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Acute-on-chronic kidney injury at hospital discharge is associated with long-term dialysis and mortality

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Existing chronic kidney disease (CKD) is among the most potent predictors of postoperative acute kidney injury (AKI). Here we quantified this risk in a multicenter, observational study of 9425 patients who survived to hospital discharge after major surgery. CKD was defined as a baseline estimated glomerular filtration rate <45 ml/min per 1.73 m^2. AKI was stratified according to the maximum simplified RIFLE classification at hospitalization and unresolved AKI defined as a persistent increase in serum creatinine of more than half above the baseline or the need for dialysis at discharge. A Cox proportional hazard model showed that patients with AKI-on-CKD during hospitalization had significantly worse long-term survival over a median follow-up of 4.8 years (hazard ratio, 3.3) than patients with AKI but without CKD. The incidence of long-term dialysis was 22.4 and 0.17 per 100 person-years among patients with and without existing CKD, respectively. The adjusted hazard ratio for long-term dialysis in patients with AKI-on-CKD was 19.8 compared to patients who developed AKI without existing CKD. Furthermore, AKI-on-CKD but without kidney recovery at discharge had a worse outcome (hazard ratios of 4.6 and 213, respectively) for mortality and long-term dialysis as compared to patients without CKD or AKI. Thus, in a large cohort of postoperative patients who developed AKI, those with existing CKD were at higher risk for long-term mortality and dialysis after hospital discharge than those without. These outcomes were significantly worse in those with unresolved AKI at discharge.

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Acute kidney injury (AKI) is a serious complication of surgery, resulting in a prolonged hospital stay and high mortality.[1] AKI develops in 5–60% of postoperative patients and is associated with hospital mortality rates of 60–90%.[2–4] Recently, the adverse effects of AKI on long-term patient outcomes were further confirmed in many studies.[5,6] Although the risk of death, cardiovascular events, and hospitalization rises sharply in patients with an estimated glomerular filtration rate (eGFR) <45 ml/min per 1.73 m^2 (ref. 7), the long-term effect after acute-on-chronic kidney disease (CKD–AKI) in the critical setting[5,6,8] is poorly studied. Globally, the increasing incidence and prevalence of chronic kidney disease (CKD) is associated with adverse health outcomes and high health-care costs. Existing CKD appears to be among the most potent predictors of AKI following major surgery;[9] until recently, little is known about clinical outcomes, especially long-term outcomes, among patients who have CKD and experience superimposed AKI (CKD–AKI).[10] The high rate of non-recovered kidney function among patients with CKD–AKI contrasts sharply with observations made among patients without prior CKD.[7] Non-recovery of renal function after AKI may be an important contributor to growth in the number of incident end-stage renal disease (ESRD) cases out of proportion to the increase in the prevalence of CKD.[11] The Acute Dialysis

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Initiative Group introduced a classification system for AKI (risk, injury, failure, loss, and end stage (RIFLE)) to provide a standardized evaluation of AKI.[12] Although the disease course and long-term outcome are thought to be different in AKI patients with or without prior CKD requiring dialysis, no study has compared the rate of mortality or long-term dialysis between CKD–AKI and non-CKD–non-AKI patients within the same cohort.[13] The current study was designed to determine the outcomes among patients grouped by different CKD and AKI status. We hypothesized that hospital survival patients with CKD–AKI have higher risks for long-term mortality and dialysis dependence than AKI patients without a prior CKD. The long-term outcomes by different levels of AKI, as defined by RIFLE criteria in the non-CKD population and by different levels of recovery of renal function in hospital survivors, were also reported.

RESULTS

Demographic characteristics of patients

Among 10,804 enrolled patients (mean age, 59.9 ± 16.8 years), 1379 patients died during hospital admission. A total of 9425 patients survived to hospital discharge and were included for analysis (Figure 1). The Charlson score was 3.5 ± 4.7 and Acute Physiology and Chronic Health Evaluation II (APACHE II) score at intensive care unit (ICU) admission was 10.3 ± 6.6. A total of 351 patients (3.7%) presented with documented CKD, and 192 patients (2%) had ESRD before major surgery. Among the patients who survived to discharge after the index admission, 4393 patients (46.6%) had an episode of AKI during the hospitalization and were categorized as follows: 2434 (25.8%) had 'simplified' RIFLE (sRIFLE)-R, 979 (10.4%) had sRIFLE-I, 745 (7.9%) had sRIFLE-F, and 235 (2.5%) had CKD–AKI. The baseline characteristics of the study population are shown in Table 1.

Of the patients who survived to discharge with or without prior CKD, 4724 (53.2%) and 116 (33.0%) had no AKI during hospital admission, respectively. The kidney recovery rate was higher in AKI patients without CKD than those with CKD (86.7 vs. 72.3%; $P<0.01$). Among patients surviving after the index admission, only 182 patients (2.0%) required long-term dialysis. The rate of patients requiring dialysis at discharge was lower in patients without CKD than in patients with CKD (1.0 vs. 25.6%; $P<0.01$).

