0.015*
Hypertension	17 (10)	29 (10)	5 (8)	8 (9)	0.65
Donor characteristics					
Age, yrs.	31 (20–42)	34 (22–45)	37 (24–45)	39 (27–49)	<0.001*
Male sex	89 (54)	149 (54)	28 (42)	35 (41)	0.019*
Cause of death					0.61
Trauma	74 (45)	117 (42)	26 (39)	36 (42)	
CVA	83 (50)	149 (54)	38 (58)	4 (51)	
Other	6 (4)	11 (4)	2 (3)	6 (7)	
Unknown	2 (1)	1 (0)	0 (0)	0 (0)	
Time of donor heart ischemia, minutes	165 (139–196)	171 (143–206)	170 (147–195)	176 (150–210)	0.09
Urgency status on waiting list					0.78
Elective	78 (47)	166 (60)	41 (62)	38 (44)	
Urgent	58 (35)	73 (26)	14 (21)	31 (36)	
Unknown	29 (18)	39 (14)	11 (17)	17 (20)	
Preoperative hemodynamic parameters at the time of transplantation listing					
Days before HTx	182 (81–331)	275 (123–545)	273 (117–505)	213 (100–534)	0.15
Heart rate, beats/min	80 (68–100)	80 (70–92)	73 (61–94)	72 (67–90)	0.06
Systolic AP, mmHg	99 (90–106)	97 (90–105)	95 (84–105)	97 (87–107)	0.27
Diastolic AP, mmHg	63 (57–70)	61 (56–69)	62 (54–69)	62 (56–72)	0.91

continued

n (%)	No AKI 165 (28)	AKI Stage 1 278 (48)	AKI Stage 2 66 (11)	AKI Stage 3 86 (14)	p-value
Mean AP, mmHg	74 (68–80)	73 (67–81)	73 (64–81)	75 (66–83)	0.61
CO, L/min	3.8 (3.1–4.6)	4.0 (3.3–4.7)	3.8 (3.2–4.5)	3.8 (3.0–4.5)	0.98
PVR, dynes sec/cm^5	172 (115–230)	149 (96–224)	154 (93–245)	144 (82–226)	0.44
SVR, dynes sec/cm^5	1442 (1192–1764)	1286 (1086–1671)	1398 (1216–1605)	1333 (1042–1630)	0.14
RAP, mmHg	7 (5–12)	7 (4–11)	8 (5–13)	11 (5–17)	0.021*
PA systolic, mmHg	44 (32–55)	42 (30–52)	44 (34–53)	45 (29–59)	0.93
PA diastolic, mmHg	23 (15–30)	21 (14–29)	21 (15–30)	23 (15–29)	0.78
PA mean, mmHg	30 (21–39)	28 (19–36)	27 (21–37)	31 (20–38)	0.84
PCWP, mmHg	21 (14–29)	20 (13–26)	20 (14–27)	22 (13–29)	0.81
TPG, mmHg	8.3 (5.0–11.0)	7.7 (4.3–10.7)	7.2 (4.4–10.3)	7.3 (4.3–10.3)	0.25
DPG, mmHg	1.0 (-2.0–4.0)	1.0 (-2.0–4.0)	0.0 (-2.0–3.0)	0.0 (-2.0–4.0)	0.93
PAPi	2.83 (1.89–5.81)	3.17 (1.61–5.67)	2.54 (1.82–5.60)	2.31 (1.01–4.57)	0.012*
RAP/PCWP ratio	0.37 (0.24–0.57)	0.36 (0.23–0.52)	0.40 (0.25–0.53)	0.47 (0.29–0.74)	0.009*
Preoperative hemodynamic support					
Inotropes	41 (25)	59 (21)	15 (23)	29 (34)	0.16
IABP / ECMO	16 (10)	20 (7)	5 (8)	10 (12)	0.68
LVAD	14 (8)	15 (5)	1 (1)	5 (6)	
Postoperative complications					
Right ventricle failure	11 (7)	14 (5)	8 (12)	24(28)	<0.001*
Re-thoracotomy	12 (7)	18 (6)	9 (14)	12 (14)	0.06
Primary graft failure	3 (2)	4 (1)	4 (6)	2 (2)	0.14
Other [a]	7 (4)	14 (5)	1 (1)	7 (8)	
Immunosuppressive therapy					
Induction therapy	148 (90)	222 (80)	47 (71)	58 (67)	<0.001*
ATG use	89 (54)	151 (54)	29 (44)	46 (53)	0.58
Anti-CD3	45 (27)	41 (15)	5 (7)	5 (6)	<0.001*
Anti-IL2	14 (9)	30 (11)	13 (20)	7 (8)	0.49
Postoperative delay CNI, days[b]	3 (2–5)	3 (1–4)	2 (0–3)	2 (0–5)	0.35
Hospital stay					
Days in ICU	3 (2–4)	3 (2–4)	4 (3–6)	8 (4–14)	<0.001*
Days in hospital	20 (16–29)	24 (17–33)	24 (17–32)	37 (23–58)	<0.001*
In-hospital mortality	4 (2)	15 (5)	9 (14)	8 (9)	0.003*

