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Risk Factors for Long-Term Mortality and Progressive Chronic Kidney Disease Associated With Acute Kidney Injury After Cardiac Surgery

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Abstract: The aim of the study was to evaluate risk factors for long-term mortality and progressive chronic kidney disease (CKD) after cardiac surgery in patients with normal preoperative renal function and postoperative acute kidney injury (AKI). From April 2009 to December 2012, we prospectively enrolled 3245 cardiac surgery patients of our hospital. The primary endpoints included survival rates and the secondary endpoint was the incidence of progressive chronic kidney disease (CKD) in a follow-up period of 2 years. Acute kidney injury was staged by KDIGO classification. Progressive CKD was defined as GFR $\leq$ 30 mL/min/1.73 m^2 or end-stage renal disease (ESRD) (starting renal replacement therapy or renal transplantation).

The AKI incidence was 39.9% (n = 1295). The 1 and 2 year overall survival (OS) rates of AKI patients were significantly lower than that for non-AKI patients (85.9% and 82.3% vs 98.1% and 93.7%, $P < 0.001$), even after complete recovery of renal function during 2 years after intervention ($P < 0.001$). The 2-year overall survival (OS) rates of patients with AKI stage 1, 2, and 3 were 89.9%, 78.6%, and 61.4% ($P < 0.001$), respectively. Multivariate Cox regression analysis of factors for 2-year survival rates revealed that besides age ($P < 0.001$), chronic cardiac failure ($P < 0.001$), diabetes ($P < 0.001$), cardiopulmonary bypass time ($P < 0.01$), and length of intensive care unit (ICU) stay ($P = 0.004$), AKI was a significant risk factor for reducing 2-year survival rates even after complete recovery of renal function ($P < 0.001$). The accumulated progressive CKD prevalence was significantly higher in AKI than in non-AKI patients (6.8% vs 0.2%, $P < 0.001$) in the 2 years after surgery. Even with complete recovery of renal function at discharge, AKI was still a risk factor for accumulated progressive CKD (RR 1.92, 95% CI 1.37–2.69).

The 2-year mortality and progressive CKD incidence even after complete recovery of renal function were significantly increased in cardiac surgery patients with postoperative AKI.

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Abbreviations: ADQI = acute dialysis quality initiative, AKI = acute kidney injury, AKIN = acute kidney injury network, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rates, ESRD = end-stage renal disease, ICU = intensive care unit, KDIGO = Kidney Disease Improving Global Outcomes, MDRD = modification of diet in renal disease, NYHA = New York Heart Association, OS = overall survival, RR = risk rate, RRT = renal replacement therapy, SCr = serum creatinine.

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INTRODUCTION

Acute kidney injury (AKI) was reported to occur in up to 30% of patients after cardiac surgery, with up to 3% of patients requiring dialysis.[1,2] Although the percentage recovery of renal function after renal replacement therapy (RRT) is satisfactory, patients with heart failure are notably less likely to recover[3] and acute renal failure with RRT after cardiac surgery is associated with enhanced mortality.[4–6] However, recent studies have shown that AKI increases the long-term risk of death even without postoperative RRT intervention and complete recovery of renal function.[7–9] In addition, AKI increased the risk of developing chronic kidney disease, particularly in elderly patients.[10–13] Nevertheless, there are problems concerning the long-term prognosis of AKI patients, because of equivocal definitions of AKI. Often, enrolled patients with a chronic kidney disease (CKD) history in a research study often lack non-AKI patients to act as an adequate control group.[14] In recent years, the acute dialysis quality initiative (ADQI),[15] acute kidney injury network (AKIN)[16] and Kidney Disease: Improving Global Outcomes (KDIGO) groups[17] have launched new AKI clinical diagnosis standards, which are based on pathological changes of serum creatinine levels and urine volumes. In view of the paucity of epidemiological data concerning the long-term prognosis and renal outcomes for AKI patients, we conducted a prospective follow-up study of Chinese AKI patients who underwent cardiac surgery in order to derive long-term prognoses and renal outcomes, as well as epidemiological data, which will inform the clinical basis for appropriate prevention strategies.

