ORIGINAL ARTICLE

Renal function at 1 year after cardiac transplantation rather than acute kidney injury is highly associated with long-term patient survival and loss of renal function – a retrospective cohort study

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SUMMARY

This study aimed to assess the association between acute kidney injury (AKI), renal function 1 year after transplantation, and long-term adverse outcomes after cardiac transplantation. A retrospective cohort study was performed including 471 adult cardiac transplantation recipients that survived the first postoperative year between 1984 and 2012. Primary outcome variables were long-term overall and renal survival. During the first postoperative week, 40% (n = 188) of the recipients developed AKI stage I, 22% (n = 104) stage II, and 13% (n = 63) stage III, and 4% (n = 17) required temporary renal replacement therapy (RRT). No crude association was found between the development of AKI and long-term mortality (P = 0.50) or chronic RRT dependence (P = 0.27). In multivariable analysis, only AKI requiring RRT was associated with an increased risk for mortality (HR = 2.59, 95% CI = 1.17–5.73) and chronic RRT dependence (HR = 13.14, 95% CI = 3.26–52.92). While less severe episodes of AKI did not affect the recipient's long-term prognosis, renal function 1 year after transplantation had a strong association with long-term outcome. An eGFR <30 ml/min/1.73 was independently associated with mortality (HR = 2.69, 95% CI = 1.68–4.32) and an eGFR <60 ml/min/1.73 with chronic RRT dependence (eGFR 30–59: HR = 3.57, 95% CI = 1.41–9.01; eGFR <30: HR = 16.53, 95% CI = 5.72–47.78). In conslusion, besides AKI requiring RRT, less severe episodes of AKI have limited implications for the recipient's prognosis and long-term outcome after cardiac transplantation is strongly determined by the degree of renal impairment 1 year after transplantation.

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Key words
acute renal failure, chronic kidney disease, end-stage renal disease, epidemiology, heart transplantation, survival analysis

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Introduction

The first successful heart transplant in 1967 was a major step forward in the treatment of irreversible heart failure [1]. By the improvement in clinical practice and the development of immunosuppressive therapy, cardiac transplantation has evolved into a well-established life-sustaining treatment for those where less invasive

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treatments are no longer considered an option [2–7]. However, due to complications of surgery, underlying comorbid conditions and the use of nephrotoxic calcineurin inhibitors (CNIs), transplantation recipients are prone for the development of acute kidney injury (AKI) [8–14]. While it was initially assumed that AKI was a transient phenomenon without any clinical consequences, AKI is no longer considered an innocent bystander. Large epidemiologic studies performed in the general ICU population have shown that the development of AKI is strongly associated with an increased risk for mortality as well as progressive deterioration in renal function which can lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD) [15]. Furthermore, it is generally accepted that this risk extends way beyond hospital discharge and that experiencing an episode of AKI can significantly compromise a patient's long-term prognosis [16]. In cardiac transplantation recipients, AKI is highly frequent during the early postoperative phase and occurs in 25–76% of the recipients [9–12]. In addition, few studies have shown that the development of AKI, especially when renal replacement therapy (RRT) is required, significantly increases the risk for mortality and deterioration in renal function during the first postoperative years [8–14]. In spite of the studies that report on the incidence and short-term outcome, little is known about the long-term sequelae of AKI after cardiac transplantation. In view of the fact that the risk for complications and therefore mortality is the highest during the first year following transplantation, we performed a study with the objective to evaluate the association between the development of AKI in the early postoperative phase and the long-term overall and renal survival in cardiac transplantation recipients that survived the first postoperative year.

Patients and methods

Study design and population

This study describes the long-term sequelae of AKI after cardiac transplantation and is a continuation of a previous study performed by our group. Materials and methods are similar to those described in the aforementioned study [14]. A retrospective cohort study was performed in the Erasmus MC (the Netherlands) evaluating all adult (age ≥18 years) cardiac transplantation recipients between 1984 and 2012 that survived the first postoperative year. Exclusion criteria were retransplantation within 7 days and RRT preceding transplantation. Data were obtained from a computerized database, electronic patient records, and chart review. Patients that required temporary RRT were treated with either continuous venovenous hemofiltration (CVVH) or continuous arteriovenous hemodialysis (CAVHD). Patients that developed chronic RRT dependence during follow-up were treated with intermitted hemodialysis (IHD), peritoneal dialysis (PD), or preemptive kidney transplantation. RRT was prescribed by the attending nephrologist and delivered by the hemodialysis nursing team.