Due to uniformity, all continuous data are presented as median and inter-quartile range (IQR); all categorical data as number and percentage (%). CO, Cardiac Output; eGFR, estimated glomerular filtration rate; HTx, heart transplantation; AP, arterial pressure; PVR,

pulmonary vascular resistance; SVR, systemic vascular resistance; RAP, right atrial pressure; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; TPG, trans-pulmonary gradient; DPG, diastolic pulmonary gradient; PAPi, pulmonary artery pulsatility index; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; ECMO, extracorporeal membrane oxygenator; ICU, Intensive Care Unit; ATG, anti-thymocyte globulins.
[a] Other includes: perioperative bleeding, cardiac arrest, dosing of inotropes, pacemaker malfunction, acute rejection and instability of unknown cause.
[b] Postoperative delay after heart transplantation before starting calcineurin inhibitor (CNI).
* p-value for linear trend <0.05 is statistically significant.

Relationship of preoperative RHH parameters with postoperative AKI severity

Figure 2 summarizes the investigated hemodynamic parameters. Table 1 shows the values of RHH parameters according to the AKI stages. Patients with a higher AKI stage had also a higher baseline RAP (median: 7, 7, 8, 11 mmHg, p-trend=0.021) and RAP/PCWP ratio (0.37, 0.36, 0.40, 0.47, p-trend=0.009) and lower PAPi values (2.83, 3.17, 2.54, 2.31, p-trend=0.012).

Table 2 and Figure S3 display the associations of the significant RHH parameters with the risk of postoperative AKI severity. In the total cohort, higher RAP and lower PAPi values were associated with AKI severity independently of the patient's BMI, baseline eGFR, diabetes, donor's age and sex, ischemia time of the donor's heart, time from right heart catheterization to HTx, postoperative RVF, and the postoperative use of induction therapy (adjusted OR[95%CI] per doubling: RAP 1.16[1.02–1.32], p=0.029; PAPi 0.85[0.75–0.96], p=0.008). Moreover, we found a significant multiplicative interaction between RAP≥6 mmHg and PAPi values (p-interaction=0.034), indicating even more pronounced association between lower PAPi values and higher probability of AKI severity in patients with elevated RAP (adjusted OR per doubling of PAPi: 0.70[0.56–0.87], p=0.002) (Table 2, Figure S4).