PATIENTS AND METHODS

Patients

The ethical committee of Zhongshan Hospital approved the study and all participants provided written informed consent. Between April 2009 and December 2012, 4551 patients received cardiac surgery treatments in the Zhongshan Hospital of Fudan University. For our prospective study, we excluded 1306 cases who were ≤ 18 years old, in various stages of CKD, with preoperative estimated glomerular filtration rates (eGFR) <60 mL/min/73 m^2 and patients who survived <24 h in the intensive care unit (ICU). The remaining 3245 cases included 1950 non-AKI and 1295 AKI patients (Table 1).

METHODS

Demographical data, the type of operation, preoperative complications, New York Heart Association (NYHA) cardiac function grading,[18] preoperative angiography history, baseline renal function (renal function was determined by serum creatinine) before discharge, intraoperative pulmonary bypass time, and aortic cross-clamping time for all participating patients were recorded. Chronic cardiac insufficiency was defined as NYHA stage III–IV. Chronic kidney disease was diagnosed according to the CKD criteria as the presence of kidney damage or decreased kidney function for ≥ 3 months.[19] Acute kidney injury was defined as the absolute value of the serum creatinine increase ≥ 26.5 μmol/L within 48 h or an increase > 50% compared to the baseline values, or a urine output < 0.5 mL/kg/h >6 h.[17] According to the Kidney Disease: Improving Global Outcomes (KDIGO) staging guide, AKI was further categorized into 3 stages according to the level of SCr increases or the degree of oliguria.[20] SCr was assessed 1 or 2 days before discharge. Complete renal recovery was defined as an SCr concentrations ≤ 44 μmol/L above baseline values, whereas incomplete renal recovery was defined as SCr values at discharge > 44 μmol/L above baseline, but without RRT treatment.[21] The estimated glomerular filtration rate (eGFR) was determined according to the simplified Modification of Diet in Renal Disease (MDRD) formula: eGFR is equal to $186 \times Scr^{-1.154} \times age^{-0.203} \times (0.742$ if female).[22] Heart functional classifications were calculated according to the New York Heart Association (NYHA) standards.[23] During the follow-up period of 2 years, the primary endpoint was all causes of mortality and the secondary end point was progressive chronic kidney disease (CKD stages 4–5 including renal replacement therapy or renal transplantation). We compared the survival times and the incidence of progressive CKD rates between the AKI group and the non-AKI group; all patients were followed up for 2 years.

Statistical Analysis

All data were analyzed using SPSS version 17.0 statistical software. Normally distributed data are expressed as the mean ± standard deviation; groups were compared using 2 independent sample *t*-tests or ANOVA. Nonparametric data are expressed as medians (25–75% interquartile range). The Wilcoxon test was used to assess 2 dependent variables, a nonparametric Mann–Whitney test for independent variables, and a chi-square test for group comparisons. Multivariate Cox regression analyses were performed to investigate the effects of multiple factors on survival rates and advanced chronic kidney disease morbidity. Survival rates and the incidence of chronic kidney disease differences in the AKI and non-AKI groups were compared using the Kaplan–Meier method. $P < 0.05$ was considered to be statistically significant.

