

Frequency and Consequences of Acute Kidney Injury in Patients With CKD: A Registry Study in Queensland Australia



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Background: Acute kidney injury (AKI) contributes to and complicates chronic kidney disease (CKD). We describe AKI documented in hospital encounters in patients with CKD from the CKD Queensland registry.

Study Design: A retrospective cohort study during 2011 to 2016.

Setting & Participants: Participants had been admitted to a hospital in Queensland.

Predictors: AKI was identified from *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification* codes.

Outcomes: All-cause mortality with or without kidney replacement therapy (KRT), start-up KRT and maintenance KRT, costs of care.

Analytical Approach: Time to outcomes for those with versus without AKI was evaluated using Cox regression models. Mann-Whitney test was used to compare number of admissions, hospitalized days and costs by AKI status.

Results: Among 6,365 patients followed up for up to 5.4 years, 2,199 (35%) had 4,711 hospital encounters with an AKI diagnosis. Those with AKI were older (68 vs 64 years old), were more often

men (36.7% vs 32.2%; $P < 0.001$), had more advanced CKD stages (stage 3b, 34%; stage 4, 35%; and stage 5, 10%), had more admissions (12 vs 5; $P < 0.001$), and stayed in the hospital longer (56 vs 14 days; $P < 0.001$) than those without AKI. Almost 90% of AKI admissions were through the emergency department. Of those with AKI, 554 (25%) subsequently died without any form of KRT and 285 (13%) started KRT, compared with 282 (6.8%) who died and 315 (7.6%) who started KRT among those without AKI; $P < 0.001$ for each. Adjusted for other significant factors, hazard ratios for all deaths or death without KRT were 2.95 (95% CI, 2.56-3.39; $P < 0.001$) and 3.02 (95% CI, 2.60-3.51; $P < 0.001$), respectively, in patients with AKI relative to those without AKI. The hazard ratio for all KRT was 1.40 (95% CI, 1.18-1.66; $P < 0.001$), and for maintenance KRT was 1.21 (95% CI, 0.98-1.48; $P = 0.07$). Mean total hospital cost in patients with AKI was more than triple that of patients with no AKI (A \$93,042 vs A \$30,778; $P < 0.001$).

Limitations: These findings may not be generalizable to CKD populations from the general community or in other health care environments.

Conclusions: AKI is associated with strikingly increased deaths, increased rates of KRT, and higher hospital costs.

Complete author and article information (including names of CKD.QLD Collaborators) provided before references.

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Kidney Med. 1(4):180-190. Published online July 13, 2019.

doi: 10.1016/j.xkme.2019.06.005

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The incidence of acute kidney injury (AKI) is increasing globally.¹⁻⁵ It is estimated that AKI occurs in about 13.3 million people and contributes to about 1.7 million deaths every year.⁶ A pooled incidence rate of AKI was 21.6% across a wide spectrum of adult patients from more than 40 countries worldwide.⁷ The pooled rate of AKI appeared higher in Southern Europe (31.5%), South America (29.6%), and Australia and New Zealand (25.6%) than in other world zones in the United Nations geoscheme classification.⁸ In Australia, hospitalizations with AKI as a principal diagnosis more than doubled between 2000 to 2001 and 2012 to 2013, an average increase of 6% per year.⁹

AKI is a sudden episode of kidney failure or kidney damage that happens within a few hours or a few days. It is a common and harmful clinical problem. Even a minor acute reduction in kidney function has an adverse prognosis.¹⁰ AKI contributes to and complicates chronic kidney disease (CKD) and can exacerbate its progression.^{11,12} Patients who survive AKI have a greater risk for CKD,

end-stage kidney disease, and other adverse outcomes compared with patients without AKI, after adjustment for confounding variables.¹³⁻¹⁶ However, AKI is potentially preventable and/or treatable, so that early detection and treatment of AKI may improve outcomes.⁶

In 2011 we established the CKD, Queensland (CKD.QLD) Registry for CKD surveillance, practice improvement, and research within the renal practice network in the public health system in Queensland.¹⁷ CKD.QLD is unique within Australia and one of few comprehensive CKD surveillance entities globally. The economics of kidney disease are dominated by the costs of dialysis and there is limited visibility of opportunities to moderate preterminal CKD because there are few quality studies of health service utilization or costs, in particular in the CKD population with AKI.

We describe AKI documented in hospital encounters in adult patients enrolled in the CKD.QLD Registry. Specifically, we describe characteristics of patients with AKI among patients with preterminal CKD, the frequency of

AKI and associated conditions, and their hospitalization and costs.