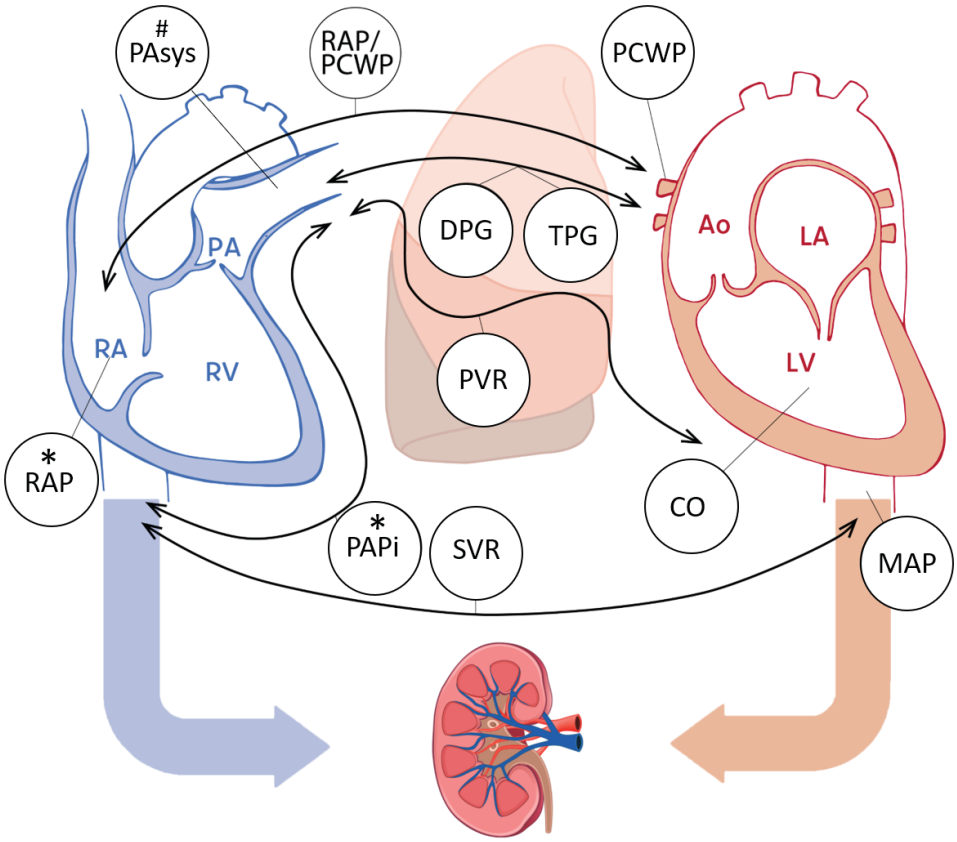

FIGURE 2 Preoperative hemodynamic parameters and their relation to postoperative right ventricular failure and acute kidney injury early (≤30 days) after heart transplantation. An illustration of the assessed hemodynamic parameters of the heart including right atrial pressure (RAP); pulmonary artery (PA) systolic, diastolic, and mean pressures ($PA_{mean\ pressure}$ = [$PA_{systolic}$ + 2*$PA_{diastolic}$] / 3); pulmonary artery pulsatility index (PAPi) (PAPi = [$PA_{systolic\ pressure}$ – $PA_{diastolic\ pressure}$] / RAP; pulmonary capillary wedge pressure (PCWP); RAP/PCWP ratio; transpulmonary gradient (TPG) (TPG = $PA_{mean\ pressure}$ – PCWP); diastolic pulmonary gradient (DPG) (DPG = $PA_{diastolic\ pressure}$ – PCWP); cardiac output (CO); pulmonary vascular resistance (PVR) (PVR = 80 * [$PA_{mean\ pressure}$ – PCWP] / CO); systolic, diastolic, and mean arterial pressure (MAP) (MAP = [$AP_{systolic}$ + 2 * $AP_{diastolic}$] / 3); systemic vascular resistance (SVR) (SVR = 80 * [MAP – RAP] / CO). * indicates significant predictor of acute kidney injury (AKI); # indicates significant predictor of right ventricular failure (RVF); RA indicates right atrium; RV indicates right ventricle; PA indicates pulmonary artery; LA indicates left atrium; LV indicates left ventricle; Ao indicates aorta.

TABLE 2 Associations between preoperative hemodynamic parameters and postoperative AKI severity early after heart transplantation.

	Univariable model		Multivariable model [f]	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Total cohort [a]				
PAPi [c]	0.88 (0.79–0.99)	0.043*	0.85 (0.75–0.96)	0.008*
RAP [c]	1.12 (0.99–1.28)	0.07	1.16 (1.02–1.32)	0.029*
RAP/PCWP [c]	1.19 (1.01–1.39)	0.033*	1.15 (0.98–1.35)	0.10
Heart rate [d]	0.90 (0.81–1.00)	0.06	0.98 (0.87–1.11)	0.75
SVR [e]	0.96 (0.91–1.00)	0.06	0.96 (0.92–1.01)	0.13
Subgroup RAP ≥6 mmHg [b]				
PAPi [c]	0.74 (0.60–0.92)	0.006*	0.70 (0.56–0.87)	0.002*
RAP [c]	1.62 (1.17–2.25)	0.004*	1.78 (1.27–2.50)	0.001*
RAP/PCWP [c]	1.44 (1.06–1.96)	0.019*	1.31 (0.95–1.08)	0.10
Heart rate [d]	0.88 (0.77–1.01)	0.08	0.95 (0.82–1.11)	0.52
SVR [e]	0.98 (0.92–1.03)	0.42	0.99 (0.93–1.05)	0.78

OR (95% CI) indicates proportional odds ratio with 95% confidence interval; for other abbreviations please see table 1. *p-value <0.05 is statistically significant.
[a] total n=595, no AKI = 165, AKI stage 1 = 278, AKI stage 2 = 66, AKI stage 3 = 86.
[b] total n=340, no AKI = 94, AKI stage 1 = 147, AKI stage 2 = 42, AKI stage 3 = 57.
[c] OR are given per doubling of a preoperative hemodynamic parameter. OR are interpreted as the odds of having a more severe renal injury for any level of AKI (stage 3, stage 2, stage 1, and no AKI). For example, if RAP increases from 7 to 14 mmHg (i.e., doubled) the odds of having AKI stage 3 versus combined AKI stages ≤2 and no AKI are 1.12 times greater. Odds of having AKI stages ≥2 versus combined AKI stage 1 and no AKI are 1.12 times greater. Finally, the odds of having AKI of any stage versus no AKI are 1.12 times greater.
[d] OR per 10 units increase in preoperative heart rate (interpretation is the same as under c).
[e] OR per 100 dynes sec/cm^5 increase in preoperative SVR (interpretation is the same as under c).
[f] preoperative hemodynamic parameters were adjusted for all variables with p<0.10 in univariable analysis and included patient's BMI, baseline eGFR, diabetes, donor's age and sex, ischemia time of donor's heart, time from catheterization to HTx, postoperative RVF, and the postoperative use of induction therapy. Associations between these variables and postoperative AKI stages are presented in Table S1.

For predicting AKI stage 3, adding each of the hemodynamic parameters, PAPi and RAP, significantly improved the models' predictive accuracy compared to the best clinical model (PAPi: IDI=0.03, p=0.013 and total continuous NRI=0.320, p=0.007 with 25% reclassification for events and 7% reclassification for non-events; RAP: IDI=0.02, p=0.040 and NRI=0.278, p=0.018 with 25% reclassification for events and 3% reclassification for non-events). In Figure 3, ROC-AUC analysis also showed significant discriminatory improvement (clinical model: AUC 76.1% [95%CI:70.4–81.3], clinical model + PAPi: 79.0% [73.8–83.8], p-delta=0.044; clini-

cal model + RAP: 78.8% [73.6–83.5], p-delta=0.049; PAPi alone: 60.7% [53.8–67.1]; RAP alone: 62.2% [54.6–69.0]). Based on Youden's index, the best cut-off point for predicting AKI stage 3 was PAPi <1.05 and RAP >11 mmHg. Finally, the associations of clinical data with postoperative AKI severity are shown in Table S1.