Long-term all-cause mortality

After discharge with a median (interquartile range) follow-up of 4.76 years (3.37–6.61 years), the incidences of all-cause mortality were 5.9, 14.0, and 16.7 per 100 person-years among patients without CKD, with CKD, and ESRD, respectively. The Cox proportional hazard model showed that ESRD patients had a significantly worse long-term survival during the follow-up period, with an adjusted hazard ratio (HR) of 4.59 and 95% confidence interval (CI) of 3.69–5.71 ($P<0.001$) with reference to patients without CKD and AKI. Patients with CKD–AKI had a similarly poor

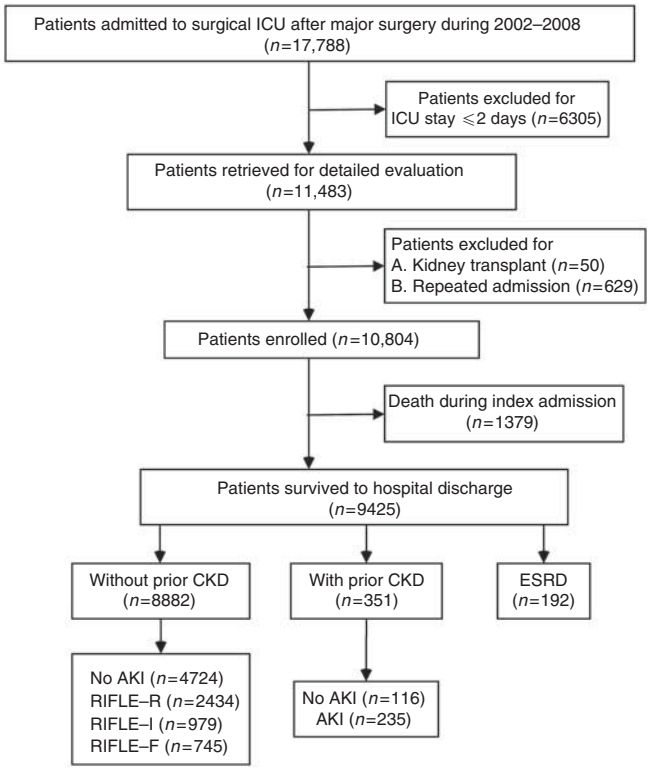

Figure 1 | Flow diagram of the study population. AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; ICU, intensive care unit; RIFLE, risk, injury, failure, loss, and end stage.

outcome (HR, 2.62; 95% CI, 1.92–3.57; $P<0.001$; Table 2). Furthermore, the HRs for death elevated with the increased severity of AKI in patients without prior CKD (HRs, 1.62 in sRIFLE-R, 2.41 in sRIFLE-I, and 3.06 in sRIFLE-F; all $P<0.001$; Table 2 and Figure 2).

Other factors significantly related to long-term mortality were older age (HR, 1.03; 95% CI, 1.02–1.03), male gender (HR, 1.36; 95% CI, 1.25–1.48), tracheostomy (HR, 1.77; 95% CI, 1.53–2.05), cardiopulmonary resuscitation (HR, 1.57; 95% CI, 1.16–2.11), congestive heart failure (HR, 1.43; 95% CI, 1.25–1.64), and coronary artery disease (HR, 1.61; 95% CI, 1.44–1.79).

Furthermore, we performed the outcome analysis by the kidney recovery at the index discharge. As compared with patients without CKD and AKI, those with CKD–AKI without renal function recovery had the highest mortality (HR, 4.59; 95% CI, 3.20–6.45), followed by patients with ESRD (HR, 4.40; 95% CI, 3.54–5.48), CKD with recovery (HR, 3.00; 95% CI, 2.35–3.84), CKD–non-AKI (HR, 2.59; 95% CI, 1.90–3.53), non-CKD without recovery (HR, 2.18; 95% CI, 1.24–3.84), and non-CKD with recovery (HR, 1.96; 95% CI, 1.78–2.16; all $P<0.001$; Figure 3).

In the sensitivity analysis, similar results were noted when we analyzed patients who underwent cardiovascular surgery. After discharge, 486 (17.0%) patients died. ESRD patients had the highest risk of long-term mortality (HR, 6.37; 95% CI, 4.51–9.02, $P<0.001$), and CKD–AKI patients had a

Table 1 | Demographics and clinical characteristics of patients at admission by status of kidney disease (*n*=9425)