METHODS

Study Design and Setting

A retrospective cohort study of patients from public renal services in Queensland who gave informed consent to participate in the CKD.QLD Registry and had been admitted or not admitted to a hospital in Queensland between May 2011 and June 2016.

Study Participants

Recruitment into the CKD.QLD Registry is described elsewhere.¹⁸ Briefly, participants older than 18 years who are referred to Queensland Health renal services and are not on kidney replacement therapy (KRT) are offered the opportunity to join the CKD.QLD Registry. Those who give consent are followed up until death, maintenance KRT, or a specified censor date.

Data Sources

A data set of participants' information was developed by linking the CKD.QLD Registry, the Queensland Hospital Admitted Patient Data Collection, the Queensland Registrar General death data, and the Activity Based Funding Model Output data for the Queensland Department of Health and Hospital and Health Services.¹⁹ The Queensland Hospital Admitted Patient Data Collection collects demographic data and clinical information for all admitted patients separated from both public and licensed private hospitals and private day surgeries in Queensland.²⁰ Death data were obtained from the Queensland Death Registry. The Activity Based Funding Model output data include hospital cost and

expenditure data, collected through the National Hospital Cost Data Collection.²¹ Data in the National Hospital Cost Data Collection include all patient-level activity for all public and private hospital facilities across Australia and the costs incurred by the hospital in relation to the activity in each financial year. [Figure 1](#) presents the data linkage components and sample size.

Study Outcomes and Predictors

The primary outcome measures were all-cause mortality, all-cause mortality without KRT, acute KRT, and maintenance KRT (long-term KRT and transplantation). "All-cause mortality without KRT" refers to patients who had died by the censor date and had not received KRT. Each patient was censored when they died or started KRT or at the censor date of June 30, 2016. Acute KRT was any dialysis that occurred as a single or repeated episode over a period of up to 3 months and long-term KRT was repeated dialysis provided beyond 3 months.

The occurrence of AKI was derived from the hospital admission data set as coded by the hospital system in accordance with the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM)*,²² listed in [Box 1](#). Patients without AKI were followed up from May 2011 until an end point (death or KRT) or until the censor date of June 30, 2016, which is the last date in the Queensland Health admission data. Survival for patients was calculated from the beginning of the observation period (May 1, 2011) until an end point (death or KRT) or until the censor date of June 30, 2016.

AKI was expressed in 2 ways: one was as a dichotomous variable (AKI vs no AKI) and the other was as a categorical variable based on the number of AKI episodes (no AKI, 1

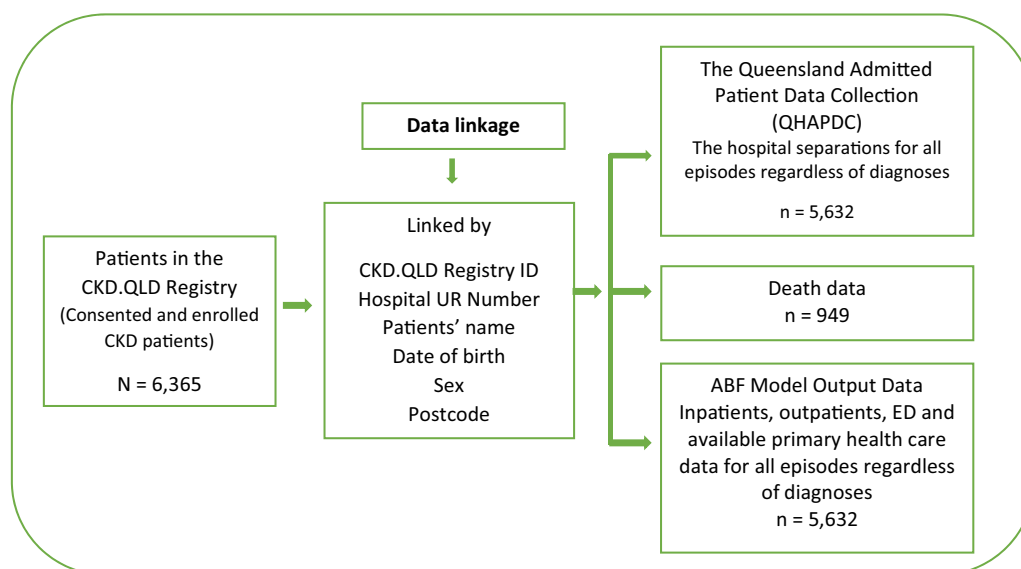


Figure 1. Data linkage components and sample size. Abbreviations: ABF, Activity Based Funding; CKD, chronic kidney disease; ED, emergency department.