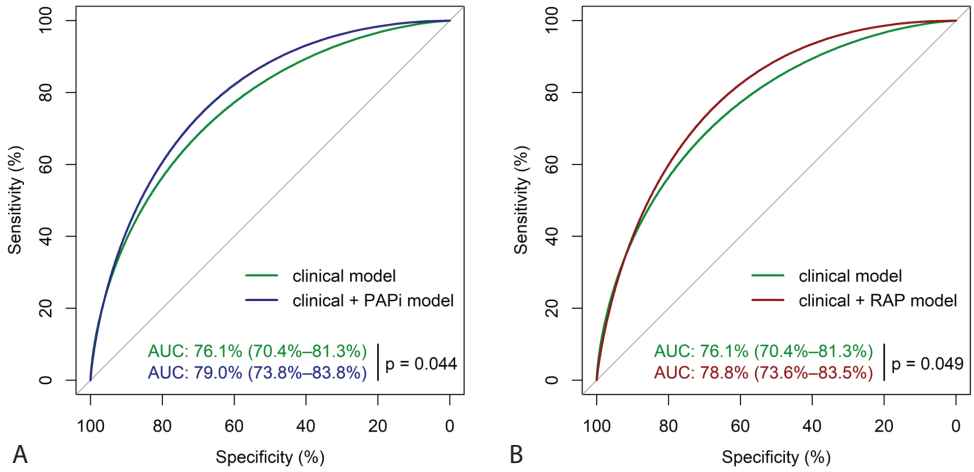

FIGURE 3 The ROC-AUC analysis for the prediction of AKI stage 3. AUC indicates area under the ROC curve with p-value for the difference between different models. Only predictors that remained significant (p<0.05) in the final model were used to assess discriminative power, and those were patient body mass index, baseline eGFR, postoperative right ventricular failure, and the postoperative use of induction therapy. **A.** The ROC curves of clinical model (green) and clinical model + PAPi (blue) for the prediction of AKI stage 3 with AUCs and corresponding 95% confidence intervals; **B.** The ROC curves of clinical model (green) and clinical model + RAP (red) for the prediction of AKI stage 3.

Predictors of RVF and its relation to AKI

Of 595 patients, 57 (10%) experienced RVF early after HTx. Table S2 shows the predictors of early RVF among which the most significant clinical predictors were the patients' impaired baseline eGFR and older donors; higher pulmonary artery systolic pressure was the only preoperative RHH parameter that predicted RVF. Furthermore, the occurrence of RVF was strongly associated with AKI severity (Table S1).

Relationship of AKI with 1-year mortality

In total, 51 deaths occurred during the first year after HTx with a cumulative mortality of 5%, 7%, 15%, and 14% for those without AKI and with AKI stages 1, 2, and 3, respectively (log-rank test, p-trend=0.021; Figure S5A). The cumulative mortality was also higher in patients who received RRT during the first month than in those who had not (22 *vs.* 8%; log-rank test, p=0.001, Figure S5B).

DISCUSSION

To the best of our knowledge, this study is the first to assess the predictive properties of different preoperative hemodynamic parameters in relation to the occurrence of postoperative AKI severity within 30 days after HTx. We found that lower PAPi and higher RAP values predict AKI severity independently of the recipient BMI, baseline eGFR, diabetes, donor age and sex, ischemia time of the donor's heart, time from right heart catheterization to HTx, postoperative RVF, and the use of induction therapy. These hemodynamic parameters routinely collected at the time of transplantation listing could be used to predict AKI severity early after HTx.

Although renal injury after HTx has traditionally been attributed to the impaired arterial perfusion and CNI nephrotoxicity[4], our results illustrate strong evidence of the independent relationship between preoperative right-sided hemodynamics and AKI severity after HTx. One of the potential explanations for this relationship may be the longstanding venous congestion that chronically compromises the kidneys. Subsequently, the kidneys may become more vulnerable to the development of AKI, especially in cases of postoperative hemodynamic instability with hypotensive episodes, or in the settings of de-novo RVF during the adaptation period of the new heart. However, we found that a de-novo RVF significantly contributed to the development of AKI but could not entirely explain the relationships of preoperative RAP and PAPi with the postoperative renal injury. Several pathophysiological mechanisms may be responsible for this peculiar renal vulnerability, including attenuated vascular reflexes, elevated renal interstitial and intra-tubular pressure, activation of the renin-angiotensin-aldosterone system, and chronic venous pressure-induced tubule-glomerular feedback dysfunction.[26,27] Moreover, we found a significant interaction between RAP and PAPi, indicating that probabilities of AKI (especially stages 2 and 3) are markedly increasing with lower PAPi values, but mostly in patients with elevated RAP (≥6 mmHg). These findings are supported by Damman et al., who found that eGFR starts to significantly decline when RAP increases above 6 mmHg.[28] Altogether, it appears that preoperatively compromised right-sided venous pressures deserve clinical attention in the context of postoperative AKI and may be even more important for kidney functioning after HTx than low systemic pressures.