Immunosuppressive protocol

The immunosuppressive protocol has changed over the last 30 years and included usually induction therapy with polyclonal antithymocyte globulins (ATG) [7,14]. The use of induction therapy was first introduced in 1987 and in the majority of cases consisted of horse ATG (1987–2008) and rabbit ATG (2009 and thereafter). Maintenance therapy after the very early postoperative phase was based on CNIs either cyclosporine-based (1984–1999) or tacrolimus-based (2000 and thereafter). From 1984 to 1999, immunosuppression was complemented usually by prednisone monotherapy, which was replaced in 2000 by a combination of prednisone and/or mycophenolate mofetil. In patients that did not receive induction therapy, the use of CNIs was initiated peri- or directly postoperative, while it was delayed in those who did receive induction therapy. The postoperative time point when therapy with either cyclosporine or tacrolimus was initiated varied from 2 to 7 days after transplantation, which depended on the former immunosuppressive protocol. Target levels for tacrolimus were set at 10–16 μg/ml within the first 9 months and 6–10 μg/ml thereafter. Target levels for cyclosporine were set at 200–250 and 80–150 μg/ml, respectively.

Study endpoints and definitions

Primary study endpoints were overall and renal survival in cardiac transplantation recipients that survived the first postoperative year. Renal survival, censored for death, was defined as the time until start of chronic RRT or kidney transplant. The secondary study endpoint was renal function, presented as estimated glomerular filtration rate (eGFR), 10 years after transplantation. This endpoint was chosen because of the decrease of cases during follow-up. To identify whether there was an association between AKI and the aforementioned endpoints, all analyses were stratified by the development of AKI defined and staged by the Kidney

Disease Improving Global Outcome (KDIGO) criteria [17] (Table 1) or AKI requiring RRT within the first 7 days following transplantation. Additional analysis was performed for long-term overall and renal survival stratified by renal function 1 year following transplantation. To identify whether the type of immunosuppressive medication (cyclosporine versus tacrolimus) or the period in which transplantation was performed (before the year 2000 vs. 2000 and thereafter) did affect the primary endpoints, subgroup analyses were performed. Due to the limited time of follow-up, these subgroup analyses were restricted to a maximum follow-up time of 10 years. To identify other potential predictors for mortality, chronic RRT dependence and renal function 10 years after transplantation, uni- and multivariable analyses were performed including demographic and clinical characteristics presented in Table 2. For the evaluation of renal function after transplantation, serum creatinine concentrations were collected at baseline, days 0–7, and from then on every successive year during follow-up. Baseline serum creatinine concentration was defined as the most recent outpatient concentration up to 6 months prior to transplantation. When unavailable, the serum creatinine concentration at hospital admission was considered baseline. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula adjusted for age and gender [18]. Patients were grouped according to their eGFR at baseline and at year one based on the Kidney Disease Outcomes Quality Initiative guidelines [19]. For multivariable analysis, eGFR at baseline was categorized as either ≥60 or <60 ml/min/1.73 m^2, due to the low number of recipients with an eGFR ≥90 or <30. For the same reason, eGFR at year one was categorized as ≥60, 30–59, or <30, due to the low number of recipients with an eGFR ≥90 or <15. The study was approved by the medical ethical review board of the Erasmus MC.

Statistical analyses

Continuous parameters were expressed as median and interquartile range and compared by Mann–Whitney *U*-test or Kruskal–Wallis test. Categorical parameters were expressed as number and percentage and compared by Fisher's exact test or chi-square test. Kaplan–Meier curves stratified by AKI stage, AKI requiring RRT, or renal function at year one were constructed for the evaluation of overall and renal survival. Differences pooled over strata were compared by log-rank test and log-rank test for trend. Multivariable Cox proportional hazards analyses were performed for identification of parameters associated with mortality or chronic RRT dependence. Furthermore, general linear model analysis was performed for the association with eGFR 10 years after transplantation. All multivariable models were constructed by a manually stepwise manner. Step 1: All parameters with a $P < 0.2$ were included in the model. Step 2: All parameters with a $P > 0.1$ were deleted one by one. Step 3: Parameters not selected at step 1 were individually evaluated in order from lowest to highest *P*-value as result from univariable analysis and included in the model when statistical significant ($P < 0.05$). The potential difference in renal function (eGFR) over time was objectified making use of linear mixed-model analyses. Two-tailed $P < 0.05$ was considered significant. Analyses were performed using statistical software SPSS, version 20.0 for Mac (SPSS Inc., an IBM company, Chicago, IL, USA) and GRAPHPAD PRISM version 5.0a for Mac (GraphPad Software, La Jolla, CA, USA).

Results

Study population and characteristics

During the study period, 597 recipients underwent cardiac transplantation in the Erasmus MC, of which 45

Table 1. Definition of AKI by the kidney disease improving global outcome criteria.

AKI stage	Serum creatinine
I	≥26.4 μmol/l within 48 h, or; 1.5–2.0 times baseline within 7 days
II	2.0–2.9 times baseline
III	≥3.0 times baseline, or; increase in SCr to ≥353.6 μmol/l, or; initiation of renal replacement therapy

AKI, acute kidney injury; SCr, serum creatinine concentration.