	Without prior CKD				Prior CKD					
9425	Non-AKI	Risk	Injury	Failure	No AKI	CKD–AKI	Without-prior CKD	Prior CKD	ESRD	
n	4724	2434	979	745	116	235	8882	351	192	*P*-value[a]
Gender (male)	2819 (59.7)	1439 (59.1)	589 (60.2)	478 (64.2)	77 (66.4)	147 (62.6)	5326 (60.0)	224 (63.8)	104 (54.2)	0.089
Age, mean (s.d.), years	57.2 (16.8)	61.0 (16.7)	61.7 (16.8)	60.6 (16.8)	70.4 (10.7)	69.0 (12.5)	59.0 (16.9)	69.4 (12.0)	63.2 (12.3)	<0.001
sCr, mean (s.d.), (mg/dl) at baseline	0.83 (0.20)	0.70 (0.22)	0.66 (0.28)	0.70 (0.33)	2.12 (0.67)	2.43 (1.10)	0.77 (0.24)	2.33 (0.99)	—	
Max sCr (mg/dl), mean (s.d.), during ICU stay	1.02 (0.27)	1.19 (0.38)	1.63 (0.70)	3.70 (2.23)	2.67 (0.86)	5.40 (2.26)	1.36 (1.04)	4.50 (2.31)	—	
APACHE II at ICU admission	8.5 (5.5)	9.6 (5.7)	11.9 (7.9)	14.2 (7.8)	11.8 (5.5)	14.8 (7.0)	10.0 (6.5)	13.9 (6.7)	16.3 (6.8)	<0.001
Comorbidity										
Charlson score, mean (s.d.)	2.8 (4.3)	4.2 (5.2)	4.6 (5.2)	4.1 (4.5)	3.8 (3.5)	3.9 (2.8)	3.5 (4.7)	3.8 (3.0)	3.0 (2.4)	0.162
Hypertension	1671 (35.4)	949 (39.0)	372 (38.0)	267 (35.8)	78 (67.2)	132 (56.2)	3260 (36.7)	210 (59.8)	68 (35.4)	<0.001
Diabetes mellitus	774 (16.4)	533 (21.9)	234 (23.9)	195 (26.2)	55 (47.4)	114 (48.5)	1737 (19.6)	169 (48.2)	89 (46.4)	<0.001
Liver cirrhosis	102 (2.2)	151 (6.2)	83 (8.5)	87 (11.7)	5 (4.3)	14 (6.0)	423 (4.8)	19 (5.4)	12 (6.3)	0.551
CHF	195 (4.1)	211 (8.7)	147 (15.0)	145 (19.5)	25 (21.6)	59 (25.1)	698 (7.9)	84 (23.9)	34 (17.7)	<0.001
Chronic hepatitis	134 (2.8)	165 (6.8)	95 (9.7)	96 (12.9)	6 (5.2)	17 (7.2)	490 (5.5)	23 (6.6)	14 (7.3)	0.414
COPD	145 (3.1)	100 (4.1)	48 (4.9)	35 (4.7)	4 (3.5)	8 (3.4)	328 (3.7)	12 (3.4)	4 (2.1)	0.487
CAD	1939 (41.1)	1062 (43.6)	393 (40.1)	253 (34.0)	34 (29.3)	56 (23.8)	3647 (41.1)	90 (25.6)	48 (25.0)	<0.001
Atrial fibrillation	246 (5.2)	195 (8.0)	96 (9.8)	74 (9.9)	6 (5.2)	26 (11.1)	611 (6.9)	32 (9.1)	19 (9.9)	0.079
Cancer	1941 (41.1)	1061 (43.6)	395 (40.4)	243 (32.6)	32 (27.6)	49 (20.9)	3640 (41.0)	81 (23.1)	47 (24.5)	<0.001
Admission subgroups										
Cardiovascular surgery	1369 (29.0)	670 (27.5)	287 (29.3)	262 (35.2)	64 (55.2)	117 (49.8)	2589 (29.2)	181 (51.57)	96 (50)	<0.001
Thoracic surgery	886 (18.8)	376 (15.5)	116 (11.9)	83 (11.1)	6 (5.2)	16 (6.8)	1461 (16.5)	22 (6.27)	5 (2.60)	
Neurosurgery	1517 (32.1)	547 (22.5)	174 (17.8)	74 (9.9)	12 (10.3)	19 (8.1)	2312 (26.0)	31 (8.83)	6 (3.13)	
General surgery	186 (3.9)	135 (5.6)	51 (5.2)	44 (5.9)	5 (4.3)	6 (2.6)	416 (4.7)	11 (3.13)	5 (2.60)	
After CPR	7 (0.2)	20 (0.8)	30 (3.1)	34 (4.6)	0 (0.0)	5 (2.1)	91 (1.0)	5 (1.42)	5 (2.6)	
Sepsis	748 (15.8)	681 (28.0)	326 (33.3)	262 (35.2)	29 (25.0)	69 (29.4)	2017 (22.7)	98 (27.9)	77 (40.1)	
Acute decompensated hepatic failure	15 (0.3)	20 (0.8)	20 (2.0)	18 (2.4)	0 (0.0)	7 (3.0)	73 (0.8)	7 (2.0)	1 (0.5)	
Interventions										
ECMO	4 (0.1)	8 (0.3)	23 (2.4)	28 (3.8)	0 (0.0)	3 (1.3)	63 (0.7)	3 (0.9)	1 (0.5)	0.906
IABP	43 (0.9)	42 (1.7)	36 (3.7)	38 (5.1)	3 (2.6)	11 (4.7)	159 (1.8)	14 (4.0)	5 (2.6)	0.009
Acute dialysis	—	5 (0.2)	38 (3.9)	140 (18.8)	—	53 (22.6)	185 (2.1)	54 (15.4)	—	<0.001
Ventilator	4135 (87.6)	2182 (89.8)	876 (89.5)	655 (88.0)	105 (90.5)	204 (86.8)	7850 (88.4)	309 (88.0)	170 (88.5)	0.975
Tracheostomy	67 (1.4)	162 (6.7)	151 (15.4)	131 (17.6)	2 (1.7)	18 (7.7)	511 (5.8)	20 (5.7)	10 (5.2)	0.954
Swan–Ganz catheter	1232 (26.1)	605 (24.9)	257 (26.3)	203 (27.3)	59 (50.9)	89 (37.9)	2297 (25.9)	148 (42.2)	77 (40.1)	<0.001
PiCCO	5 (0.1)	9 (0.4)	8 (0.8)	9 (1.2)	0.0	2 (0.9)	54 (0.6)	0.0	2 (1.0)	—
S–B tube	4 (0.9)	9 (0.4)	4 (0.4)	8 (1.1)	0.0	0.00	25 (0.3)	0.0	0.0	—
ICP monitor	180 (3.8)	141 (5.8)	56 (5.7)	20 (2.7)	1 (0.9)	5 (2.1)	397 (4.5)	6 (1.7)	1 (0.5)	0.001
TCP	10 (0.2)	8 (0.3)	11 (1.1)	9 (1.2)	1 (0.9)	1 (0.4)	38 (0.4)	2 (0.6)	4 (2.1)	0.004