Box 1. ICD-10-AM Codes Used to Define Acute Kidney Injury

N17 Acute kidney failure
 N17.0 Acute kidney failure with tubular necrosis
 N17.1 Acute kidney failure with acute cortical necrosis
 N17.2 Acute kidney failure with medullary necrosis
 N17.8 Other acute kidney failure
 N17.9 Acute kidney failure, unspecified

Abbreviation: ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification.

AKI, 2 AKI, and ≥ 3 AKI episodes). Because clinical information in the linked data included principal and additional diagnoses, AKI as the principal diagnosis or as additional diagnoses were further described. A number of individual characteristics, including age group, sex, CKD stage, and primary diagnosis at consent, were included to control for potential confounders in the relationship between the end points and AKI because these factors are also independent predictors of the outcomes. Age was grouped as younger than 55, 55 to 64, 65 to 74, and 75 years or older, and CKD was categorized into the 5 stages as described by KDIGO (Kidney Disease: Improving Global Outcomes).²³ The primary renal diagnosis was classified as diabetic nephropathy, renovascular, glomerulonephritis, genetic renal disease, uncertain diagnosis, and other diagnosis based on the highly prevalent diagnoses that were coded according to ANZDATA (Australian and New Zealand Dialysis and Transplant Registry) codes.²⁴ Total number of hospital admissions, total length of stay, and admission type for each patient who was hospitalized in the observation interval were described. Total cost of hospital admissions during the same interval was also calculated.

Statistical Analysis

We report the median, first, and last quantiles with minimum and maximum range for length of stay and admissions among admitted patients and the average costs according to the diagnosis/es associated with the hospital episodes of AKI versus no AKI. Characteristics of participants and health service utilization were examined according to the presence or not of diagnoses associated with the hospital episodes of AKI, using χ^2 test for categorical variables and Mann-Whitney test for length of stay, admissions, and costs. We calculated rates of the end points (death or start of KRT) by the number of AKI episodes divided by 100 person-years of follow-up since May 1, 2011.

Cox regression was used to explore the relationship between AKI and outcomes, adjusting for potential confounders using 2 models: model 1 used AKI as a dichotomous variable (AKI vs no AKI) and model 2 used the number of AKI episodes. Some were missing data for CKD stage ($n = 716$) and primary diagnosis ($n = 604$) at consent because some incidence patients were included for

the data linkage and their data were not obtained when the data analysis was conducted. Those missing data were excluded in all regression analyses, and the final sample size for Cox regression analyses was 5,453. All analyses were undertaken using Stata, version 15.1 (StataCorp LLC, 2017; Release 15). The P value for statistical significance was defined as $P < 0.05$ (2 tail).

Ethics Approval and Consent to Participate

This study was approved by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/15/QRBW/294) and the University of Queensland Medical Research Ethics Committee (number: 2011000029). The study accessed the data linkage set through an approved Public Health Act application (RD006802).²⁵

RESULTS**Characteristics of Study Participants**

There were 6,365 participants with a mean age of 65 years; 54% were men. Table 1 presents characteristics of study participants categorized according to whether a diagnosis of AKI was coded in 1 or more of their hospital admissions. Participants with AKI were older than those without AKI (68 vs 64 years; $P < 0.001$). The majority of episodes of AKI occurred in those 65 years and older (67.6%). More men than women had AKI (36.7% vs 32.2%; $P < 0.001$). Those with AKI had more advanced CKD stages (stage 3B, 32.6%; stage 4, 35.6%; and stage 5, 10.2%; $P < 0.001$), and their primary diagnosis was more likely to be diabetic nephropathy (30.2% vs 21.8%) and renovascular disease (32% vs 29%; $P < 0.001$) compared with those without AKI.

Health Services Utilization

A total of 6,365 participants were followed up for 0 to 5.4 years, with a mean of 2.5 years and median of 2.8 years, for a total of 15,954 person-years, and 88.5% ($n = 5,632$) of these patients were hospitalized. Among these, 2,199 (34.5%) had 4,711 hospital episodes with an AKI diagnosis code (as the principal and/or an additional diagnosis). Half ($n = 1,110$) had only 1 AKI episode; 539 had 2, and 550 had 3 or more AKI episodes.

