Chronic progression of cardiac surgery associated acute kidney injury: Intermediary role of acute kidney disease

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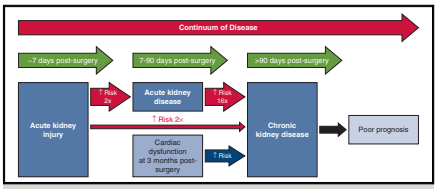
ABSTRACT

Objective: The association between acute kidney injury (AKI) and chronic kidney disease (CKD) remains elusive in cardiac surgery. We investigated the association between postoperative AKI and CKD development, emphasizing the intermediary role of acute kidney disease (AKD), in patients undergoing valvular heart surgery.

Methods: We assessed the occurrence of postoperative AKI (7 days postsurgery), AKD (3 months postsurgery), and CKD (12 months postsurgery) in 1386 patients. The primary outcome was the development of AKD and CKD according to AKI occurrence. Relevant risk factors of AKI, AKD, and CKD were identified through multivariable regression analysis.

Results: AKI occurred in 23.9% of patients with normal preoperative renal function. Even with early recovery of renal function within 3 days, AKI increased the risk of AKD (odds ratio [OR], 3.21; 95% confidence interval [CI], 1.98-5.20, $P < .001$) and CKD (OR, 2.86; 95% CI, 1.68-4.86, $P < .001$), whereas persistent AKI further increased the risk of AKD (OR, 12.07; 95% CI, 5.56–26.21, $P < .001$) and CKD (OR, 10.54; 95% CI, 4.01-27.76, $P < .001$). We also found these relationships in patients with pre-existing renal dysfunction. Multivariable analysis identified 3-month postoperative heart failure and high right ventricular systolic pressure as independent risk factors for CKD.

Conclusions: Even after early recovery, postvalvular heart surgery AKI was associated with increased risk of CKD via AKD in a graded manner related to AKI severity and persistence. Postoperative cardiac dysfunction assessed 3 months postsurgery also significantly influenced CKD development, indicating a need for close follow-up of cardiac and renal function to improve patient outcomes. (J Thorac Cardiovasc Surg 2021;161:681-8)



AKD and cardiac dysfunction 3 months postsurgery impose significant influences on CKD.

CENTRAL MESSAGE

Postvalvular heart surgery AKI was associated with increased risk of CKD development even after early recovery. AKD and cardiac dysfunction at 3-month follow-up were independent risk factors of CKD.

PERSPECTIVE

The presence of AKD and cardiac dysfunction 3 months after valvular heart surgery are predictors of CKD development, which may guide physicians to perform early interventions to favorably alter prognoses. Further research is needed to determine whether close follow-up of concomitant renal and cardiac function in patients with AKI can detect early renal deterioration and improve prognoses.

See Commentaries on pages 689 and 691.

Acute kidney injury (AKI) is a threat to public health; contrary to previous notions, complete AKI recovery can still progress to chronic kidney disease (CKD).[1,2] AKI and CKD have been solidly linked and are regarded as a continuum of disease process.[3,4] Accordingly, the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup proposed that acute kidney disease (AKD) is an ongoing pathophysiological phase between AKI and CKD, which could be an important time window for critical interventions to modify disease progression.[5]

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Abbreviations and Acronyms

AKD = acute kidney disease
AKI = acute kidney injury
CI = confidence interval
CKD = chronic kidney disease
CPB = cardiopulmonary bypass
eGFR = estimated glomerular filtration rate
HF = heart failure
KDIGO = Kidney Disease: Improving Global Outcomes
LVEF = left ventricular ejection fraction
MACEs = major adverse cardiac events
OR = odds ratio
RAP = right atrial pressure
RVSP = right ventricular systolic pressure
sCr = serum creatinine
TTE = transthoracic echocardiography

AKI is a common complication related to a discouraging prognosis after cardiac surgery.[6] As in the general population, there seems to be an association between postoperative AKI and CKD progression in patients undergoing cardiac surgery.[2,7] However, AKI pathophysiology and kidney disease progression after cardiac surgery may be different from that in the general population because of a unique inciting factor, cardiopulmonary bypass (CPB).[8] No comprehensive study has yet found evidence showing the progression of AKI to CKD through AKD in patients who undergo cardiac surgery; however, such a study would provide a valuable framework for selecting patients who would benefit from close postsurgical follow-up.

Of note, heart and kidney functions are closely related, and combined heart failure (HF) and renal impairment accelerates progressive dysfunction in both organs.[9] AKI and CKD are risk factors for cardiovascular disease,[10] whereas HF is a significant risk factor for renal dysfunction.[11] Despite this important crosstalk, simultaneous observation of cardiac and renal function has barely been studied to describe the link between AKI and CKD in cardiac surgery patients.

The aim of this retrospective study was to investigate the development of AKD and CKD according to AKI occurrence and to assess the associated risk factors for AKI, AKD, and CKD during a 12-month follow-up period in patients undergoing valvular heart surgery.