Modified from the Kidney Disease Improving Global Outcome: Acute Kidney Injury Workgroup [17].

Serum creatinine concentration at baseline was defined as the most recent outpatient serum concentration up to 6 months prior to transplantation ($n = 400$). When unavailable, serum creatinine concentration at hospital admission was considered baseline ($n = 71$). Urine output criteria were not used, because required data were not available.

Table 2. Clinical and demographic characteristics of study population (n = 471).

Age at transplantation in years	51 (42–56)
Male gender	371 (78.8)
BMI in kg/m^2	23.1 (21.0–25.2)
eGFR at baseline in ml/min/1.73 m^2	
Baseline	61 (48–73)
Year one	47 (38–58)
Primary cardiac disease	
Cardiomyopathy	208 (44.2)
Ischemic cardiac disease	243 (51.6)
Valvular disease	20 (4.2)
Comorbid conditions	
Diabetes mellitus	28 (5.9)
Hypertension	44 (9.3)
Previous thoracic surgery	129 (27.4)
Hemodynamic support	
Inotropic medication	116 (24.6)
IABP	35 (7.4)
LVAD	13 (2.8)
ECMO	2 (0.4)
Urgency status on waiting list	
Elective	243 (51.6)
Urgent	140 (29.7)
Unknown	88 (18.7)
Days on waiting list	131 (44–300)
Hospitalized before transplantation	183 (38.9)
Donor	
Age in years	32 (21–43)
Male gender	252 (53.5)
Donor cause of death	
Trauma	213 (45.2)
CVA/SAB	237 (50.3)
Other	18 (3.8)
Unknown	3 (0.6)
Time of ischemia donor heart in minutes	166 (142–197)
Transplantation complication	
None	371 (78.8)
RV failure*	36 (7.6)
Reoperation	42 (8.9)
Overall graft failure*	7 (1.5)
Other†	15 (3.2)
Induction therapy	362 (76.9)
CNI at 1 year	
Cyclosporine	348 (73.9)
Tacrolimus	123 (26.1)
AKI stage	
No AKI	116 (24.6)
Stage I	188 (39.9)
Stage II	104 (22.1)
Stage III	63 (13.4)
AKI requiring RRT	17 (3.6)
Length of ICU stay in days	3 (2–4)
Length of hospital stay in days	23 (17–33)

AKI, acute kidney injury; BMI, body mass index; CNI, calcineurin inhibitor; CVA, cerebrovascular accident; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; ICU, intensive care unit; LVAD, left ventricular assist device; RRT, renal replacement therapy; RV, right ventricle; SAB, subarachnoid bleeding.

Continuous variables are presented as median and interquartile range, and categorical variables are presented as number and percentage.

*Right ventricle and primary graft failure were defined by the International Society for Heart and Lung Transplantation consensus guidelines [33].

†Transplantation complications categorized as "other" included hemodynamic instability caused by perioperative bleeding, cardiac arrest, under dosing of inotropic medication, pacemaker malfunction, fluid overload, acute rejection, and instability of an unknown cause. In two cases, it was not possible to close the thoracic cavity directly after transplantation procedure.

recipients were under 18 years old, two required retransplantation within 1 week, 18 died within 48 h, and one recipient required RRT preliminary to transplantation, respectively. Of the remaining 531 recipients that constituted the initial study cohort, 471 survived the first postoperative year of which 355 (75.4%) met the AKI criteria during the first postoperative week. One hundred and eighty-eight recipients (39.9%) developed AKI stage I, 104 (22.1%) stage II, and 63 (13.4%) stage III, respectively. Of those who developed stage III, temporarily support by RRT was required in 17 (3.6%) recipients (Fig. 1). Thirteen recipients were treated with CVVH and four with CAVHD with a median duration of 5 (IQR: 3–17) days. Demographic and clinical characteristics of the study population are presented in Table 2. Extended information on the demographic and clinical characteristics of the initial study cohort can be found in Table S1. The median age in the study population was 51 years (IQR: 42–56) and 371 (78.8%) of the recipients were of male gender. Median eGFR at baseline was 61 (IQR: 48–73) ml/min/1.73 m^2 and 47 (IQR: 38–58) 1 year after transplantation. At 1 year, four recipients had an eGFR <15, of which two were treated with IHD and one with PD and the fourth recipient did not receive chronic RRT yet.