As shown in Table 2, the median total length of stay among participants with AKI (40 days) was significantly greater than length of stay for those without AKI (8 days); $P < 0.001$. The difference in length of stay between patients with AKI and with no AKI remained significant even after excluding length of stay for KRT (37 vs 8 days; $P < 0.001$). The median total number of hospital admissions, with and without KRT, during the follow-up period among those with AKI were greater than for those without AKI (9 vs 4; $P < 0.001$ for both).

Among the 4,711 admissions with an AKI diagnosis code, AKI was recorded as a principal diagnosis in only 782 (16.6%). In the remaining 3,929 (83.4%)

Table 1. Characteristics of Study Participants According to Occurrence of AKI

Characteristics	Total Patients	With AKI	Without AKI	P
Total sample	6,365	2,199 (34.6%)	4,166 (65.4%)	
Age at consent, y	65.1 ± 15.3	68.2 ± 13.9	63.5 ± 15.8	<0.001
Age group				<0.001
<55 y	1,389 (21.8%)	340 (15.5%)	1,049 (25.2%)	
55-64 y	1,189 (18.7%)	371 (16.9%)	818 (19.6%)	
65-74 y	1,831 (28.8%)	667 (30.3%)	1,164 (27.9%)	
≥75 y	1,956 (30.7%)	821 (37.3%)	1,135 (27.2%)	
Sex				<0.001
Female	2,933 (46.1%)	944 (42.9%)	1,989 (47.7%)	
Male	3,432 (53.9%)	1,255 (57.1%)	2,177 (52.3%)	
CKD stage				<0.001
1	367 (5.6%)	28 (1.3%)	339 (8.1%)	
2	607 (9.5%)	124 (5.6%)	483 (11.6%)	
3A	1,055 (16.6%)	269 (12.2%)	786 (18.9%)	
3B	1,737 (27.3%)	633 (28.8%)	1,104 (26.5%)	
4	1,458 (22.9%)	691 (31.4%)	767 (18.4%)	
5	425 (6.7%)	198 (9.0%)	227 (5.5%)	
Missing	716 (11.3%)	256 (11.6%)	460 (11.0%)	
Primary diagnosis				<0.001
Glomerulonephritis	748 (11.8%)	190 (8.6%)	558 (13.4%)	
Genetic renal disease	329 (5.2%)	66 (3.0%)	263 (6.3%)	
Diabetic nephropathy	1,422 (22.3%)	598 (27.2%)	824 (19.8%)	
Renovascular	1,730 (27.2%)	635 (28.9%)	1,095 (26.3%)	
Uncertain	397 (6.2%)	107 (4.9%)	290 (7.0%)	
Others	1,135 (17.8%)	386 (17.6%)	749 (18.0%)	
Missing	604 (9.5%)	217 (9.9%)	387 (9.3%)	

Note: Values expressed as number (percent) or mean ± standard deviation. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease.

hospitalizations, AKI was recorded as an additional diagnosis. AKI was recorded as the principal diagnosis slightly more often in men (55.2%) than women (44.8%); $P = 0.02$. When AKI was the principal diagnosis code, the leading associated diagnoses were congestive heart failure, urinary tract infection, pneumonia, myocardial infarction, chronic obstructive pulmonary disease with infection, gastroenteritis/colitis, and sepsis (Box 2). When AKI was an associated condition, the leading principal diagnoses included essential hypertension, type 2 diabetes with nephropathy and complications, CKD stages 3 to 4, and volume depletion (Box 3).

Of the total 4,711 admissions with an AKI diagnosis, 88.1% were through the emergency department (Fig 2). This was significantly higher than the 62.4% among the AKI admissions with no AKI diagnosis.

Death or KRT According to AKI

There were 949 deaths among the 6,365 participants (14.9%). As shown in Table 3, of those with AKI, 627 (28.5%) subsequently died and 285 (13.0%) started KRT compared with 322 (7.7%) who died and 315 (7.6%) who started KRT among those who did not have AKI; $P < 0.001$ for each.

Table 2. Health Services Utilization According to the Occurrence of AKI Among Admitted Patients

	Total Patients	With AKI	Without AKI	P
Length of stay, d	16 (5, 48, 1-2,352)	40 (18, 81, 1-2,352)	8 (3, 22, 1-804)	<0.001 ^a
Length of stay without KRT, d	15 (5, 41, 0-2,352)	37 (17, 7, 0-2,352)	8 (3, 19, 1-547)	<0.001 ^a
Admissions	6 (3, 12, 1-759)	9 (5, 17, 1-665)	4 (2, 8, 1-759)	<0.001 ^a
Admissions without KRT	5 (3, 10, 0-229)	9 (5, 15, 1-229)	4 (2, 7, 0-213)	<0.001 ^a
Dialysis				<0.001
No dialysis	5,040 (89.5)	1,918 (87.2)	3,122 (90.9)	
Acute dialysis	178 (3.2)	95 (4.3)	83 (2.4)	
Long-term dialysis	414 (7.4)	186 (8.5)	228 (6.6)	

Note: N = 5,632. Values expressed as median (p25, p75, minimum-maximum) unless otherwise noted.