MATERIALS AND METHODS

Study Population

The Institutional Review Board and Hospital Research Ethics Committee of Severance Hospital at Yonsei University College of Medicine approved the study protocol and granted a waiver for patient consent (#4-2018-0832; October 17, 2018). Patients aged 18 years or older who underwent valvular heart surgery from January 2013 to December 2016 were included. Patients who presented for surgery primarily due to valvular heart disease were enrolled, including those who required concomitant coronary bypass graft surgery, aortic procedures, or other

TABLE 1. Clinical data in the normal preoperative renal function group

	Patients without AKI (n = 906)	Patients with AKI (n = 284)	*P* value
Patient characteristics			
Age, y	61 (52-69)	66 (58-72)	<.001
Sex, M:F	467:439	153:131	.493
Preoperative serum creatinine, mg/dL	0.78 (0.66-0.90)	0.82 (0.67-0.93)	.039
Preoperative eGFR, mL/min/1.73 m^2	95.1 (81.2-111.5)	88.0 (74.6-108.2)	.002
Type of surgery			
Aortic valve surgery	268 (82.7)	56 (17.3)	.001
Mitral valve surgery	295 (71.8)	116 (28.2)	.010
Double-valve surgery	122 (71.3)	49 (28.7)	.112
Valve + CABG surgery	56 (74.7)	19 (25.3)	.758
Valve + aorta surgery	103 (79.2)	27 (20.8)	.380
Tricuspid valve surgery	37 (78.7)	10 (21.3)	.671
Others*	25 (78.1)	7 (21.9)	.789
Renal outcomes			
Acute kidney disease at 3 mo	43/906 (4.7)	43/284 (15.1)	<.001
Chronic kidney disease at 12 mo	36/866 (4.2)	31/248 (12.5)	<.001
Postoperative outcomes			
In-hospital mortality	6 (0.7)	19 (6.7)	<.001
30-d mortality	5 (0.6)	10 (3.5)	<.001
In-hospital renal replacement therapy	0	27 (9.5)	<.001

Values are median (interquartile range) or number (percent). AKI, acute kidney disease (at 3 months), and chronic kidney disease (at 12 months) were defined according to Kidney Disease: Improving Global Outcomes guidelines. Normal preoperative renal function group = patients with baseline estimated glomerular filtration rate ≥60 mL/min/1.73 m^2. Double-valve surgery = aortic and mitral valve surgery. *AKI*, Acute kidney injury; *M*, male; *F*, female; *eGFR*, estimated glomerular filtration rate; *CABG*, coronary bypass grafting. *Others surgery included atrial fibrillation surgery (n = 5), ventricular septal defect repair (n = 1), myomectomy (n = 9), myxoma excision (n = 16), and pericardiectomy (n = 1).

cardiac procedures (Table 1). Patients <18 years old, undergoing combined congenital heart surgery, or with acute coronary syndrome or ST-elevation myocardial infarction were excluded.

Data Collection

Data on patients from the electronic database of the medical record system were retrospectively reviewed. Retrieved preoperative data included demographics, morbidities, European System for Cardiac Operative Risk Evaluation, contrast use within 5 preoperative days, and medications. Intraoperative data included the type of surgery, CPB and aortic crossclamp time, fluid balance and blood loss, and transfusion requirement. Postoperative data included complications, length of stay in the intensive care unit and hospital, and in-hospital mortality. Laboratory data included serum creatinine (sCr) level, hematocrit concentration, and albumin level. In addition, we reviewed reports of transthoracic echocardiography (TTE) preoperatively, at discharge, and 3 and 12 months after surgery. Variables included left ventricular ejection fraction (LVEF), left atrial volume index, right atrial pressure (RAP), right ventricular systolic pressure (RVSP), and the severity of valvular stenosis or regurgitation. HF diagnosis was based on signs or symptoms of volume overload (shortness of breath, orthopnea, edema, or paroxysmal nocturnal dyspnea) and correlated structural/functional abnormalities in TTE (LVEF <40%).[12,13]

Institutional routine sCr assessment included the most recent sCr within 30 days before surgery (median 2.0 [interquartile range 1.0–6.4] days) and daily until discharge. The most recent preoperatively measured sCr within 30 days was used for evaluation of baseline renal function, and sCr values within the postoperative 7 days as well as during 3- and 12-month follow-ups were used for diagnosis of AKI, AKD, and CKD, respectively. We calculated the estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease Formula.[14]

AKI, AKD, and CKD were defined according to the KDIGO guidelines.[15] AKI was defined as a 0.3 mg/dL increase in sCr within 48 hours or a 50% increase within the first 7 postoperative days. Persistent AKI (nonrecovery) was defined as AKI stage ≥1 persisting ≥3 days after AKI diagnosis.[5] In patients with normal preoperative renal function (baseline eGFR ≥60 mL/min/1.73 m^2), AKD and CKD were defined as an eGFR <60 mL/min/1.73 m^2 or end-stage renal disease requiring renal-replacement therapy 3 and 12 months after surgery.[15] In patients with pre-existing renal dysfunction (baseline eGFR <60 mL/min/1.73 m^2), AKD was defined as a 35% decline in eGFR 3 months postsurgery and CKD at 12 months as an eGFR <60 mL/min/1.73 m^2 or end-stage renal disease requiring renal replacement therapy 12 months postsurgery.[15]

Outcomes Assessment

The primary outcome was the development of AKD and CKD according to AKI occurrence in patients with normal preoperative renal function (eGFR ≥60 mL/min/1.73 m^2). For this outcome, the risk of AKD and CKD was assessed according to AKI occurrence, severity, and persistence.

The secondary outcome was the influence of AKI on morbidity and mortality in patients with normal preoperative renal function. At 3 and 12 months after surgery, major adverse kidney events, defined as composite outcomes of death, new dialysis, and worsened kidney function (25% decline in eGFR from baseline),[16,17] and major adverse cardiac events (MACEs), defined as composite outcomes of stroke, HF, and myocardial infarction,[16,17] were assessed. Risk factors contributing to the development of postoperative AKD and CKD were identified. In addition, to investigate the effect of baseline eGFR on kidney disease progression, patients with pre-existing renal dysfunction (baseline eGFR <60 mL/min/1.73 m^2) were followed.