RESULTS

Basic Clinical Data of AKI and Non-AKI Patients

Of the 3245 cases, 890 (50.3%) patients underwent cardiac valve operations, 314 (17.7%) were treated with coronary artery bypass grafting, 138 (7.8%) received aortic operations, and 306 (17.3%) underwent total correction of congenital heart disease. Other types of operations carried out included 28 (1.6%) cardiac transplantations and 94 (5.3%) coronary artery bypass grafts combined with valve operations as well as 306 (17.3%) other types of heart operations. The study participants were divided into a non-AKI group (n = 1950, 60.1%) and an AKI group (n = 1295, 39.9%). Between the AKI and non-AKI patients, there were significant differences in age (51 ± 14 vs 56 ± 14 years, $P < 0.001$), gender (58.6% male vs 73.5% male, $P < 0.001$), and baseline serum creatinine (73.5 ± 26.1 vs 86.4 ± 28.3 μmol/L, $P < 0.001$). Furthermore, comparisons of preoperative complications between the 2 groups were significantly different in the AKI group. The complications hypertension (24.4% vs 31.4%, $P < 0.001$), diabetes (8.3% vs 11.1%, $P = 0.001$), preoperative angiography history (33.1% vs 40.1%, $P < 0.001$), chronic cardiac insufficiency (57.1% vs 60.8%, $P = 0.038$), cardiopulmonary bypass (82.3% vs 87.6%, $P = 0.022$) incidences, cardiopulmonary bypass time (72 ± 45 vs 89 ± 58, $P < 0.001$), and aortic cross-clamping time (41 ± 31 vs 53 ± 48 min, $P < 0.001$). The probability of suffering from

TABLE 1. Basic Characteristics of Cardiac Surgery Patients in the AKI and Non-AKI Groups Before Operation

	Non-AKI n = 1950	AKI n = 1295	*P* Value
Age (years)	51 ± 14	56 ± 14	<0.001
Male (n [%])	1142 (58.6%)	952 (73.5%)	<0.001
Serum creatinine μmol/L	73.5 ± 26.1	86.4 ± 28.3	<0.001
Hypertension (n [%])	475 (24.4%)	406 (31.4%)	<0.001
Diabetes (n [%])	161 (8.3%)	144 (11.1%)	0.006
Atrial fibrillation (n [%])	548 (28.1%)	405 (31.3%)	0.282
Preoperative angiography history (n [%])	645 (33.1%)	519 (40.1%)	<0.001
Chronic cardiac insufficiency* (n [%])	1113 (57.1%)	787 (60.8%)	0.038
Cardiopulmonary bypass (n [%])	1604 (82.3%)	1135 (87.6%)	0.022
Cardiopulmonary bypass time (min)	72 ± 45	89 ± 58	<0.001
Aortic cross clamping time (min)	41 ± 31	53 ± 48	<0.001

AKI = acute kidney injury; NYHA = New York Heart Association.
* Patients in NYHA stages III–IV.

TABLE 2. Multivariate Cox Regression Analysis of Factors for 2-Year Death Prognosis After Cardiac Surgery

Risk Factors	AHR	95% CI	P
Age	1.06	1.04–1.07	<0.001
Gender	1.13	0.84–1.52	0.413
Hypertension	0.98	0.73–1.36	0.920
Atrial fibrillation	1.001	0.98–1.02	0.270
Chronic cardiac insufficiency	1.71	1.27–2.54	<0.001
A history of diabetes mellitus	3.39	2.46–4.68	<0.001
Renal function before surgery	0.998	0.992–1.008	0.780
Operation classification			
Valve	1.011	0.624–1.640	0.964
CABG	1.113	0.54–2.29	0.772
Aneurysm	2.92	1.79–4.74	<0.001
CABG + valve	2.99	1.62–5.52	<0.001
Cardiopulmonary bypass time	1.033	1.012–1.052	0.010
Aortic cross clamping time	0.999	0.994–1.002	0.859
AKI after operation	1.74	1.27–2.37	0.001
AKI with different extent of renal recovery	4.007	2.76–5.82	<0.001
ICU stay time	1.001	1.001–1.002	0.004
Hospitalization time	0.99	0.97–1.012	0.788

AKI = acute kidney injury, CABG = coronary artery bypass grafting, CI = confidence interval, ICU = intensive care unit.

postoperative AKI correlated with preoperative complications (Table 1).