Abbreviations: AKI, acute kidney disease; APACHE, Acute Physiology and Chronic Health Evaluation II; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CKD–AKI, acute-on-chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; IABP, intra-aortic balloon pump; ICP, intracranial pressure; ICU, intensive care unit; S–B tube, Sengstaken–Blakemore tube; sCr, serum creatinine; TCP, transcutaneous pacemaker.

The items are expressed by number (percentage) or mean (s.d.).

[a]Trend analysis by analysis of variance among without prior CKD, prior CKD, and ESRD.

Sepsis, with at least two signs of systemic inflammatory response syndrome and clinical evidence of infection.[36]

Acute decompensated hepatic failure, defined for cases in which encephalopathy occurred within 7 days of the onset of jaundice with the acute form of liver failure.[32] CAD; defined by the diagnosis of ischemic heart disease before admission and positive electrocardiographic findings, and CHF; defined as New York Heart Association functional class III or IV, COPD; required long-term bronchodilators or steroids, and CAD is defined by the diagnosis of ischemic heart disease before admission and positive electrocardiographic findings.

Table 2 | Rates and factors adjusted hazard ratio for outcomes in patients with and without prior CKD

	Without prior CKD				Prior CKD		
n at hospital discharge (9425)	Non-AKI 4724	Risk 2434	Injury 979	Failure 745	Non-AKI 116	AKI 235	ESRD 192
Length of hospital stay (days)	19.88 (21.84)	35.57 (32.55)	54.01 (52.88)	73.82 (74.02)	23.72 (37.29)	39.27 (33.70)	42.95 (47.08)
Long-term mortality, *n* (%)	676 (14.3)	666 (27.4)	383 (39.1)	335 (45.0)	45 (38.8)	111 (47.2)	97 (50.5)
HR (95% CI)[a]	1 (reference)	2.08 (1.86–2.31)***	3.22 (2.84–3.65)***	3.75 (3.29–4.27)***	3.09 (2.28–4.17)***	4.19 (3.42–5.11)***	4.43 (3.51–5.37)
HR (95% CI)[b]	1 (reference)	1.62 (1.45–1.81)***	2.41 (2.11–2.75)***	3.06 (2.66–3.53)***	2.62 (1.92–3.57)***	3.58 (2.91–4.41)***	4.62 (3.71–5.76)***
Renal outcomes at hospital discharge							
Recovery[c]	—	1725 (70.9)	380 (38.8)	164 (22.0)	—	170 (72.3)	—
Non-recovery[d]	—	709 (29.1)	599 (61.2)	581 (78.0)	—	65 (27.7)	—
Long-term dialysis, n (%)	13 (0.3)	14 (0.6)	7 (0.7)	58 (5.1)	21 (18.1)	69 (30.3)	—
HR (95% CI)[a]	1 (reference)	2.28 (1.07–4.85)*	3.10 (1.24–7.76)*	22.69 (12.08–42.60)***	79.42 (39.48–159.77)***	181.89 (100.27–329.95)***	
HR (95% CI)[b]	1 (reference)	2.09 (0.97–4.52)	3.19 (1.27–8.03)***	22.35 (11.9–42.1)***	52.0 (25.6–105.8)***	122.9 (66.8–253.9)***	—

Abbreviations: Af, Atrial fibrillation; AKI, acute kidney disease; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; HR, hazard ratio; HTN, hypertension; IABP, intra-aortic balloon pump; ICP, intracranial pressure; RRT, renal replacement therapy; sCr, serum creatinine; TCP, transcutaneous pacemaker.
All $P<0.01$.
[a]Unadjusted HR (95% confidence interval) by log-rank test.
[b]Adjusted HR (95% confidence interval) estimated from logistic regression model, adjusted for age, gender, admission subgroups, intervention (ECMO, ventilator, IABP, ICP, TCP, Swan-Ganz tube, PiCCO, and Sengstaken-Blakemore tube), comorbidity (HTN, DM, liver cirrhosis, CHF, chronic hepatitis, COPD, CAD, Af, and cancer), admission subgroups (Charlson score) by Cox regression modeling.
[c]Kidney recovery existed if the discharge sCr was <50% above the baseline sCr.
[d]Non-recovery existed if there was a persistent increase in sCre >50% above baseline sCr, or need for RRT.
Comparison of outcomes with patients without CKD and AKI: *$P<0.05$; ***$P<0.001$.

Figure 2 | Long-term survival stratified by CKD and AKI. Cox proportional hazard model for long-term survival of patients alive at hospital discharge, stratified by severity of AKI for non-CKD patients and by occurrence of AKI for CKD patients (non-CKD patients were categorized into non-AKI, risk, injury, and failure groups; CKD patients were categorized into non-AKI and AKI groups, all $P<0.001$, non-CKD–non-AKI was the reference). AKI, acute kidney injury; CKD, chronic kidney disease; CKD–AKI, acute-on-chronic kidney disease; ESRD, end-stage renal disease.