Acute or chronic cardiac dysfunction has negative effects on kidney function and vice versa. This complex cross-talk was recently described as cardio-renal syndrome (CRS).[29] Chronic HF leading to chronic renal congestion in the pre-HTx period is classified as CRS Type-2. On the other hand, early AKI post-HTx could be considered as CRS Type-1. Recognition of post-HTx CRS may provide possibilities of prevention and treatment strategies in the settings of HTx. Importantly, early prediction of postoperative AKI based on preoperative RAP and PAPi could help to timely and

more proactively intervene in the patients who are at high risk, in terms of giving more attention to the perioperative volume overload, postponing the introduction of nephrotoxic CNI, prolonging the support of the right ventricle with inotropes, NO ventilation, and early introduction of pulmonary vasodilators (e.g., sildenafil).[11,27,30-33] Furthermore, these patients could possibly benefit from functional kidney stress tests to assess the renal functional reserve and identify patients who will progress to AKI post-HTx.[34,35] In addition to decreasing values, PAPi can also go in the opposite direction. Hence, the recovery of PAPi values may indicate improvement of right-sided pressure, which may be used to optimize perioperative hemodynamic support to preserve the kidneys from injury. However, prospective studies, preferably interventional in nature, are needed to elucidate this promising concept.

The overall AKI incidence was 72%, which fits at the high-end of the reported incidence range of 22 to 76% in HTx recipients.[4-7] This widespread distribution probably results from the large heterogeneity between studies and deserves closer attention. Previously, most studies reported the older Risk Injury Failure Loss End-stage Renal Disease (RIFLE) criteria or the Acute Kidney Injury Network (AKIN) criteria.[6,36] However, we used the newer KDIGO criteria to define AKI stages.[37] Second, time-intervals for the occurrence of AKI were different from the present study.[4-7,38,39] We targeted one month as the clinically relevant time-interval, whereas previous studies mainly focused on the first week.[4,6,7,38] Our results show that, although all AKI stages peaked on day 7, the risk of AKI remains through the first month. This late postoperative peak of AKI could be attributed to the delay in starting of CNI. For this purpose, we use induction therapy especially in patients with impaired kidneys and/or hemodynamic instability early after HTx to postpone CNI nephrotoxicity. In our data, the use of induction therapy was protective for the occurrence of AKI. Another important and more worrisome observation is that AKI incidence increased in recent years. This is probably explained by an increasing proportion of HTx recipients being listed with more comorbidities such as chronic renal failure and diabetes, older heart donors, and probable changes in clinical management with more pro-active treatments protocols.[2,40]

Study limitations

First, this was a single-center study, and therefore, the clinical management and treatment modalities may differ from other transplant centers. However, patient selection for transplantation listing and cardiac procedures were performed according to generally accepted international criteria.[11] Second, its retrospective nature precluded the inclusion and evaluation of additional parameters such as echocardiography. Furthermore, we were not able to analyze the postoperative RHH parameters due to un-

availability and incompleteness of the historical data. Therefore, postoperative RVF could only been retrieved as reported or the need for postoperative RVAD. Further studies are needed to analyze the incremental value of post-HTx RHH parameters. Third, we did not include urine output in the definition of AKI because these patients were on intensive diuretic therapy, which would lead to misinterpretation of the urine output values. Altogether, this study is currently the largest HTx cohort in which the associations between preoperative hemodynamics and postoperative AKI were investigated.

CONCLUSIONS

Preoperative PAPi and RAP strongly predict the postoperative AKI early after heart transplantation and can be used as early AKI predictors.

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SUPPLEMETARY INFORMATION

TABLE S1 Associations of clinical data with postoperative AKI severity early after heart transplantation.

	Univariable model [a]		Multivariable model [b]	
Clinical data	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Preoperative				
BMI per 1 kg/m^2 increase	1.10 (1.05–1.15)	<0.001*	1.06 (1.01–1.12)	0.019*
Diabetes	2.00 (1.12–3.57)	0.019*	1.38 (0.73–2.60)	0.32
eGFR per 10ml/min/1.73m^2 decrease	1.18 (1.10–1.26)	<0.001*	1.11 (1.02–1.19)	0.011*
Donor's age per 5 years increase	1.11 (1.05–1.17)	<0.001*	1.06 (1.00–1.13)	0.07
Donor's female gender	1.40 (1.03–1.88)	0.029*	1.19 (0.86-1.66)	0.29
Ischemia time per 30 minutes longer	1.10 (0.99–1.21)	0.07	1.07 (0.96–1.19)	0.25
Time from RHC to HTx per 100 days longer	1.05 (1.01–1.10)	0.022*	1.06 (1.01–1.11)	0.027*
Postoperative				
RVF	3.95 (2.37–6.57)	<0.001*	3.82 (2.22–6.57)	<0.001*
Induction therapy	0.42 (0.29–0.61)	<0.001*	0.29 (0.19–0.44)	<0.001*

BMI indicates body mass index; eGFR indicates estimated glomerular filtration rate; RVF indicates right ventricular failure; RHC indicates right heart catheterization; HTx indicates heart transplantation. OR (95% CI) indicates proportional odds ratio with 95% confidence interval, and are interpreted as the odds of having a more severe renal injury for any level of AKI. [a] Covariates that were found to be univariably associated with AKI severity (p<0.10) were entered into a multivariable ordinal regression model applying the full likelihood ratio method. [b] adjusted for each other. * p-value <0.05 is statistically significant.