AKI and long-term overall survival

Median follow-up was 9.5 (IQR: 5.6–13.7) years with a maximum of 26 years and 258 deaths were observed during follow-up. The most frequent cause of death was sepsis (n = 50, 19.4%) followed by malignancy (n = 41,

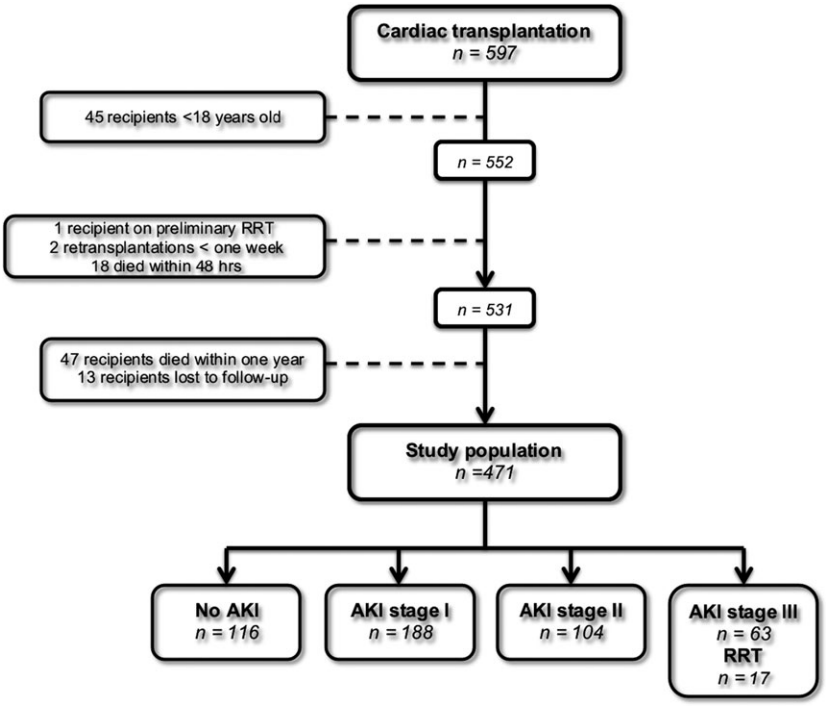

Figure 1 Flowchart of study population stratified by AKI stage. AKI, acute kidney injury; RRT, renal replacement therapy.

15.9%), graft failure: chronic failure or acute myocardial infarction (n = 31, 12.0%), hypovolemic shock (n = 16, 6.2%), rejection (n = 12, 4.7%), cerebrovascular accident or other intracranial bleeding (n = 12, 4.7%), ESRD (n = 8, 3.1%), and other (n = 4, 1.6%). In 84 (32.6%) recipients, the cause of death was either unclear or considered multifactorial. Cumulative long-term overall and renal survival rates stratified by AKI stage or AKI requiring RRT are presented in Fig. 2a,b and Table S2. No crude association was found between the development of AKI stratified by stage of severity (log-rank test for trend, P = 0.50) or AKI requiring RRT (log-rank test, P = 0.27) and an increased risk for mortality. Univariable analysis identified several demographic and clinical characteristics associated with mortality including age, year of transplantation, eGFR at baseline, eGFR at year one, ischemic and valvular cardiac disease as primary cardiac disease, hypertension, previous thoracic surgery, days on waiting list, and AKI requiring RRT. Factors independently associated with an increased risk for mortality were higher age, an eGFR <30 ml/min/1.73 m^2 at 1 year, ischemic cardiac disease, and AKI requiring RRT (Table 3). A protective factor was a more recent year of transplantation. Additional, overall survival curves stratified by renal function 1 year after transplantation are presented in Fig. 3a and show a significant increased risk for mortality in recipients with lower renal function 1 year following transplantation

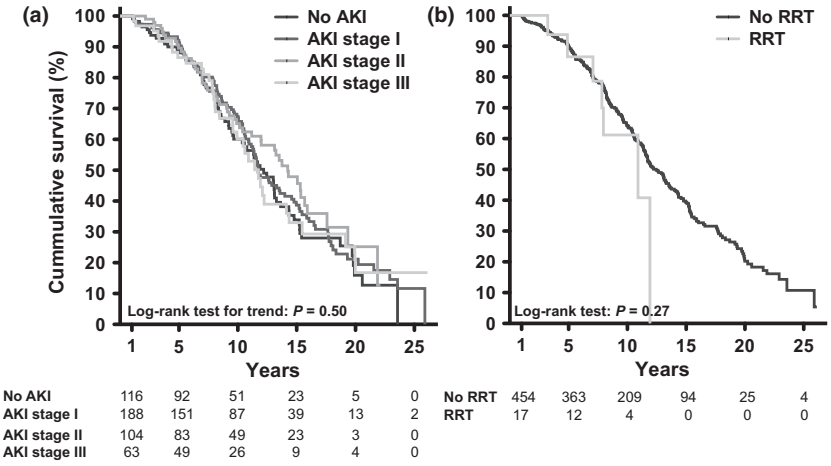

Figure 2 Kaplan–Meier curves for long-term overall survival. (a) Analysis stratified by AKI stage. (b) Analysis stratified for RRT in the first 7 postoperative days. AKI, acute kidney injury; RRT, renal replacement therapy.