Figure 3 | Long-term survival stratified by kidney recovery. Cox proportional hazard model for long-term survival of patients alive at hospital discharge, stratified by the status of kidney recovery. AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; R, recovery; non-R, non-recovery; Non-CKD–non-AKI was the reference; all $P<0.001$.

similar risk of long-term mortality (HR, 3.94; 95% CI, 2.79–5.28; $P<0.001$), as compared with patients without CKD and AKI as a reference. When compared with patients without CKD and AKI, AKI patients without prior CKD had HRs of 1.35, 2.38, and 3.28 in sRIFLE-R, -I, and -F classification, respectively. After discharge, 87 (3%) CKD–AKI patients died and had the highest HR (60.02; 95% CI, 26.94–133.72; $P<0.001$) for long-term dialysis. By including

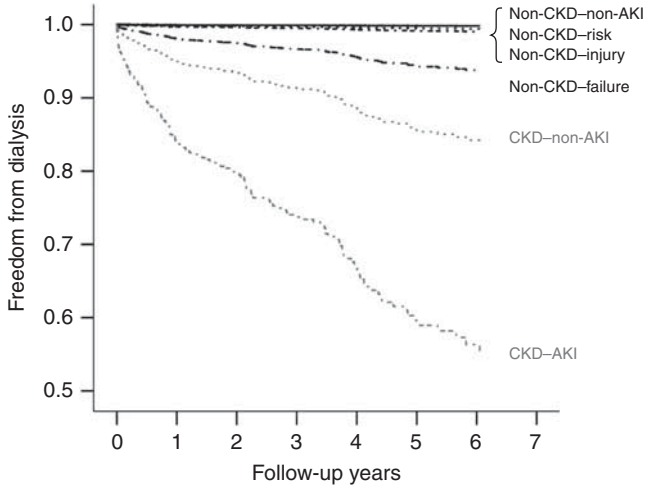

Figure 4 | Long-term dialysis dependence stratified by CKD and AKI. Proportion of freedom from dialysis dependence of patients alive at hospital discharge, stratified by severity of AKI for non-CKD patients and by occurrence of AKI for CKD patients. AKI, acute kidney injury; CKD, chronic kidney disease; CKD–AKI, acute-on-chronic kidney disease; risk, $P = 0.056$; injury, $P = 0.017$; all others $P < 0.001$. Non-CKD–non-AKI was the reference.

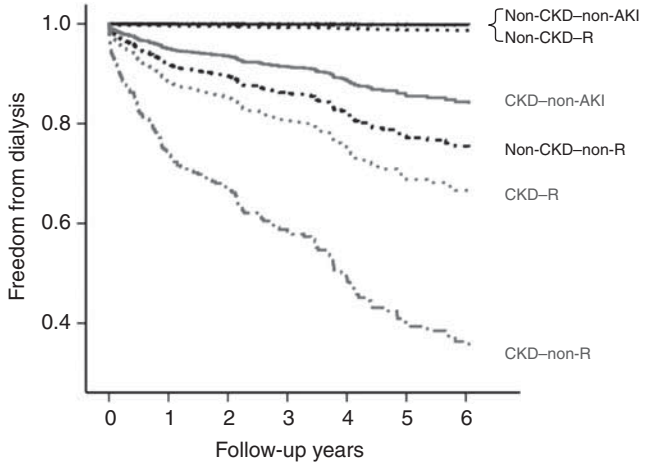

Figure 5 | Long-term dialysis dependence stratified by kidney recovery. Proportion of freedom from dialysis dependence of patients alive at hospital discharge, stratified by the status of kidney recovery. AKI, acute kidney injury; CKD, chronic kidney disease; non-R, non-recovery; R, recovery; all $P < 0.001$. Non-CKD–non-AKI was the reference.

patients without CKD and AKI as a reference among cardiovascular surgery patients, AKI patients without prior CKD had HRs of 1.78 ($P = 0.270$), 4.01 ($P = 0.017$), and 15.64 ($P < 0.001$) in sRIFLE-R, -I, and -F, respectively.

Long-term dialysis

Although 40 non-CKD AKI patients (0.96%) required dialysis at the time of discharge, only a small proportion of discharged patients without prior CKD ($n = 92$, 1.0%) progressed to ESRD in the follow-up period; however, 90 CKD patients (25.6%) progressed to ESRD. After a median (interquartile range) follow-up of 4.62 years, the total incidence rate of ESRD was 17.8 and 0.15 per 100 person-years among hospital survival patients with and without prior CKD, respectively. Patients with CKD–AKI had the highest risk for long-term dialysis (HR, 122.9; 95% CI, 66.8–253.9; $P < 0.001$;), followed by patients with CKD and non-AKI (HR, 52.0; 95% CI, 25.6–105.8; $P < 0.001$; Table 2 and Figure 4). Furthermore, the HRs for long-term dialysis elevated with the increased severity of AKI in patients without prior CKD (HRs, 2.09 in sRIFLE-R, 3.19 in sRIFLE-I, and 22.35 in sRIFLE-F; all $P < 0.001$, compared with patients without CKD and AKI).