TABLE S2 Associations of preoperative clinical and hemodynamic data with postoperative RVF early after heart transplantation.

	Univariable model [a]		Multivariable model [b,c]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Preoperative clinical data				
BMI per 1 kg/m^2 increase	1.07 (0.99–1.16)	0.10		
Diabetes	2.42 (1.06–5.52)	0.036*		
eGFR per 10ml/min/1.73m^2 decrease	1.22 (1.06–1.41)	0.005*	1.19 (1.02–1.36)	0.031*
Donor's age per 5 years increase	1.21 (1.10–1.34)	<0.001*	1.21 (1.08–1.35)	0.001*
Donor's female gender	2.40 (1.34–4.31)	0.003*		
Preoperative hemodynamic data				
PA systolic per 5 mmHg increase	1.09 (0.99–1.17)	0.07	1.14 (1.03–1.25)	0.008*
TPG per 5 mmHg increase	1.28 (1.00–1.63)	0.05		
IABP or ECMO use	2.21 (1.02–4.82)	0.045*		

OR indicates odds ratio for having a postoperative RVF; 95% CI indicates 95% confidence interval for the corresponding OR; RVF indicates right ventricular failure; BMI indicates body mass index; eGFR indicates estimated glomerular filtration rate; PA systolic indicates pulmonary artery systolic pressure; TPG indicates transpulmonary gradient. [a]All preoperative data from Table 1 were related to the early RVF; only variables with p<0.10 in univariate analysis were reported in this table. [b]Variables that were found to be univariably associated with early RVF (p<0.10) were entered into a multivariable binary logistic regression model applying the stepwise backward likelihood ratio method with a value of p=0.05 as a removal criterion for the final model. [c]AUC for the final multivariable model was 67.8% (95% CI: 59.8–74.7), p<0.001. *p-value <0.05 is statistically significant.

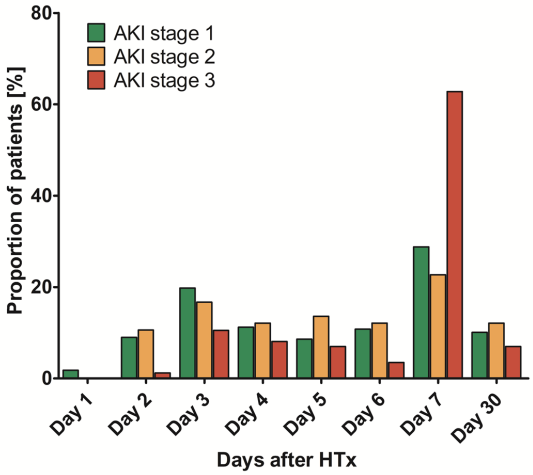


FIGURE S1 Time distribution of AKI occurance according to the severity stage during the first postopearative month. The X-axis depicts time in days; the Y-axis depicts proportion of patients per AKI stage. AKI, acute kidney injury; HTx, heart transplantation.

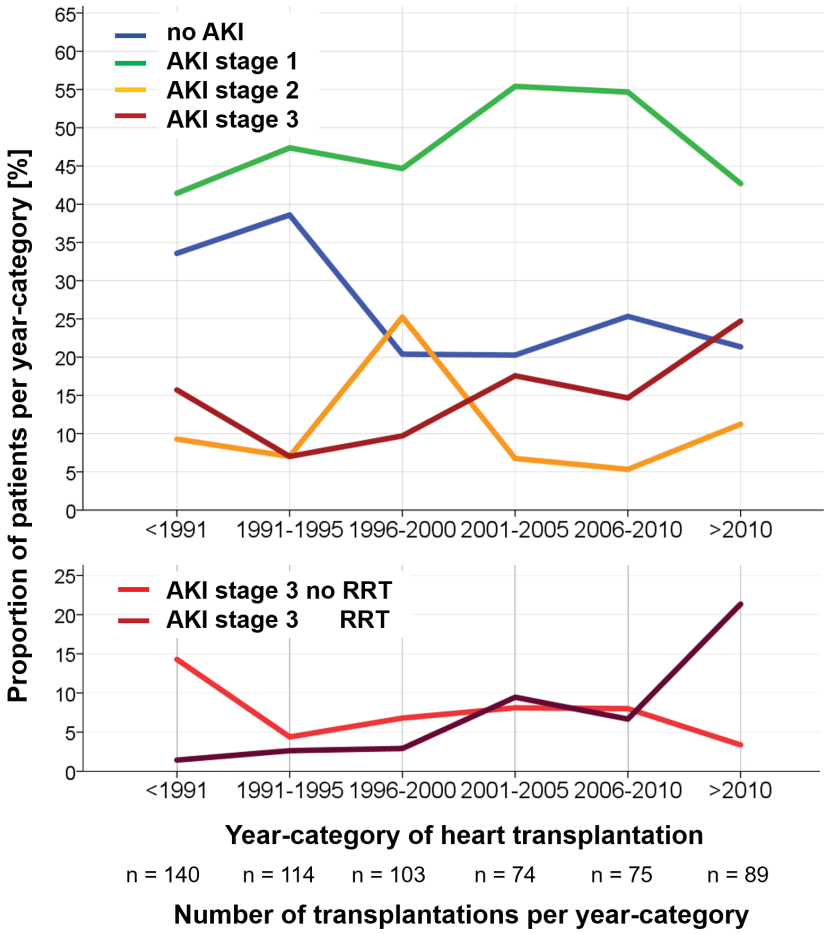


FIGURE S2 Temporal trend in the incidence of postoperative AKI according to severity stage during the period from 1984 until 2016. The X-axis depicts 5-year intervals. The Y-axis depicts proportion of patients per 5-year category according to AKI stage.