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Table 3. Multivariable Cox proportional hazards analysis for the association with mortality (n = 471).

	HR	95% C.I.	*P*-value
Age at transplantation in years	1.03	1.02–1.05	<0.001*
Year of transplantation	0.93	0.90–0.95	<0.001*
eGFR at year one in ml/min/1.73 m^2			
≥60	1		
30–59	1.29	0.91–1.83	0.15
<30	2.69	1.68–4.32	<0.001*
Primary cardiac disease			
Cardiomyopathy	1		
Ischemic cardiac disease	1.36	1.04–1.78	0.03*
Valvular disease	1.69	0.94–3.04	0.08
AKI requiring RRT	2.59	1.17–5.73	0.02*

eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

*P < 0.05.

(log-rank test for trend, $P < 0.001$). Subgroup analyses demonstrated that this significant difference was lost when a recipient was either transplanted after the year 2000 (log-rank test for trend, $P = 0.9$) or received tacrolimus as immunosuppressive medication (log-rank test for trend, $P = 0.5$), respectively (Figures S1 and S2).

AKI and long-term renal survival

During follow-up, a total of 74 recipients became chronic RRT dependent of which three recipients were excluded for further analyses because they were already RRT dependent at 1 year following transplantation. Regarding the RRT modality, 40 recipients received IHD, 31 PD, and three underwent preemptive kidney transplantation, respectively. Cumulative long-term renal survival censored for death stratified by AKI stage or requirement for RRT are presented in Fig. 4a,b and Table S2. No crude association was found between the development of AKI of any stage of severity and long-term renal survival (log-rank for trend, $P = 0.47$). Stratified by the need for RRT, a crude association was found between AKI requiring RRT and long-term renal survival (log-rank, $P = 0.03$). Univariable analysis identified several demographic and clinical characteristics associated with chronic RRT dependence including year of transplantation, eGFR at year one, the preoperative use of inotropic medication, and urgent status on the waiting list, days on waiting list, donor age, tacrolimus usage at 1 year following transplantation and AKI requiring RRT. Factors independently associated with an increased risk for chronic RRT dependence were male gender, eGFR <60 ml/min/1.73 m^2 at 1 year, and AKI requiring RRT (Table 4). A protective factor was a more recent year of transplantation. Additional, renal survival curves stratified by renal function 1 year after transplantation are presented in Fig. 3b and show a significant increased risk for chronic RRT dependence in recipients with lower renal function 1 year following transplantation (log-rank test for trend, $P < 0.001$). Subgroup analyses demonstrated that this significant difference was lost when a recipient was either transplanted after the year 2000 (log-rank test for trend, $P = 0.6$) or received tacrolimus as immunosuppressive medication (log-rank test for trend, $P = 1.0$), respectively (Figures S3 and S4).

AKI and renal function 10 years after cardiac transplantation

The course of renal function (eGFR) during follow-up, stratified by AKI stage or RRT requirement, is presented in Fig. 5a,b. Linear mixed-model analyses demonstrated

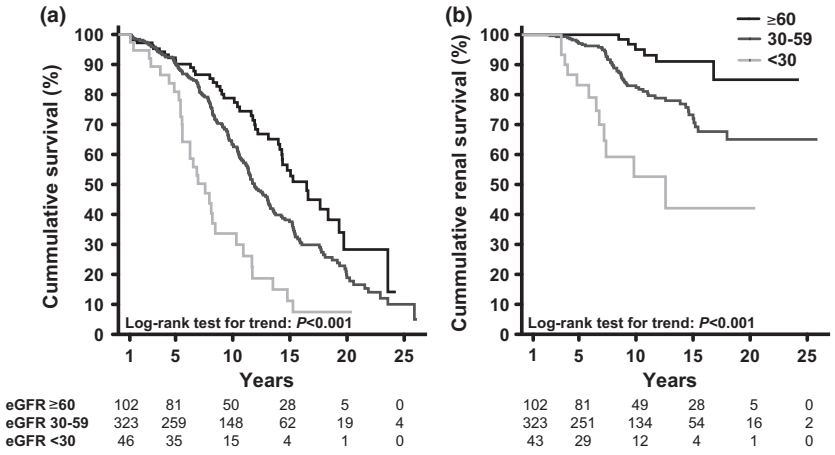

Figure 3 Kaplan–Meier curves for long-term overall and renal survival stratified by renal function (eGFR) at year one. (a) Overall survival. (b) Renal survival. eGFR, estimated glomerular filtration rate in ml/min/1.73 m^2.