Statistical Analysis

Statistical analyses were performed using SPSS, version 23.0 (IBM Corp, Armonk, NY) and SAS, version 9.4 (SAS Institute Inc., Cary, NC). Continuous variables did not show normal distribution in the Kolmogorov–Smirnov test for normality of distribution, and were analyzed using the Mann–Whitney U test and expressed as median (interquartile range). Dichotomous variables were compared using χ^2 or Fisher exact tests, and expressed as absolute number (percent). The association of postoperative AKI with the development of AKD and CKD was analyzed using the generalized estimating equation method to account for the correlation of the events. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated using logistic regression models. Variables of interest, including "postoperative AKI occurrence," "echocardiographic variables," and "clinically important characteristics potentially affecting renal function," were entered into a multiple logistic model to assess their impact on AKD and CKD development. Only echocardiographic data obtained before the point at which each kidney event was assessed were included in the multivariable model. In addition, variables with a P value < .05 in the univariate analysis were preferentially included within the scope of satisfying the rule of 10 and increasing the predictive power of the model. P values < .05 were considered statistically significant.

RESULTS

Of the 1519 cases, 52 patients <18 years old and 81 patients undergoing combined congenital heart surgery were excluded. A total of 1386 patients were enrolled and divided into a normal preoperative renal function group (baseline eGFR ≥60 mL/min/1.73 m^2, n = 1190 [85.9%]) and a pre-existing renal dysfunction group (baseline eGFR <60 mL/min/1.73 m^2, n = 196 [14.1%]). There were no missing data until 3 months after surgery, and 6.8% of patients were lost to follow-up 12 months after surgery in the normal preoperative renal function group.

Normal Preoperative Renal Function Group

Baseline characteristics. Patients who developed AKI were older and had a greater incidence of congestive HF and lower serum albumin levels preoperatively compared with patients who did not develop AKI (Table 1 and Table E1).

Postoperative AKI and development of AKD and CKD. The incidence of postoperative AKI was 23.9% (n = 284). The prevalence of AKD (15.1% vs 4.7%, P < .001) and CKD (12.5% vs 4.2%, P < .001) was significantly greater in patients with AKI than in patients without AKI (Table 1 and Figure 1).

AKI occurrence increased the risk of AKD 3 months after surgery (OR, 3.58; 95% CI, 2.29-5.59, P < .001) and CKD 12 months after surgery (OR, 3.21; 95% CI, 1.96–5.29, P < .001) according to the generalized estimating equation method for analyzing the primary outcome of the study. As AKI stages increased, the risk of AKD (P = .027) and CKD (P = .003) increased in a graded manner. Early AKI recovery, defined as an absence of AKI diagnostic criteria 3 days after AKI diagnosis, occurred in 88.4% of patients with AKI. However, even though there was full recovery of renal function within 3 days after AKI diagnosis, these patients were still at increased risk for AKD and CKD, with relative risks of 3.21 and 2.86, respectively. Furthermore, in patients with persistent AKI, the relative risk for AKD and CKD was 4 times greater than the patients who had AKI that was not

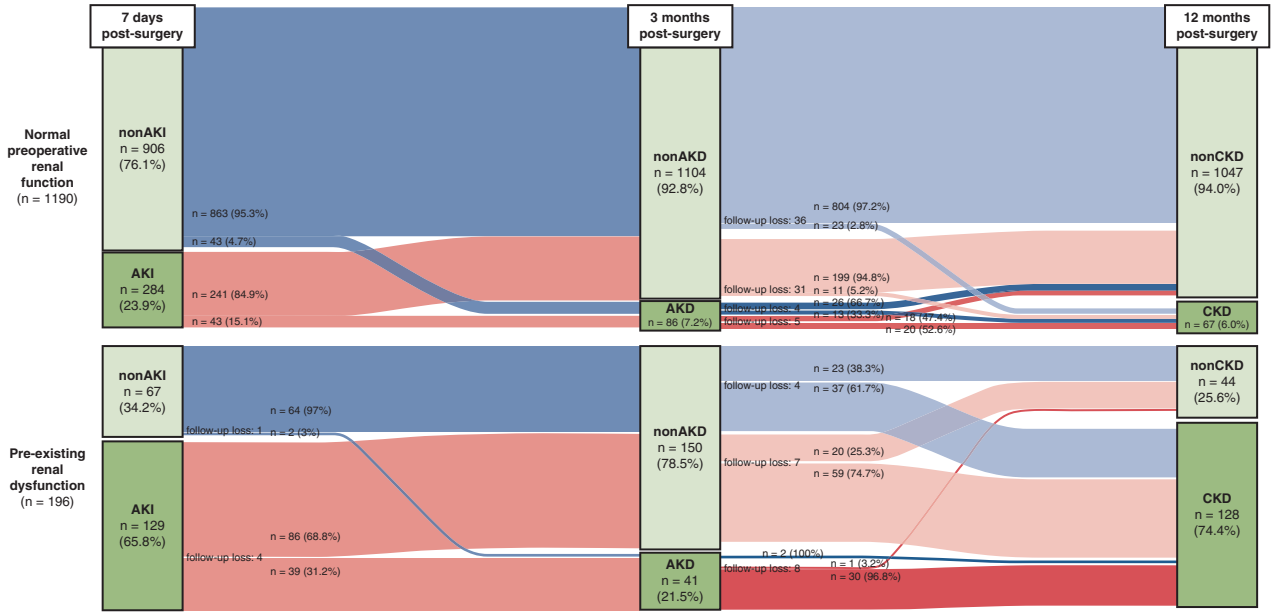

FIGURE 1. A Sankey diagram showing postoperative AKI and the development of AKD and CKD in valvular heart surgery. AKI, AKD, and CKD were diagnosed at postoperative 7 days, 3 months, and 12 months, respectively, according to the Kidney Disease: Improving Global Outcomes guidelines. Normal preoperative renal function group = baseline eGFR ≥60 mL/min/1.73 m^2; pre-existing renal dysfunction group = baseline eGFR <60 mL/min/1.73 m^2. *AKI*, Acute kidney injury; *AKD*, acute kidney disease; *CKD*, chronic kidney disease.

persistent, with relative risks equal to 12.07 and 10.54, respectively (Table 2).