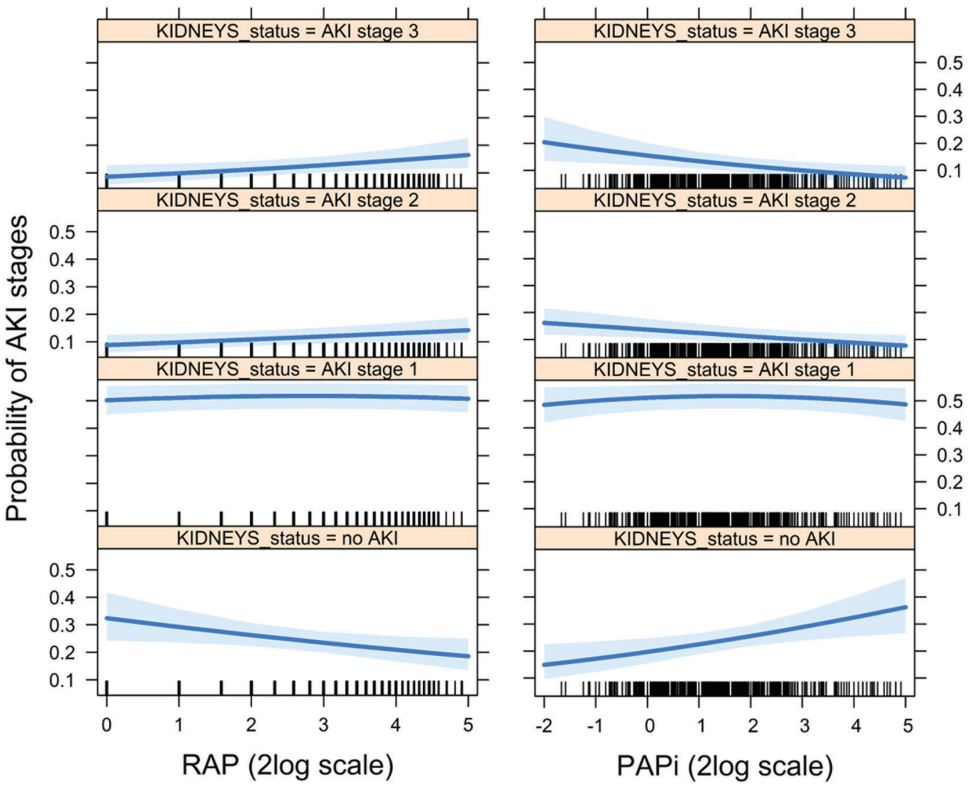


FIGURE S3 The relationships between preoperative RAP and PAPi values and the probabilities of different postoperative AKI stages early after heart transplantation. The X-axis on the left panel depicts the right atrial pressure (RAP) values on the ^{2}log scale, whereas the X-axis on the right panel depicts pulmonary artery pulsatility index (PAPi) values on the ^{2}log scale. Probabilities of each acute kidney injury (AKI) stage are presented in the Y-axis in descending order from AKI stage 3 to no AKI. The figure shows that probabilities of AKI stages 2 and 3 are increasing with higher RAP and lower PAPi values, while the corresponding probabilities for no AKI are decreasing.