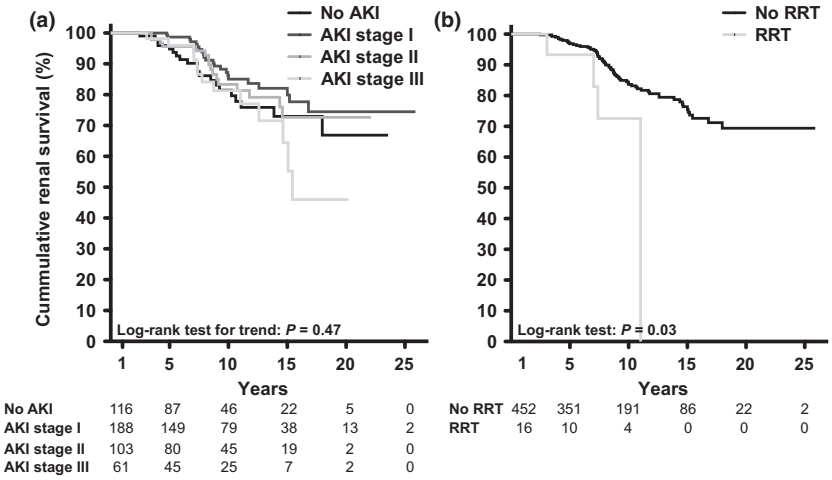

Figure 4 Kaplan–Meier curves for long-term renal survival. (a) Analysis stratified by AKI stage. (b) Analysis stratified for RRT in the first 7 postoperative days. AKI, acute kidney injury; RRT, renal replacement therapy.

Table 4. Multivariable Cox proportional hazards analysis for the association with chronic RRT dependence (n = 468#).

	HR	95% C.I.	*P*-value
Male gender	2.27	1.08–4.77	0.03*
Year of transplantation	0.84	0.79–0.90	<0.001*
eGFR at year one in ml/min/1.73 m^2			
≥60	1		
30–59	3.57	1.41–9.01	0.007*
<30	16.53	5.72–47.78	<0.001*
AKI stage			
No AKI	1		
Stage I	0.55	0.30–1.02	0.06
Stage II	1.20	0.61–2.34	0.61
Stage III	0.79	0.35–1.75	0.56
AKI requiring RRT	13.14	3.26–52.92	<0.001*

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

#Recipients (n = 3) on chronic RRT at year one were excluded.

*P < 0.05.

a significant decrease in eGFR during 10 years of follow-up ($P < 0.001$) and a significant difference in eGFR between AKI stages ($P = 0.03$). However, no significant difference in slope was demonstrated ($P = 0.93$). A similar pattern was demonstrated when stratified by AKI requiring RRT. Univariable analysis identified several demographic and clinical characteristics associated with renal function 10 years following transplantation including age, male gender, eGFR at baseline, eGFR at year one, and tacrolimus usage at 1 year following transplantation. Factors independently associated with lower renal function 10 years after transplantation were an eGFR <60 ml/min/1.73 m^2 and AKI requiring RRT (Table 5). A protective factor was the use of tacrolimus at 1 year following transplantation.

Discussion

This study is the continuation of a former study by Fortrie *et al.* published in 2015, which demonstrated that AKI is a highly frequent complication during the first week following cardiac transplantation that occurred in 76% of the recipients. Furthermore, it demonstrated that only a severe episode of AKI requiring RRT was associated with an increased risk for mortality during the first postoperative year, while AKI stage I or higher was strongly associated with an impaired renal function 1 year after transplantation [14]. The current results are conditional to one-year survival and this study addresses the long-term sequelae of AKI following cardiac transplantation with extensive follow-up with a maximum of 26 years. In contrast to what we expected, the main results of this study show that AKI defined and staged by the KDIGO AKI criteria is not associated with an impaired long-term prognosis in cardiac transplantation recipients. However, when temporary RRT was required, AKI was independently associated with an increased risk for long-term mortality and loss of renal function thereafter. Strikingly, after 12 years of follow-up none of the recipients that experienced AKI requiring RRT were alive, while after 25 years of follow-up cumulative survival in those who did not require RRT was still 10.7%, respectively. A similar pattern was demonstrated for the association between AKI requiring RRT and renal survival.

While only few studies have evaluated the association between AKI and outcome in the cardiac transplantation setting, none of them described its long-term sequelae. However, AKI has been extensively studied in a wide variety of clinical settings and two large meta-analyses by Coca *et al.* [16,20] evaluated the impact of AKI on either long-term overall as well as renal survival.