After index discharge, CKD patients without kidney recovery at the time of discharge had the worst risk of long-term dialysis (HR, 212.73; 95% CI, 105.53–428.83), followed by CKD patients with recovery (HR, 74.07; 95% CI, 38.82–141.32), non-CKD without recovery (HR, 60.95; 95% CI, 24.13–153.97), CKD–non AKI (HR, 42.63; 95% CI, 20.82–87.29), and non-CKD with recovery (HR, 4.50; 95% CI, 2.43–8.35) compared with patients with non-CKD–non-AKI (reference group; all $P < 0.001$, Figure 5).

Long-term outcomes stratified by CKD and AKI status

Table 3 showed the HR of each risk group stratified by CKD and AKI status, and the HRs are compared with a different reference. The AKI patients who had prior CKD were at higher risk for long-term dialysis and mortality after major surgery than those without prior CKD. Moreover, the AKI itself confers a risk for long-term dialysis and mortality no matter in CKD or without prior CKD patients.

DISCUSSION

We used the most standard definition with a full spectrum of severity for AKI and CKD, which provided a better-defined comparison of a more homogeneous population.[5] Relatively little attention has been paid to the relationship between prior CKD, especially CKD–AKI, and the risk of long-term dialysis and mortality in postoperative patients.

Long-term mortality among CKD–AKI patients

Our long-term results do not concur with two previous studies that showed lower mortality rate associated with AKI in prior CKD patients, both at ICU discharge and at 90 days in the critical setting.[8,14] Khosla *et al.*[8] reported that CKD–AKI is associated with less short-term mortality than *de novo* AKI because of earlier nephrology consultation. However, in the long-term follow-up, CKD–AKI had the worst prognosis among AKI and is comparable to ESRD patients after adjustment for perioperative confounding factors. These comorbidities *per se* may lead to more frequent exposure to nephrotoxis insults and/or alter the response to an acute insult.[15] It was supposed that the postoperative complications induce a cascade of inflammatory processes that ultimately influence survival beyond hospital discharge.[16] Alterations to the metabolic and hormonal milieu of the CKD, including reduced nitric oxide activity, increased levels of angiotensin II and so on, could increase the

susceptibility to injury in AKI.[15] The existing literature reports preoperative CKD as a recognized risk factor for in-hospital and postdischarge morality.[17,18] We further found that CKD is associated with long-term adverse outcomes in postsurgical AKI patients, although this does not imply causality. Patients with CKD are often sicker than those without prior CKD. In this multivariate analysis, the strength of association between CKD and mortality was greater than that associated with other established risk factors, including congestive heart failure, coronary artery disease, and perioperative management in critical settings.

Several studies have shown that underlying CKD markedly increases the risk of AKI, and the risk increases in proportion to the CKD stage.[19,20] Our results further showed that CKD–AKI patients had a worse survival than AKI patients without CKD at all time points up to 4 years following surgery. As CKD is a well-recognized risk factor for cardiovascular morbidity and mortality,[6] more aggressive close follow-up in AKI patients with prior CKD may be warranted.

Long-term dialysis among acute-on-chronic kidney injury patients

CKD patients without AKI still had a higher risk than non-CKD patients with AKI of long-term dialysis after major surgery. When risk factors for AKI are assessed, preoperative baseline CKD was shown to be a significant and consistent risk for the development of AKI.[21,22] A baseline CKD is also a strong risk factor for more severe CKD, including ESRD.[23] Although some non-CKD–AKI patients required dialysis, only a small proportion of discharged patients may progress to ESRD, and most patients had a full restoration of renal function;[21,24] however, in postoperative critical patients with prior CKD, greater than one-fourth of patients progressed to ESRD. Our long-term result enforced the recent report that AKI superimposed on CKD leads to ESRD at a higher incidence than doses of AKI alone.[20,21]

Most studies have suggested that patients with prior CKD are more likely to remain dialysis dependent after an episode of AKI requiring dialysis.[25,26] CKD has been identified as a risk factor for AKI after multivariate adjustment for comorbidities of radiocontrast administration, sepsis, and cardiac surgery.[27] Various adaptations in physiology of CKD can alter the response to AKI.[15] This would emphasize the importance of nephrology follow-up in CKD–AKI survivors. CKD itself may require specialized care for rigorous avoidance of potentially nephrotoxic drug or metabolic factors after discharge, which may hasten progression to ESRD.

Kidney recovery and long-term outcomes

Postoperative temporary worsening of kidney function is associated with higher long-term mortality.[28] It was postulated that CKD after discharge is one of the potential mechanisms that exposed these patients to increased cardiovascular morbidity and mortality.[29] In our study,

Table 3 | Hazard ratio of long-term outcomes using Cox proportional hazard model among subgroups stratified by CKD and AKI status‖

CKD	AKI	Long-term mortality, HR (95% CI)[a]				Long-term dialysis, HR (95% CI)[a]		
Without prior CKD	Non-AKI	1 (reference)				1 (reference)		
	AKI	1.94 (1.76–2.14)***	1 (reference)			4.64 (2.51–8.56)***	1 (reference)	
Prior CKD	Non-AKI	2.64 (1.95–3.59)***	1.39 (1.03–1.87)*	1 (reference)		40.86 (20.01–83.50)***	8.82 (5.20–14.96)***	1 (reference)
	AKI	3.28 (2.66–4.03)***	1.73 (1.42–2.10)***	1.26 (1.09–1.78)*	1 (reference)	91.6 (49.3–170.1)***	19.8 (13.6–28.7)***	2.24 (1.35–3.72)**
ESRD		4.27 (3.42–5.32)***	2.27 (1.84–2.80)***	1.66 (1.17–2.37)**	1.30 (0.99–1.71)	—		

Abbreviations: Af, Atrial fibrillation; AKI, acute kidney disease; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CKD–AKI, acute-on-chronic kidney disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; HR, hazard ratio; HTN, hypertension; IABP, intra-aortic balloon pump; ICP, intracranial pressure; TCP, transcutaneous pacemaker.