Postoperative AKI and prognosis. Compared with patients without AKI, patients with AKI had significantly greater incidences of major adverse kidney events and MACEs 3 and 12 months after surgery (all $P < .001$) (Table 3). Among patients with AKI, patients having persistent AKI had significantly greater mortality rates at postoperative months 3 (29.7% vs 3.6%, $P < .001$) and 12 (32.4% vs 4.5%, $P < .001$) as well as dialysis rates at postoperative months 3 (48.6% vs 5.7%, $P < .001$) and 12 (48.6% vs 5.7%, $P < .001$), compared with patients having early recovery of AKI.

Of the MACEs, HF incidence was significantly greater in patients with AKI than in patients without AKI at postoperative months 3 (9.3% vs 3.0%, $P < .001$) and 12 (10.4% vs 3.4%, $P < .001$), whereas there was no difference in the incidences of stroke (2.8% vs 4.6%, $P = .128$ and 3.0% vs 4.6%, $P = .193$) and myocardial infarction (0.4% vs 0, $P = .262$ and 0.4% vs 0, $P = .262$).

Risk factors for AKI, AKD, and CKD. In the multivariable logistic regression analysis, advanced age and low preoperative albumin level were risk factors for AKI (Table 4). Independent risk factors for persistent AKI included diabetes (OR, 2.76; 95% CI, 1.31–5.82, $P = .008$),

TABLE 2. Risks for development of AKD and CKD according to AKI occurrence, stage, and persistence in the normal preoperative renal function group

	AKD		CKD	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
AKI occurrence	3.58 (2.29-5.59)	<.001	3.21 (1.96-5.29)	<.001
AKI stage				
0	Reference	–	Reference	–
1	3.02 (1.82-5.02)	<.001	2.34 (1.31-4.19)	<.001
2	5.20 (2.26-12.00)	<.001	6.11 (2.61-14.30)	<.001
3	6.20 (2.65-14.51)	<.001	10.19 (2.94-35.34)	<.001
Non-AKI	Reference	–	Reference	–
Early recovery	3.21 (1.98-5.20)	<.001	2.86 (1.68-4.86)	<.001
Nonrecovery	12.07 (5.56-26.21)*	<.001	10.54 (4.01-27.76)*	<.001

Normal preoperative renal function group = patients with baseline estimated glomerular filtration rate ≥60 mL/min/1.73 m^2. AKI, AKD (at 3 months), and CKD (at 12 months) were defined according to Kidney Disease: Improving Global Outcomes guidelines. Early recovery or non-recovery AKI was defined as absence or presence of AKI at 3 days after AKI diagnosis. *AKD*, Acute kidney disease; *CKD*, chronic kidney disease; *OR*, odds ratio; *CI*, confidence interval; *AKI*, acute kidney injury. *$P < .001$ compared with early recovery of AKI.

TABLE 3. Morbidity and mortality in patients without and with AKI in the normal preoperative renal function group

	Patients without AKI (n = 906)	Patients with AKI (n = 284)	*P* value
Postoperative 3 mo			
Death	6 (0.7)	20 (7.0)	<.001
Dialysis	2 (0.2)	32 (11.3)	<.001
MAKE	83 (9.2)	77 (27.1)	<.001
MACE	51 (5.6)	39 (13.7)	<.001
Postoperative 12 mo			
Death	9 (1.0)	23 (8.1)	<.001
Dialysis	2 (0.2)	32 (11.3)	<.001
MAKE	150 (16.6)	94 (33.1)	<.001
MACE	57 (6.3)	42 (14.8)	<.001

Values are number (percent). Normal preoperative renal function group = patients with baseline estimated glomerular filtration rate ≥60 mL/min/1.73 m^2. *AKI*, Acute kidney injury; *MAKEs*, major adverse kidney events, which were defined as composite outcomes of death, new dialysis, and worsen kidney function (defined as 25% decline from baseline in estimated glomerular filtration rate); *MACEs*, major adverse cardiac events, which were defined as composite outcomes of stroke, heart failure, and myocardial infarction.

preoperative LVEF (OR, 0.98; 95% CI, 0.95-1.00, $P = .034$), preoperative albumin level (OR, 0.30; 95% CI, 0.17-0.52, $P < .001$), and intraoperative erythrocyte transfusion (OR, 1.65; 95% CI, 1.32-2.07, $P < .001$).

AKI was an independent risk factor associated with the development of both AKD (OR, 2.33; 95% CI, 1.45-3.73, $P < .001$) and CKD (OR, 2.00; 95% CI, 1.05-3.79, $P = .034$), after adjusting for other influencing factors. Advanced age and low preoperative albumin level were also risk factors for AKD and CKD (Table 4). When AKD was introduced instead of AKI to the multivariable model for CKD, AKD was the most powerful risk factor for CKD (OR, 16.75; 95% CI, 8.20-34.23, $P < .001$), and the statistical significance of albumin as a risk factor vanished. In addition, HF and greater RVSP 3 months after surgery were identified as risk factors for CKD development (Table 4). LVEF was not revealed as an independent risk factor for AKI, AKD, or CKD.