COX Regression Analysis of Factors Affecting the Cumulative Survival Rate of Patients 2 Years After Cardiac Surgery

Using a Cox multivariate regression analysis, we found that the factors that significantly correlated with the 2-year cumulative survival rate of cardiac surgery were age, chronic cardiac insufficiency, history of diabetes mellitus, type of operation, ICU and general hospitalization periods, as well as the occurrence of postoperative AKI (AHR 1.74, 95% CI 1.27–2.37, $P = 0.001$). Acute kidney injury was an independent death-risk factor for patients who underwent cardiac surgery (Table 2).

Short-Term Outcome of AKI Patients After Cardiac Surgery

The hospital mortality of cardiac surgery AKI patients was significantly higher than that in the non-AKI group (6.2% vs 0.4%, $P < 0.001$) with AKI severity increases leading to enhanced mortality rates, reaching 31.4% for AKI stage 3 cases. Similarly, the proportion of patients with complete renal function recovery at discharge declined gradually with the severity of AKI. In the stage 1 AKI group (10.3% of cases) and the AKI stage 2 group (7.4% of cases) the patients achieved complete renal function recovery, whereas in the AKI stage 3 group the ratio was 5.4%. Consequently, the length of stay in the ICU as well as the hospital was significantly longer in AKI compared to non-AKI patients. The lengths of stay were also much longer according to the degree of AKI. In summary, the hospital stay and ICU times were significantly longer and mortality significantly higher for postoperative AKI patients compared to the non-AKI group ($P < 0.001$). The same outcome parameters were significantly poorer in higher than in lower grade AKI patients ($P < 0.001$) (Table 3).

Comparison of Cumulative Survival Rates (Long-Term Prognoses) Between AKI and Non-AKI Patients

For AKI patients, the 1-year and 2-year overall survival (OS) rates were 85.9% and 82.3%, respectively, whereas in the non-AKI group they were 98.1% and 93.7% (Fig. 1A). The Kaplan–Meier OS rates of AKI patients were significantly lower than that of non-AKI patients ($P < 0.001$). Next, we observed the cumulative survival rates of AKI patients in stage 1, stage 2, and stage 3, which were 93.2%, 86.8%, and 65.2% at 1 year and 89.9%, 78.6%, and 61.4%, respectively, 2 years after the operation (Figure 1B). With increased AKI staging, the survival rates of patients decreased ($P < 0.001$). The 1-year and 2-year OS rates of AKI patients with complete renal recovery were 92.6% and 88.6%, respectively, and for AKI patients with complete renal recovery 60.9% at 1 year and 57.4% 2 years after surgery (Figure 1C). The Kaplan–Meier curves indicated that the 2-year OS rates of AKI patients were significantly lower than that for non-AKI patients even when their renal function has been completely restored ($P < 0.001$), and this difference persisted over time.

TABLE 3. The Short-Term Prognosis of AKI Patients After Cardiac Surgery

	Non-AKI n = 1950	AKI n = 1295	AKI-1 n = 854	AKI-2 n = 234	AKI-3 n = 207	P of AKI grade differences
In hospital mortality (n [%])	8 (0.4%)	80 (6.2%)*	3 (0.4%)	12 (5.1%)	65 (31.4%)	<0.001
AKI with different extents of renal recovery						
Complete recovery (n [%])		299 (23.1%)	134 (10.3%)	94 (7.3%)	71 (5.4%)	
Incomplete recovery (n [%])		996 (76.9%)	720 (55.6%)	140 (10.8%)	136 (10.5%)	
RRT (n [%])		126 (3.9%)	14 (0.4%)	29 (0.9%)	83 (2.6%)	
Hospitalization time (day)	14 ± 8	18 ± 12*	17 ± 10	19 ± 10	27 ± 18	<0.001
ICU stay time (h)	48 (35, 71)	69 (42, 143)*	67 (42, 97)	89 (43, 125)	156 (61, 362)	<0.001

AKI = acute kidney injury, ICU = intensive care unit, RRT = renal replacement therapy.
* $P < 0.001$, comparing AKI and non-AKI.