[a]HRs of long-term mortality and dialysis in each group are compared with different reference.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

‖Adjusted hazard ratio (95% CI) estimated from logistic regression model, adjusted for age, gender, admission subgroups, intervention (ECMO, ventilator, IABP, ICP, TCP, Swan-Ganz tube, PiCCO, and Sengstaken-Blakemore tube), comorbidity (HTN, DM, liver cirrhosis, CHF, chronic hepatitis, COPD, CAD, Af, and cancer), admission subgroups (Charlson score) by Cox regression modeling.

Note, Table 2 has non-CKD–AKI as three groups and therefore the HR of prior CKD or ESRD come out differently even for other groups in Table 3.

CKD patients without kidney recovery after AKI had the greatest risk for death compared with other patients, including ESRD. Furthermore, we found that CKD patients even with kidney recovery from AKI still had a high risk for long-term dialysis compared with non-CKD–AKI patients with non-recovery. This risk was independent of other perioperative comorbidities, complications, and procedures. (Figure 5).

Earlier identification of CKD–AKI

CKD–AKI should no longer simply be viewed by its overall severity of illness, but rather CKD itself can exhibit important adverse effects on outcome and may extend well beyond the hospital period. This result suggests an expected poor outcome for postsurgical AKI patients with prior CKD with regard to long-term dialysis and mortality.

Earlier identification of AKI among patients with prior CKD could have modified the process of care delivered to these patients. On the contrary, prior CKD should demand more concern for kidney function monitor. This is an important insight for physicians who take care of post-operative patients, and determine the optimal postdischarge follow-up of kidney function for CKD patients even with recovery at the time of discharge. Taken together, it is reasonable to make efforts to find a prior history of CKD before operation. Different strategies may apply to AKI patients with and without prior CKD because of its different effects on long-term mortality and dialysis dependence, especially in postoperative patients.

Study limitations

There are some important limitations to our analysis. There is a lack of linkage between individual patients and their AKI etiologies; however, most severe postoperative AKIs are due to acute tubular necrosis. No conclusive data exist to demonstrate that the traditional etiological categories of AKI have meaningful prognostic differences.[10] As an observational study, results could be influenced by residual confounding factors for which we could not adjust. Heterogeneous definitions of AKI are an important issue in research pertaining to AKI. Most of our patients received cardiovascular surgery (30.4%); however, in our sensitivity analysis, trends to long-term mortality and dialysis dependence remained the same. Therefore, it is unlikely that difference in outcome risk was solely due to surgical categories. The designation of CKD was multidimensional, and we could not define the duration of CKD. However, the risks of mortality and long-term dialysis associated with serum creatinine (sCr) change were constant over time.

In conclusion, in a large cohort of AKI patients after major surgery, those with prior CKD were at a higher risk for long-term mortality and dialysis dependence after hospital discharge than those without CKD. The HRs of long-term mortality were in a disease severity-response manner, classified by sRIFLE criteria in those patients without prior CKD. For CKD patients with kidney recovery from AKI at discharge, the risk for death or long-term dialysis was higher compared with patients without CKD. Further study is necessary to devise strategies to retard the development of kidney failure for optimal follow-up for CKD–AKI patients after discharge in clinical practice.

PATIENTS AND METHODS

Study cohort

This study was an observational study of prospectively collected data based on the database of the National Taiwan University Hospital Study Group on Acute Renal Failure. The database was constructed prospectively for outcome assurance between January 2002 and January 2008 in one medical center (National Taiwan University Hospital in Taipei, Taiwan) and its three branch hospitals in different cities.[30–34] Data related to individual identification were removed and the patients remained anonymous during the entire study. The study was approved by the Institutional Review Board of the National Taiwan University Hospital (no. 31MD03). Informed consent was waived because there was no breach of privacy and the study did not interfere with clinical decisions related to patient care.

There were 17,788 admissions to the ICU after major surgery during the study period. Surgical procedures were considered major if the length of stay for patients in a given diagnosis-related group exceeded 2 days.[35] Patients were excluded if they stayed in the ICU for $\leqslant 2$ days ($n = 6305$). Repeated ICU admission after the index discharge was excluded ($n = 629$). Kidney transplant recipients were excluded as well ($n = 50$). To determine the long-term outcomes,[5] we also excluded patients who died during hospital admission ($n = 1379$).