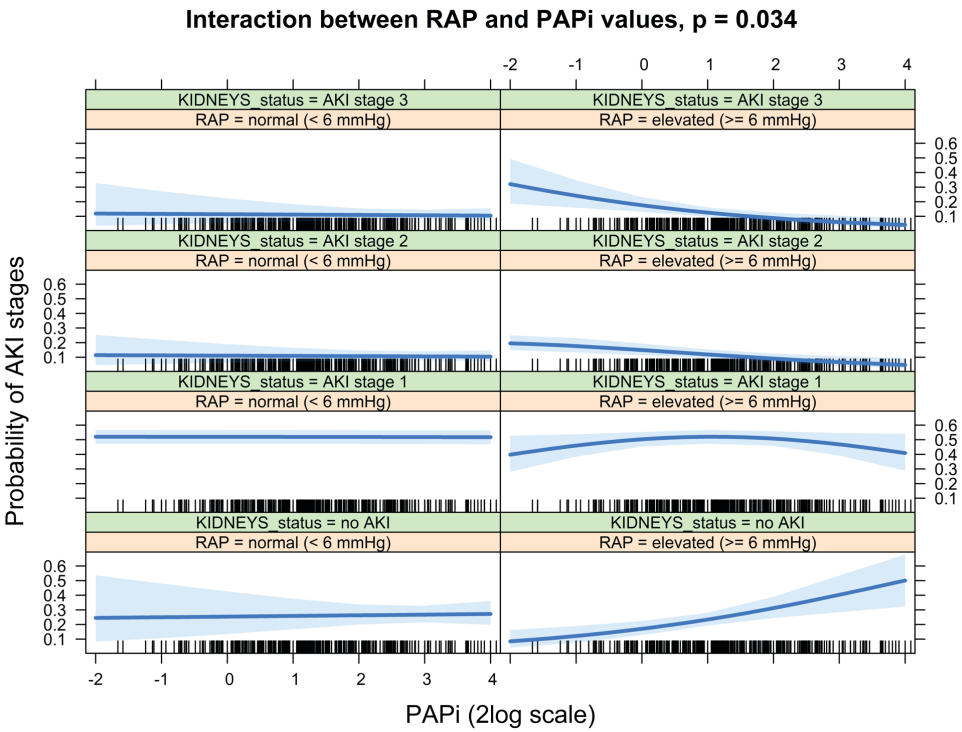
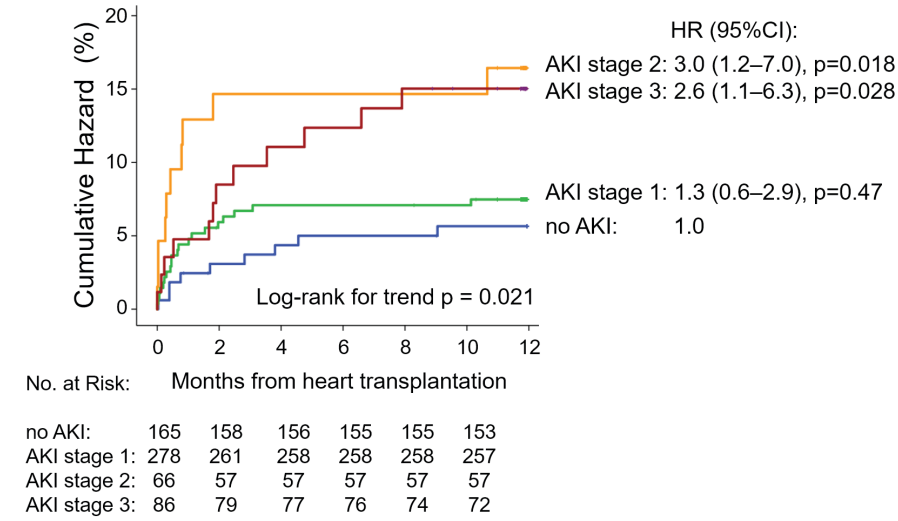


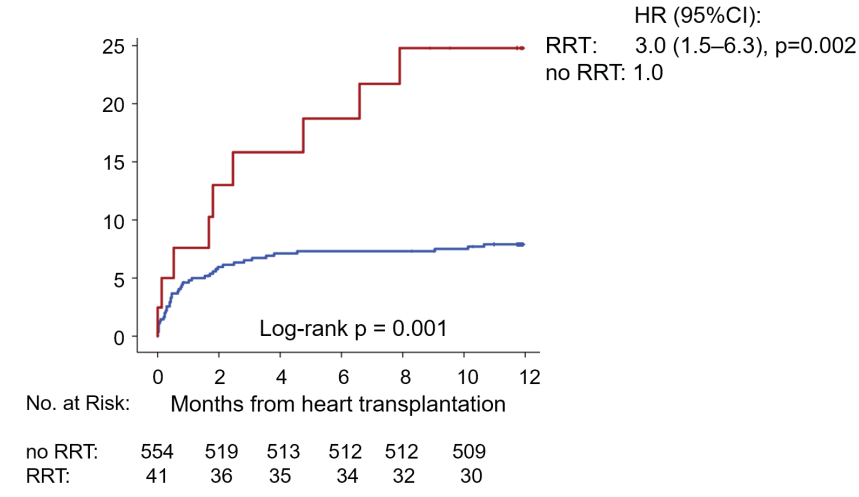
FIGURE S4 Graphical display of the interaction effect between preoperative RAP and PAPi on the probabilities of different postoperative AKI stages early after heart transplantation. The X-axis on the left panel depicts the pulmonary artery pulsatility index (PAPi) values on the ^{2}log scale in patients with normal right atrial pressure (RAP <6 mmHg), whereas the X-axis on the right panel depicts PAPi values in patients with elevated RAP (≥6 mmHg). Probabilities of each acute kidney injury (AKI) stage are presented in the Y-axis in descending order from AKI stage 3 to no AKI. The figure shows that probabilities of AKI stages 2 and 3 are markedly increasing with lower PAPi values in patients with elevated RAP, which is not the case in patients who had RAP within the reference range (p-interaction=0.034).

The following table displays the number of patients per category:

Number of patients	**Right atrial pressure**		
Kidneys status	< 6 mmHg	≥ 6 mmHg	Total
AKI stage 3	29	57	86
AKI stage 2	24	42	66
AKI stage 1	131	147	278
no AKI	71	94	165
Total	255	340	595



A



B

FIGURE S5 Kaplan-Meier curves for time to death during the first year after heart transplantation. A. Survival distribution analysis stratified by AKI stage with crude hazard ratios (95% confidence intervals) relative to no AKI. **B.** Analysis stratified by requirements for RRT during the first month after heart transplantation.