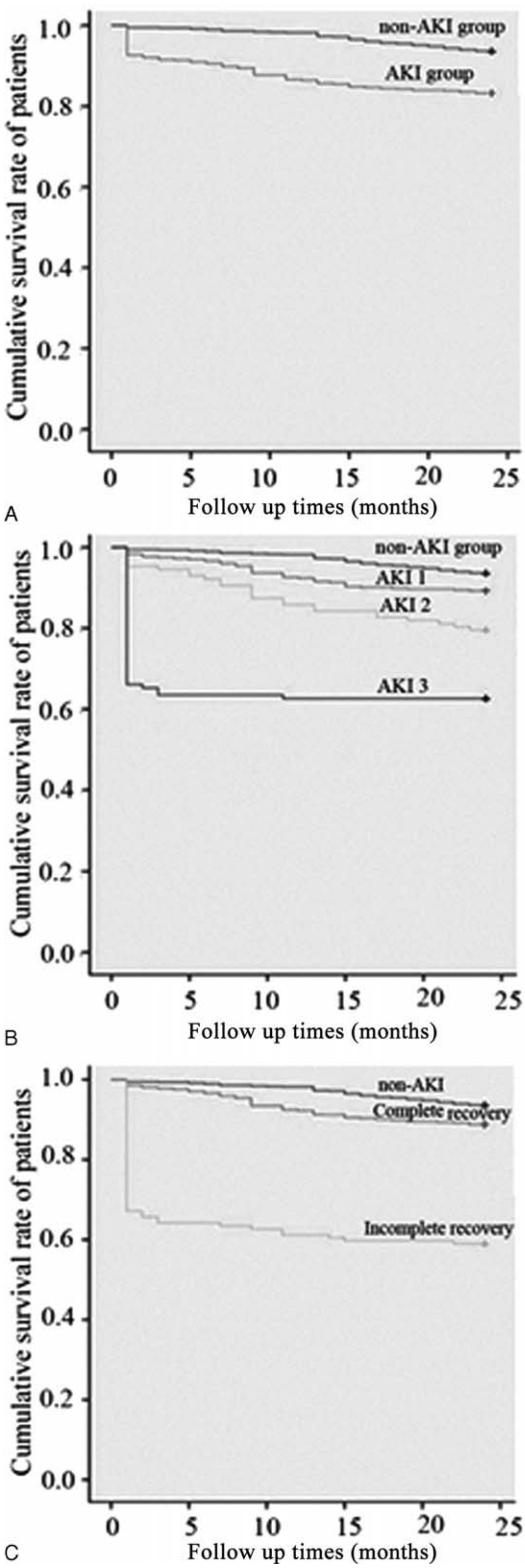


FIGURE 1. Kaplan–Meier cumulative survival rates of (A) AKI and non-AKI patients, (B) non-AKI patients and AKI stage 1, 2, and 3 patients, and (C) non-AKI patients and AKI patients, with complete as well as incomplete renal function recovery. AKI = acute kidney injury.

Long-Term Prognosis of AKI Patients Related to Their Stages and Renal Function Recovery

With increased AKI staging, the risk of death also increased, with the 2-year survival rate being correlated with the AKI stage. Risk rate (RR) values of AKI stage 1, stage 2, and stage 3 patients were 1.73 ($P < 0.001$), 3.44 ($P < 0.001$), and 7.75 ($P < 0.001$), respectively. For all AKI patients with completely renal recovery, the RR was 1.79 ($P = 0.001$) whereas for AKI patients with incomplete recovery, the RR was 8.64 ($P < 0.001$) (Table 4), indicating that AKI was independant of the extent of renal recovery and always a risk factor for the 2-year survival rate.