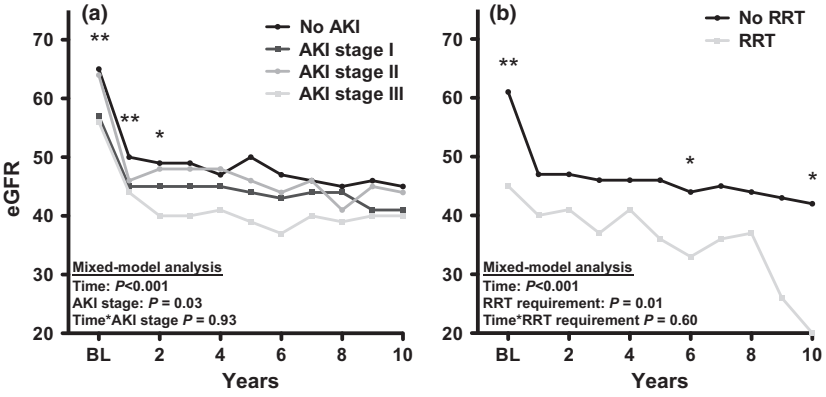

Figure 5 Renal function during the 10 years after transplantation presented as median eGFR. (a) Renal function stratified by AKI stage. (b) Renal function stratified by AKI requiring renal replacement therapy. AKI, acute kidney injury; BL, baseline; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy. Differences in median eGFR at time of baseline, 1–10 years are calculated by Kruskal–Wallis or Mann–Whitney *U*-test. *$P < 0.05$, **$P < 0.01$.

Table 5. Multivariable general linear model analysis of characteristics for the association with renal function (eGFR) 10 years after cardiac transplantation (n = 203#).

	β	95% C.I.	*P*-value
eGFR in ml/min/1.73 m^2			
Baseline			
≥60	0		
<60	−5.56	−11.67; 0.55	0.07
Year one			
≥60	0		
30–59	−19.67	−26.78; −12.56	<0.001*
<30	−34.12	−46,68; −21.56	<0.001*
CNI at year one			
Cyclosporine	0		
Tacrolimus	17.91	6.8; 29.03	0.002*
AKI requiring RRT	−29.72	−54.57; −4.87	0.02*

AKI, acute kidney injury; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy.

#Recipients alive at 10 years following transplantation.

*P < 0.05.

They demonstrated in a pooled analysis that AKI, even in a mild form, was associated with an increased risk for long-term mortality and that patients with AKI requiring RRT had a threefold increased risk for long-term mortality compared with those without the need for RRT [16]. Furthermore, they demonstrated that patients that experienced AKI requiring RRT had an up to eightfold increased risk for chronic RRT dependence [20]. Thus, the results of our study suggest that the impact of AKI requiring RRT on the long-term prognosis after cardiac transplantation is of a similar order of magnitude compared with its impact in other clinical settings. When specifically focussed on the outcome of AKI after cardiac surgery, two large single-center studies by Hobson *et al.* (n = 2973) and Lopez-Delgado *et al.* (n = 2940) concluded that patients who developed AKI after general cardiac surgery had a significant higher risk for long-term mortality, which proportionally increased with AKI stage of severity as defined by the Risk, Injury, Failure, Loss, and ESRD (RIFLE) criteria [21–23]. In addition, a large nationwide study performed in Sweden (n = 29 330) [24] demonstrated that patients who received a coronary artery bypass graft (CABG) had an almost threefold and fourfold increased risk for ESRD in patients that developed AKI stage I and AKI stage II or greater, respectively, as defined by the Acute Kidney Injury Network (AKIN) criteria [25].

However, we did not demonstrate an association between less severe episodes of AKI and an increased risk for mortality or chronic RRT dependence. This may be partly explained by the results of the difference in sample size. However, it is unlikely that the smaller sample size alone accounts for the reported difference. Another explanation for this difference could be that, in

contrast to the current study, the aforementioned studies included patients that deceased during the first year following an episode of AKI. The results of previous studies clearly show that the greatest difference in patient survival occurs within the first year following transplantation and that the survival curves thereafter show a more or less parallel slope [22,23]. Therefore, in order to prevent that the high incidence of death during the first year obscures the long-term results, we specifically decided to exclude recipients that died during the first postoperative year. Furthermore, in comparison with the current literature, our study population had a distinct lower median age and patients were less likely to suffer from comorbid conditions such as diabetes mellitus and hypertension [22,23], which most likely has a positive effect on the recipients prognosis. On the other hand, it is possible that the AKI criteria do not offer the ideal measurement for an acute episode of renal deterioration in the cardiac transplantation setting due to the large proportion of recipients with preliminary prerenal kidney disease. As demonstrated previously, a large proportion of recipients (27%) showed a significant improvement (≥20%) in renal function compared with baseline during the first month following transplantation, which can lead to misclassification and obscure the prognostic value of the AKI criteria [14].