Pre-existing Renal Dysfunction Group

Compared with the normal preoperative renal function group, the pre-existing renal dysfunction group was older and had significantly greater incidences of in-hospital mortality and renal-replacement therapy (all $P < .001$) (Table E2). The incidence of postoperative AKI was 65.8%. The prevalence of AKD (31.2% vs 3.0%, $P < .001$) and CKD (80.9% vs 62.9%, $P = .009$) was greater in patients with AKI than in patients without AKI (Figure 1). The proportion of patients who did not have an eGFR that was back to the baseline value 12 months after surgery was also greater in patients with AKI (55.5% vs 24.2%, $P < .001$). AKI occurrence increased the risk of AKD and CKD 12 months after surgery, with relative risks of 14.51 and 2.60, respectively. The risk of AKD ($P < .001$) and CKD ($P = .011$) increased in a graded manner related to AKI stages and persistence (Table E3).

In the pre-existing renal dysfunction group, the incidences of AKI, AKD, and CKD 12 months after surgery were greater (all $P < .001$) than in the normal preoperative

TABLE 4. Multivariate logistic regression analysis of risk factors for AKI, AKD, and CKD in the normal preoperative renal function group

Event	Risk factor	OR (95% CI)	*P* value
AKI	Age, y	1.03 (1.02-1.05)	<.001
	Preoperative heart failure	1.68 (1.12-2.52)	.012
	Preoperative right atrial pressure, mm Hg*	1.03 (1.00-1.06)	.034
	Preoperative albumin level, g/dL	0.52 (0.39-0.70)	<.001
	Cardiopulmonary bypass time (per 10 min)	1.09 (1.06-1.13)	<.001
	Previous cardiac surgery	1.55 (1.05-2.30)	.028
AKD	Age, y	1.05 (1.03-1.08)	<.001
	Diabetes	1.81 (1.09-3.03)	.023
	Preoperative albumin level, g/dL	0.45 (0.29-0.68)	<.001
	Intraoperative erythrocyte transfusion, units	1.28 (1.07-1.53)	.008
	Postoperative AKI	2.33 (1.45-3.73)	<.001
CKD	Age, y	1.07 (1.03-1.11)	<.001
	Preoperative albumin level, g/dL	0.40 (0.22-0.72)	.002
	Postoperative AKI	2.00 (1.05-3.79)	.034
	Heart failure at postoperative 3 mo*	7.18 (1.61-32.08)	.010
	Right ventricular systolic pressure at postoperative 3 mo, mm Hg*	1.03 (1.01-1.06)	.006

Normal preoperative renal function group = patients with baseline estimated glomerular filtration rate ≥60 mL/min/1.73 m^2. *OR*, Odds ratio; *CI*, confidence interval; *AKI*, acute kidney injury; *AKD*, acute kidney disease; *CKD*, chronic kidney disease. *Values were measured with transthoracic echocardiography.

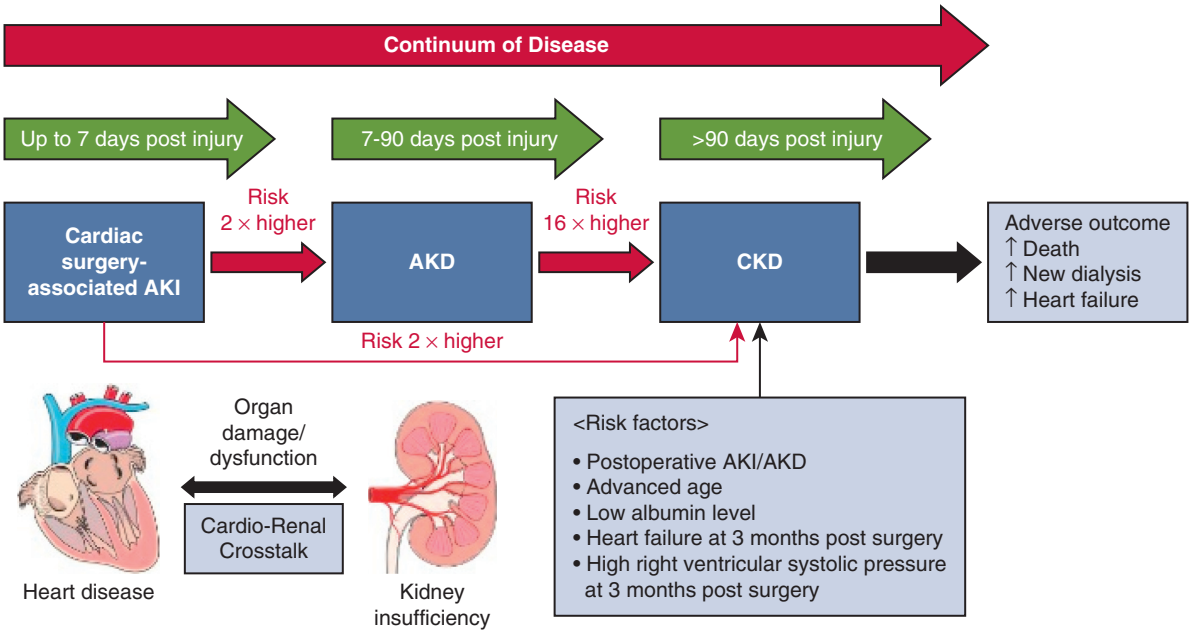

FIGURE 2. A close link between postoperative AKI and CKD with an intermediary role for AKD, and the importance of cardiorenal cross talk. *AKI*, Acute kidney injury; *AKD*, acute kidney disease; *CKD*, chronic kidney disease.

renal function group (Table E2). Pre-existing renal dysfunction itself was associated with increased risk of AKD (OR, 3.51; 95% CI, 2.33-5.28, $P < .001$) and CKD (OR, 45.46; 95% CI, 29.80-68.35, $P < .001$). Although pre-existing renal dysfunction is a major risk factor of CKD 12 months after surgery, AKI also remained as an important risk factor of CKD 12 months after surgery (even after adjusting for the influence of pre-existing renal dysfunction; the effect of the interaction between pre-existing renal dysfunction and postoperative AKI on the development of CKD yielded an OR of 0.87 (95% CI, 0.37-2.00, $P = .719$).