Comparison of 2-Year Progressive Chronic Kidney Disease (CKD 4–5 Stages) Prevalence in AKI and Non-AKI Patients After Cardiac Surgery

Finally, the progressive CKD occurrence in AKI and non-AKI patients were compared and it was found that after cardiac surgery the 2-year cumulative advanced CKD prevalence in AKI patients was significantly higher than that in the non-AKI group (6.8% vs 0.2%) (Log-Rank test, $P < 0.001$) (Fig. 2). With the increase of AKI stage (stage 1 [RR 2.19 {95% CI 1.56–3.09, $P < 0.001$}], stage 2 [RR 4.85 {95% CI 3.22–7.30, $P < 0.001$}], stage 3 [RR 10.32 {95% CI 7.18–14.84, $P < 0.001$}]), the risk of progression into CKD also increased. Compared with non-AKI patients, the renal recovery of AKI patients affected progression into CKD. The RR was 1.92 (95% CI 1.37–2.69, $P < 0.001$) for complete recovery and 15.05 (95% CI 10.88–20.82, $P < 0.001$) for incomplete recovery (Table 5).

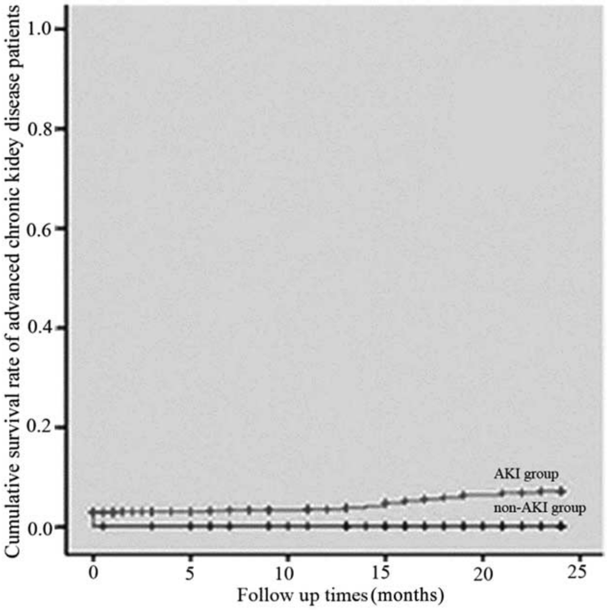
Analysis of Factors Associated With the Cumulative Incidence of Progressive CKD After Cardiac Surgery

A multivariate Cox regression analysis revealed that AKI was the most significant factor associated with the prevalence of 2-year postoperative advanced CKD (AHR 20.32, 95% CI, 4.55–97.31, $P < 0.001$). Other significant factors were a preoperative history of diabetes, cardiopulmonary bypass time, and the ICU stay period, as well as age. The results indicated that even after adjusting the influence of other factors, AKI was still a strong independent factor for an increased risk of developing progressive CKD (Table 6).

TABLE 4. Relative Long-Term Death Risk Analysis of AKI Severity Subgroups and Renal Function Recovery (AKI Subgroups Compared to Non-AKI Patients)

Risk Factors	RR	95% CI	P
Acute kidney injury stage			
Stage 1	1.73	1.20–2.49	<0.001
Stage 2	3.44	2.19–5.40	<0.001
Stage 3	7.75	5.28–11.36	<0.001
AKI with different extents of renal recovery			
Complete recovery	1.79	1.28–2.52	0.001
Incomplete recovery	8.64	6.04–12.34	<0.001

AKI = acute kidney injury, CI = confidence interval, RR = risk rate.



	Starting point	After 2- years
Non-AKI group	0	4
AKI group	0	88

FIGURE 2. Incidence of cumulative chronic kidney disease (stages 4 and 5) after 2 years in AKI and non-AKI patients. AKI = acute kidney injury.