While a mild to modest episode of AKI does not seem to play a significant role in predicting long-term outcome, a strong association was found between an impaired renal function at 1 year following transplantation and an increased risk for mortality, deterioration in renal function, and chronic dialysis dependence. These findings are in accordance with the results of previous studies, which showed that a decreased renal function at 1 year after transplantation was significantly associated with a continuing decline in the consecutive years thereafter [26] and an increased risk for mortality [27–29]. Furthermore, the greatest degree of deterioration in renal function occurs within the first year following transplantation after which a stable or slow deterioration in renal function occurs [29–31]. As demonstrated previously, the development of AKI was in fact independently associated with a the decrease in renal function during the first year following transplantation creating a paradox as renal function at 1 year but not AKI in the week after cardiac transplantation was associated with overall and renal survival. However, at 12 months after transplantation, the differences in eGFR between the AKI groups were relatively small with a tendency to converge, which could be partly explained by adjustments in CNI dosing to lower trough levels in the AKI group. In addition, the relation between AKI stage and survival post-transplantation was most pronounced within the first 6 months. Therefore, our results support the contention that the negative effects of even severe post-transplantation AKI become irrelevant after 1 year, unless RRT was needed. Our data strongly advocate the importance of conserving renal function after transplantation, which shows the greatest decrease within the first year even in the no AKI group [14].

The current study has several limitations, which need to be considered for interpretation of the results. First, the retrospective observational study design lacks the ability to identify a causal relationship. However, the data related to cardiac transplantation recipients is carefully and for the most part prospectively collected in the Erasmus MC. In addition, because of the large study population and extensive and in-depth evaluation of the patient records, multivariable analyses were performed to rule out confounding or modifying effects as far as possible. Second, the single-center study design has its inherent drawbacks and it is not known whether the results can be transposed to other cardiac transplantation populations. For instance, our study population contained a low proportion of recipients with DM, hypertension, and previous thoracic surgery prior to transplantation compared with cardiac transplantation recipients in the USA [32]. The long inclusion period may offer a possible explanation, because the selection criteria for cardiac transplantation during the early study period were much more strictly compared to the criteria nowadays. Furthermore, underreporting is possible because of the retrospective nature of the study. Third, as aforementioned the current study has a long period of inclusion, which could significantly affect the results of this study due to improvement in medical care, a difference in selection criteria and immunosuppressive regime during the study period. Therefore, the effect of the year of transplantation was evaluated and included in the multivariable model, when applicable, to adjust for difference in study period and additional subgroup analyses were performed stratified by the type of immunosuppressive medication (tacrolimus versus cyclosporine) or the period in which transplantation was performed (before the year 2000 vs. 2000 and thereafter). Interestingly, the effect of renal function at 1 year on overall and renal survival was lost in recipients transplanted after the year 2000 or treated with tacrolimus, respectively. However, due to the low number of events and limited follow-up, these subgroup analyses do not offer the possibility to draw conclusions yet and therefore further research is warranted.

In conclusion, the results of the current study demonstrate that AKI requiring RRT following cardiac transplantation is independently associated with an increased risk for long-term mortality and chronic dialysis dependence. However, when a less severe episode of AKI is experienced and the deterioration in renal function during the first postoperative year can be limited, the cardiac transplantation recipient has a relatively good long-term prognosis. Therefore, the results of the current study emphasize the need for prospective studies that focus on renoprotective strategies during the early postoperative phase and the years thereafter.

Authorship

GF: participated in data collection, research design, writing of the manuscript, performance of the research and data analysis. OM and MB: participated in research design, data collection, writing of the manuscript and performance of the research. AC and PW: participated in data collection and writing of the manuscript.

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Conflicts of interest

The authors declare that they have no relevant conflicts of interest or financial support to disclosure, with regard to the current project.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Kaplan–Meier curves for survival stratified by renal function (eGFR) at year one. (a) Era <2000, (b) Era ≥2000. eGFR, estimated glomerular filtration rate in ml/min/1.73 m^2

Figure S2. Kaplan–Meier curves for survival stratified by renal function (eGFR) at year one. (a) Cyclosporine (b) Tacrolimus. eGFR: estimated glomerular filtration rate in ml/min/1.73 m^2

Figure S3. Kaplan–Meier curves for renal survival stratified by renal function (eGFR) at year one. (a) Era <2000 (b) Era ≥2000. eGFR, estimated glomerular filtration rate in ml/min/1.73 m^2.

Figure S4. Kaplan–Meier curves for renal survival stratified by renal function (eGFR) at year one. (a) Cyclosporine, (b) Tacrolimus. eGFR, estimated glomerular filtration rate in ml/min/1.73 m^2.

Table S1. Demographic and clinical characteristics of study population stratified by AKI stage.

Table S2. Long-term overall and renal survival in cardiac transplantation recipients that survived the first postoperative year.

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