DISCUSSION

In this retrospective review of patients undergoing cardiac valvular surgery, we found a close link between the occurrence of postoperative AKI and CKD development with a distinct intermediary role for AKD, which was associated with dismal prognoses in terms of renal, cardiac, and mortality outcomes. The AKI-associated risk for CKD development escalated in a graded manner related to the degree and persistence of AKI, independent of preoperative renal function. Cardiac dysfunction, manifested as HF and elevated RVSP at the 3-month follow-up, was an independent risk factor for CKD in patients with normal preoperative renal function (Figure 2).

As evidenced by a firm bidirectional relationship between AKI and CKD, these conditions are viewed as an integrated clinical syndrome of diminished renal mass that decreases GFR.[10] Consistent with this view, AKD was recently defined to be acute or subacute kidney damage and/or loss of kidney function from 7 to 90 days after insult.[10] Ninety days after renal injury is suggested to be an appropriate time point to assess the post-AKI transition to CKD, allowing time for both recovery of muscle mass and renal function.[16] In the continuum of the disease process, the AKD phase could be an important window in which critical interventions or harm to the kidney might alter the course of disease progression.[5] However, no study has comprehensively addressed AKI to CKD progression via AKD in patients undergoing cardiac surgery with the unique AKI-instigating factor CPB. Current evidence is limited to delineating the relationship between postoperative AKI and long-term CKD development,[2,4,7,18] without data showing the intermediary role of AKD and other relevant risk factors. Moreover, related studies of patients with valvular heart surgery are even more scarce, despite a greater AKI incidence in valvular heart surgery than in coronary artery bypass graft surgery patients.[19]

In our analyses, AKI significantly increased the risk of development of AKD and CKD 12 months after surgery, regardless of pre-existing renal dysfunction. Although the pre-existing renal dysfunction group had a greater prevalence and increased risk of AKD and CKD 12 months after surgery than the normal preoperative renal function group, the effect of AKI on the development of AKD and CKD did not differ with regards to patient baseline renal function. In the context of AKI severity, the incidences of AKD and CKD 12 months after surgery increased as the AKI stage increased. Although one study found a close link between AKI and AKD,[20] it did not define AKD according to the KDIGO guidelines and involved various types of cardiac surgeries. Moreover, it did not assess actual progression to

CKD and had a considerable amount of missing data (80%) related to AKD assessment, which limits further direct comparisons to our study. In terms of AKI duration, patients with AKI lasting more than 3 days were reported to have a 13-fold increased risk of CKD development than patients without AKI.[2] Further, incomplete recovery of renal function after AKI also increased the risk of CKD progression.[7,21] Here, we found that patients with AKI with early recovery of renal function still had 3 times greater risk of progression to AKD and CKD than patients without AKI, whereas the risk increased to 12 times greater in patients with persistent AKI.

The association of pre-existing renal dysfunction and AKI with a poor postoperative outcome is well-demonstrated.[3,20] We found that the pre-existing renal dysfunction group had a greater incidence of in-hospital mortality and renal-replacement therapy than the normal preoperative renal function group. Even after we excluded patients with pre-existing renal dysfunction, compared with patients without AKI, patients with AKI with preserved baseline renal function had a significantly greater prevalence of new dialysis, worsened kidney function, and death at 3- and 12-month follow-ups. Our results are consistent with previous studies showing a strong association between postoperative AKI and short- and long-term morbidity and mortality.[22,23]

Interestingly, the incidences of MACEs, including HF 3 and 12 months after surgery, were also significantly greater in patients with AKI than patients without AKI. Cross-talk between the kidney and heart has recently become more acknowledged. After cardiac surgery, the risk of cardiac dysfunction, including HF and myocardial infarction, was greater in patients with AKI than in patients without AKI.[23,24] Furthermore, in patients with CKD, HF was associated with a 29% greater composite risk of either end-stage renal disease or a 50% decline in eGFR.[11] However, in patients undergoing cardiac surgery, the influence of cardiac dysfunction on progressive kidney disease is not well studied. Notably, our study identified HF 3 months after surgery to be an independent risk factor for CKD development. In patients with impaired cardiac output, forward failure from a decrease in arterial perfusion[25] as well as backward failure from right ventricular dysfunction[26] might contribute to renal dysfunction. In most patients with valvular heart disease, pulmonary hypertension is not readily resolved after surgery,[27,28] and chronic right ventricular pressure overload gradually leads to structural and functional deterioration of the right ventricle.[29] Accordingly, we found that the median values for RAP and RVSP in TTE (before surgery, at discharge, as well as 3 and 12 months after surgery) were significantly greater in patients with AKI than in patients without AKI (all $P < .001$) (Table E4). Notably, elevated RVSP 3 months after surgery was an independent risk factor for CKD 12 months after surgery.