DISCUSSION

By analyzing the 2-year death risk factors after cardiac surgery, we found that age, diabetes, chronic cardiac insufficiency and cardiopulmonary bypass time, type of surgery, postoperational AKI and AKI severities were significant factors influencing the 2-year survival rate. Though AKI with different extents of renal recovery may affect the 2-year survival, the 2-year mortality risk after surgery of AKI patients was significantly higher than in non-AKI patients, even when complete renal recovery from AKI had occurred. In addition, our AKI patients had a higher prevalence of progressive CKD (stage 4–5 CKD) within 2 years after cardiac surgery. Our results are similar to a previous retrospective analysis study of 864,933 patients who survived not <90 days after discharge. Of these patients, 82,771 met the AKI diagnostic criteria, resulting in an incidence rate of 9.6%. The 2-year cumulative survival rate was 47.9% and the long-term mortality risk rate of AKI compared to non-AKI patients was 1.45.[9] Hobson et al retrospectively observed 2973 cardiac surgery patients without pre-operational CKD histories. They used RIFLE's criteria to diagnose the stage of AKI and also found that the long-term survival rate of non-AKI patients was significantly higher than that of AKI patients, with the severity of AKI escalating the adjusted mortality risk.[8] In the present study, the cumulative incidence of progressive CKD in AKI patients 2 years after cardiac surgery was 6.7% and significantly higher than that in non-AKI patients (0.2%), suggesting that AKI after cardiac surgery may increase the prevalence of long-term progressive CKD, a finding in line with previous reports. Lo et al retrospectively observed 343 adult AKI patients undergoing RRT, and their glomerular filtration rates were estimated as $\geq$ 45 mL/min/1.73 m^2 before admission. They found that even after adjustment for confounding factors such as age, diabetes, hypertension, albuminuria, and others, the risk of developing long-term 4–5 phase CKDs, who needed RRT, increased 28 times in AKI patients, whereas their mortality risk increased 2 times.[11] Also, Mammen et al, who adopted AKIN criteria to diagnose and stage 126 children in ICU, found that the prevalence of CKD in AKI children was significantly increased.[24] A drawback of our study is that although there was a large cohort of patients, it was only a single center study and the follow-up period was not long enough. In addition, other prognostic factors such as the patient's overall condition at ICU admission (such as APACHE II score) and other postoperative complications were not considered.

TABLE 5. Influence of AKI Severity and Renal Function Recovery Status on Progressive CKD Compared With Non-AKI Patients

Risk Factor	RR	95% CI	P
AKI stage			
Stage 1	2.19	1.56–3.09	<0.001
Stage 2	4.85	3.22–7.30	<0.001
Stage 3	10.32	7.18–14.84	<0.001
AKI with different extents of renal recovery			
Complete recovery	1.92	1.37–2.69	<0.001
Incomplete recovery	15.05	10.88–20.82	<0.001

AKI = acute kidney injury, CKD = chronic kidney disease, CI = confidence interval, RR = risk rate.

TABLE 6. Multivariate Cox Regression Analysis of the 2-Year Cumulative Incidence of Progressive CKD in Patients After Cardiac Surgery

Risk Factors	AHR	95% CI	P Value
Age	1.05	1.04–1.07	<0.001
A history of diabetes mellitus	3.64	2.70–4.92	<0.001
Cardiopulmonary bypass time	1.003	1.001–1.006	0.004
AKI after operation	20.32	4.55–97.31	<0.001
AKI with different extent of renal recovery	8.84	6.41–12.19	<0.001
ICU time	1.002	1.001–1.003	<0.001

AKI = acute kidney injury, CKD = chronic kidney disease, CI = confidence interval, ICU = intensive care unit.

CONCLUSIONS

The results of our prospective study showed that postoperative AKI after heart surgery was associated with a significant increase in the long-term risk of death, even after complete renal function recovery. The incidence of CKDs in patients with postoperative AKI was also significantly enhanced 2 years after surgery. In order to improve the long-term prognosis, more attention should be paid to the prevention of AKI after cardiac surgery and regular follow-ups should be conducted which focus on the protection of renal function after patient discharge.

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