Clinical assessment of study patients

Demographics and baseline clinical characteristics were assessed at the time of hospital admission. Clinical evaluations included medical history, physical examination, and identification of comorbid diseases. Pertinent medical history included hypertension (defined as taking antihypertensive drugs, or systolic and diastolic blood pressures $>145/95$ mm Hg at the time of hospitalization), diabetes mellitus (defined as being treated with oral hypoglycemic agents or insulin), cirrhosis (defined by image studies with computed tomography or sonagraphy), congestive heart failure (defined as New York Heart Association functional class III or IV), chronic obstructive pulmonary disease (defined as requiring long-term bronchodilators or steroids), and coronary artery disease (defined by the diagnosis of ischemic heart disease before admission and positive electrocardiographic findings). Sepsis was defined as at least two signs of systemic inflammatory response syndrome with clinical evidence of infection.[36] Acute decompensated hepatic failure was defined for cases in which encephalopathy occurred within 7 days of the onset of jaundice.[32] Patients with associated diseases were assessed using the Charlson comorbidity score.[37]

The eGFR was obtained by using the Chinese Modification of Diet in Renal Disease Study equation (GFR = $175 \times (\text{sCr})^{-1.234} \times \text{age}^{-0.179} \times (0.79$, if women)). The eGFR values were proportioned to 1.73 m^2 of the body surface area.[38] CKD was defined according to an eGFR $\leqslant 45$ ml/min per 1.73 m^2 (ref. 7). AKI was classified according to the RIFLE criteria, which was introduced by the Acute Dialysis Initiative Group as a standardized evaluation tool.[12] Similar to previous studies,[34,39–41] we used the sRIFLE classification in which only creatinine was used for classification. AKI was stratified according to the maximum sRIFLE classification during the hospital admission.[5] The baseline sCr was the nadir value obtained from the previous admission in those who had more than one admission within 1 year before the index admission,[39] or the nadir sCr value during the admission after emergency department measurement.[6,42] CKD–AKI was defined as patients with a baseline eGFR $\leqslant 45$ ml/min per 1.73 m^2 who had acute elevation of sCr $>50\%$ ($\times 1.5$) or a decrease of eGFR $>25\%$ (more than the 'risk' of RIFLE). A baseline sCr $\geqslant 4.0$ mg/dl with an acute rise of at least 0.5 mg/dl[13] was defined as 'failure.'

Recovery of renal function

Kidney recovery existed if the discharge sCr remained $<50\%$ above baseline sCr,[6] whereas non-recovery existed if there was a persistent increase in sCr $>50\%$ above the baseline sCr or need for dialysis at the time of hospital discharge.

Renal replacement therapy

The choice of renal replacement therapy modality was made according to the evaluation of the attending physicians after considering the clinical characteristics of the patients. The indications for renal replacement therapy were the same as described in previous reports[32–34], namely azotemia, blood urea nitrogen >80 mg/dl, and sCre >2 mg/dl with uremic symptoms; fluid overload with a central venous pressure level >12 mm Hg or pulmonary edema with a PaO_2/FiO_2 <300; hyperkalemia, serum K^+ >5.5 mmol/l despite medical treatment; oliguria, urine output <100 ml/8 h with or without the use of diuretics; and acidosis, pH <7.2 on arterial blood gas analysis. Long-term dialysis was defined as dialysis for at least 90 days.[43]

Outcome measurement

Patient survival after discharge was determined through the databank of the National Health Insurance Research Database in January 2009.[44] The National Health Insurance Research Database contains health-care data from $>99\%$ of the entire population in Taiwan (23.74 million), and covers all inpatient and outpatient medical benefit claims. We also crosslinked our study population with the nationally comprehensive Taiwan Society Nephrology registry, which receives the data reports of all dialysis patients every 3 months. The long-term all-cause mortality was the primary end point of the study. The secondary end point was the event of long-term dialysis dependence. The long-term outcomes in different stages of AKI classified by sRIFLE criteria in the non-CKD population and in different levels of renal function recovery of inhospital survivors were also reported.

Role of the funding source

There were no conflicts from funding source for this study. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit the findings for publication.

Statistical analysis

Statistical analyses were performed with SPSS for Windows (version 15.0; SPSS, Chicago, IL). A two-sided P-value $\leqslant 0.05$ was considered statistically significant. The continuous variables were summarized as mean ± s.d. unless otherwise specified, whereas the categorical variables were presented as number (percentage). Two-sample Student's t-test was used to analyze continuous data and χ^2-test or Fisher's exact test was used to analyze categorical data.

The long-term survival rates use Cox proportional hazard model adjusted for age, gender, admission subgroups, intervention (ECMO, Intra-aortic balloon pump, ventilator, intracranial pressure, Swan–Ganz tube, PiCCO, Sengstaken–Blakemore tube, and transcutaneous pacemaker, comorbidity (hypertension, liver cirrhosis, congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, hepatitis, cancer, and atrial fibrillation), admission subgroups, Charlson score) and censored on 1 January 2009. Age and Charlson score were modeled as continuous variables. Survival curves for all-cause mortality or freedom from dialysis were generated from adjusted Cox models. For long-term dialysis, an individual who survived at index discharge was censored at death or at the end of the study period. Crude HRs and 95% CIs were derived from a Cox proportional hazard model. Incidence rates of chronic dialysis and all-cause mortality were determined for participants with and without AKI. The proportionality assumption of the Cox models was confirmed with Schoenfeld residual plots.

Sensitivity analysis was undertaken among the subset of patients undergoing cardiovascular surgery because it represented a large proportion of our study population.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed with the manuscript as written.

DISCLOSURE

All the authors declared no competing interests.

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