In addition to avoiding further renal insults, identifying risk factors for progressive kidney disease could guide timely follow-up and application of therapeutic measures in patients at risk for CKD progression after cardiac surgery-associated AKI. In this regard, our study has several strengths. This is the first study to encompass comprehensive data sets of serially assessed renal and cardiac functions during the postoperative 12 months in a cohort of patients undergoing valvular heart surgery. Our study provides primary evidence that AKI, regardless of early recovery, is associated with CKD development, and concomitantly demonstrates the importance of an intermediary role for AKD (the most powerful risk factor for CKD 12 months after surgery), connecting these 2 diseases. We also provide detailed risk profiles for an association between AKI and CKD in relation to AKI degree, persistence, and patient baseline renal function. Furthermore, we identified the importance of cardiorenal crosstalk in relation to kidney disease progression, showing that the presence of HF or increased RVSP at the 3-month follow-up are predictive of CKD development and discouraging renal/cardiac outcomes. Lastly, we reaffirmed well-known risk factors for progressive kidney disease, including diabetes, long CPB time, and blood transfusion.[3,30,31] Advanced age and low preoperative albumin levels were common risk factors for AKI, AKD, and CKD 12 months after surgery. These findings may be helpful for identifying patients without AKI with preserved baseline renal function who may benefit from close postsurgery follow-up because 4.7% and 2.5% of these patients in our study developed de novo AKD and CKD, respectively. Future studies are warranted to confirm whether correcting the preoperative albumin levels[32] or reducing RVSP via aggressive therapies may improve renal function and overall outcomes.

This study is inherently limited by its retrospective nature. Although HF and greater RVSP 3 months postsurgery were identified as independent risk factors for CKD development in the present study, we could not determine the cause-and-effect relationship between kidney disease progression and cardiac dysfunction. Another limitation is the competing risk imposed by in-hospital mortality cases after AKI (6.7%) and the lost data at the 12-month follow-up (6.8% patients), although perioperative and 3-month follow-up data were complete. In addition, the sole use of sCr measurement without urine output may have underestimated the AKI incidence.[33] However, a previous meta-analysis of cohort studies reported no differences among cohorts that included urine output in the definition of AKI and those that did not.[34] Lastly, elevated RVSP 3 months after surgery was an independent risk factor for CKD 12 months after surgery, whereas RAP 3 months after surgery did not show an association. RAP assessment through echocardiography is only a rough estimate based on collapsibility and diameter of the inferior vena cava,

which may have confounded our results. Increased RVSP as a significant risk factor of CKD could incorporate the meaning of increased RAP that results in organ congestion, which can only be accurately assessed by invasive measurements.

In conclusion, we observed a close relationship between AKI occurrence and CKD development with a distinct intermediary role for AKD in patients undergoing valvular heart surgery. Thus, all patients with postoperative AKI should be assessed for adverse renal and cardiac outcomes, even after early and complete recovery. Multidisciplinary and close follow-ups to assess renal and cardiac functions should also be considered when patients without AKI normal preoperative renal function have the proposed risk factors and/or develop de novo AKD. Future prospective studies are required to determine the management strategies to detect early renal deterioration and promote recovery.

Conflict of Interest Statement

All authors have nothing to disclose with regard to commercial support.

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Key Words: acute kidney disease, acute kidney injury, chronic kidney disease, heart failure, valvular heart surgery

TABLE E1. Clinical data in the normal preoperative renal function group

	Patients without AKI (n = 906)	Patients with AKI (n = 284)	*P* value
Comorbidities			
Hypertension	395 (43.6)	134 (47.5)	.247
Diabetes mellitus	136 (15.0)	62 (21.8)	.007
Congestive heart failure	101 (11.1)	63 (22.2)	<.001
Myocardial infarct within 1 mo	11 (1.2)	4 (1.4)	.798
Cerebrovascular disease	113 (12.5)	46 (16.2)	.107
Peripheral vascular disease	4 (0.4)	6 (2.1)	.007
Chronic obstructive pulmonary disease	20 (2.2)	14 (5.0)	.015
Previous cardiac surgery	120 (13.2)	76 (26.8)	<.001
Medications			
ACEi/ARB	424 (46.8)	133 (46.8)	.993
β-blockers	284 (31.3)	94 (33.1)	.580
Calcium channel blockers	164 (18.1)	59 (20.8)	.314
Diuretics	536 (59.2)	222 (78.2)	<.001
Non-steroidal anti-inflammatory drugs	38 (4.3)	16 (5.7)	.321
Statin	361 (39.8)	116 (40.8)	.764
Perioperative conditions			
Left ventricular ejection fraction (%)	64 (58-70)	60 (49-67)	<.001
EuroSCORE	4 (3-6)	5 (3-8)	<.001
Contrast use with 5 d before surgery	173 (19.1)	58 (20.4)	.622
Hematocrit concentration, %	38 (35-41)	36 (33-40)	<.001
Serum albumin level, g/dL	4.1 (3.8-4.4)	3.9 (3.5-4.2)	<.001
Aortic crossclamp time, min	77.5 (55.0-106.3)	90.0 (68.0-125.8)	<.001
Cardiopulmonary bypass time, min	105.0 (77.5-139.0)	126.0 (95.0-167.3)	<.001
Postoperative outcomes			
Prolonged ventilation (>48 h)	32 (3.5)	64 (22.5)	<.001
Reintubation	13 (1.4)	22 (7.8)	<.001
Reoperation due to bleeding	31 (12.2)	30 (30.0)	<.001
Wound infection	17 (1.9)	16 (5.6)	.001
Intensive care unit stay, d	2 (1-2)	2 (2-4)	<.001
Hospital stay, d	11 (9-14)	15 (10-23)	<.001

Values are median (interquartile range) or number (percent). Normal preoperative renal function group = patients with baseline estimated glomerular filtration rate $\geq$60 mL/min/1.73 m^2. *AKI*, Acute kidney injury; *ACEi*, angiotensin-converting enzyme inhibitors; *ARB*, angiotensin receptor blockers; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation.

TABLE E2. Clinical data in the normal preoperative renal function and pre-existing renal dysfunction groups

	All patients (N = 1386)	Normal preoperative renal function group (n = 1190)	Pre-existing renal dysfunction group (n = 196)	*P* value
Patient characteristics				
Age, y	63 (54-71)	62 (53-70)	70 (61-75)	<.001
Sex, M:F	709:677 (48.8)	620:570 (47.9)	89:107 (54.6)	.082
Preoperative sCr, mg/dL	0.83 (0.68-0.99)	0.79 (0.66-0.91)	1.43 (1.15-2.21)	<.001
Preoperative eGFR, mL/min/1.73 m^2	89.2 (71.7-107.6)	93.7 (79.1-110.9)	45.5 (30.3-52.8)	<.001
Type of surgery				
Aortic valve surgery	380 (27.4)	324 (27.2)	56 (28.6)	.696
Mitral valve surgery	471 (34.0)	411 (34.5)	60 (30.6)	.282
Double-valve surgery	201 (14.5)	171 (14.4)	30 (15.3)	.730
Valve + CABG surgery	97 (7.0)	75 (6.3)	22 (11.2)	.012
Valve + aorta surgery	144 (10.4)	130 (10.9)	14 (7.1)	.108
Tricuspid valve surgery	61 (4.4)	47 (3.9)	14 (7.1)	.043
Others*	32 (2.3)	32 (2.7)	0	.020
Renal outcomes				
Acute kidney injury	413/1386 (29.8)	284/1190 (23.9)	129/196 (65.8)	<.001
Acute kidney disease	127/1381 (9.2)	86/1190 (7.2)	41/191 (21.5)	<.001
Chronic kidney disease	195/1286 (15.2)	67/1114 (6.0)	128/172 (74.4)	<.001
Postoperative outcomes				
In-hospital mortality	41 (3.0)	25 (2.1)	16 (8.2)	<.001
30-day mortality	21 (1.5)	15 (1.3)	6 (3.1)	.056
In-hospital renal-replacement therapy	89 (6.4)	27 (2.3)	62 (31.6)	<.001

Values are median (interquartile range) or number (percent). Normal preoperative renal function group = patients with baseline eGFR ≥60 mL/min/1.73 m^2; pre-existing renal dysfunction group = patients with baseline eGFR <60 mL/min/1.73 m^2; double-valve surgery = aortic and mitral valve surgery. *M*, Male; *F*, female; *sCr*, serum creatinine; *eGFR*, estimated glomerular filtration rate; *CABG*, coronary bypass grafting. *Others surgery included atrial fibrillation surgery (n = 5), ventricular septal defect repair (n = 1), myomectomy (n = 9), myxoma excision (n = 16), and pericardiectomy (n = 1).

TABLE E3. Risk for development of AKD at 3 months and CKD at 12 months according to AKI occurrence, stage, and persistence in the pre-existing renal dysfunction group

	AKD		CKD	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
AKI occurrence	14.51 (3.38-62.32)	<.001	2.60 (1.28-5.27)	<.001
AKI stage				
0	Reference	–	Reference	–
1	5.42 (1.07-27.33)	.041	1.93 (0.82-4.53)	.132
2	5.42 (0.69-42.26)	.107	1.44 (0.41-5.13)	.570
3	31.45 (7.06-140.10)	<.001	4.10 (1.52-11.12)	.006
Non-AKI	Reference	–	Reference	–
Early recovery	9.78 (2.21-43.22)	.003	2.53 (1.21-5.33)	.014
Non-recovery	38.86 (8.04-187.74)*	<.001	2.68 (0.83-8.67)	.101

Pre-existing renal dysfunction group = patients with baseline estimated glomerular filtration rate <60 mL/min/1.73 m^2. *AKD*, Acute kidney disease; *CKD*, chronic kidney disease; *OR*, odds ratio; *CI*, confidence interval; *AKI*, acute kidney injury. *P < .001 compared with early recovery of AKI.

ADULT

TABLE E4. Echocardiographic findings and heart failure in the normal preoperative renal function group

	Patients without AKI (n = 906)	Patients with AKI (n = 284)	*P* value
Right atrial pressure, mm Hg			
Preoperative	5 (5-10)	10 (5-15)	<.001
At discharge	5 (5-10)	10 (5-15)	<.001
Postoperative 3 mo	5 (5-10)	10 (5-10)	<.001
Postoperative 12 mo	5 (5-5)	5 (5-10)	<.001
Right ventricular systolic pressure, mm Hg			
Preoperative	40 (30-51)	46 (35.5-56.5)	<.001
At discharge	35 (28-43)	39.5 (33-49.8)	<.001
Postoperative 3 mo	33 (26-40)	37 (30-48.5)	<.001
Postoperative 12 mo	28 (24-35)	35 (25.8-41)	<.001
Heart failure, n*			
Preoperative	101 (11.1)	63 (22.2)	<.001
At discharge	22 (2.4)	24 (8.5)	<.001
Postoperative 3 mo	27 (3.0)	26 (9.2)	<.001
Postoperative 12 mo	31 (3.4)	29 (10.2)	<.001

Values are median (interquartile range) or number (percent). Normal preoperative renal function group = patients with baseline estimated glomerular filtration rate ≥60 mL/min/1.73 m^2. *AKI*, Acute kidney injury. *Heart failure diagnosis was based on signs or symptoms of volume overload and correlated structural/functional abnormalities in transthoracic echocardiography (left ventricular ejection fraction <40%).