Abbreviations: AKI, acute kidney injury; KRT, kidney replacement therapy.

^aNonparametric tests (2-sample Wilcoxon rank sum [Mann-Whitney] test).

Box 2. The 10 Leading Associated Diagnoses by ICD-10-AM Codes When AKI Was the Principal Diagnosis

1. Congestive heart failure
2. Urinary tract infection, site not specified
3. Pneumonia, unspecified
4. Care involving use of rehabilitation procedure, unspecified
5. Acute subendocardial myocardial infarction
6. Extracorporeal dialysis (due to their AKI)
7. Cellulitis of lower limb
8. Chronic obstructive pulmonary disease with acute lower respiratory infection
9. Gastroenteritis and colitis of unspecified origin
10. Sepsis, unspecified

Abbreviations: AKI, acute kidney injury; ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification.

In the AKI cohort, 554 (25.2%) died without KRT compared with 282 (6.8%) in those without AKI ($P < 0.001$). One hundred ninety (8.6%) people with an AKI diagnosis converted to maintenance dialysis compared with 232 (5.6%) people without AKI ($P < 0.001$) who converted to maintenance dialysis. Figures 3 and 4 show the crude incidence rate of death without KRT and of commencement of KRT in individuals by number of AKI episodes. The incidence rates of death without KRT in participants with no AKI and with 1, 2, and 3 or more episodes of AKI were 2.6, 9.0, 11.0, and 14.9 per 100 person-years, respectively, and the incidence rates of KRT were 2.9, 4.3, 6.0, and 8.2 per 100 person-years, respectively.

Adjusted for all other significant factors, the hazard ratio of patients with AKI relative to those without AKI for the end points of all deaths or death without KRT were 2.95 (95% confidence interval [CI], 2.56-3.39); $P < 0.001$ and 3.02 (95% CI, 2.60-3.51); $P < 0.001$ (Table 4, model 1 described in Methods) respectively. The hazard ratio for all KRT was 1.40 (95% CI, 1.18-1.66); $P < 0.001$, and for

Box 3. The 10 Leading Principal Diagnoses by ICD-10-AM Codes, When AKI Was an Additional Diagnosis

1. Essential (primary) hypertension
2. Type 2 diabetes mellitus with other specified renal complication
3. Type 2 diabetes mellitus with established diabetic nephropathy
4. Personal history of tobacco use disorder
5. Chronic kidney disease, stage 3
6. Chronic kidney disease, stage 4
7. Personal history of long-term (current) use of medicaments, insulin
8. Volume depletion
9. Type 2 diabetes mellitus with features of insulin resistance
10. Type 2 diabetes mellitus with multiple microvascular or other specified nonvascular complications

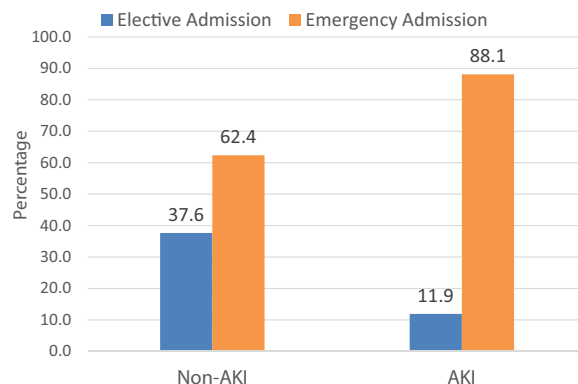


Figure 2. Admission type (elective vs emergency) by acute kidney injury (AKI) diagnosis.

maintenance KRT was 1.21 (95% CI, 0.98-1.48); $P = 0.07$ (Table 5, model 1).

AKI episodes predicted death, with hazard ratios for all deaths of those with 1, 2, and 3 or more episodes compared with those with no AKI of 2.46 (95% CI, 2.07-2.91), 3.00 (95% CI, 2.48-3.64), and 3.99 (95% CI, 3.31-4.80). Even in the group that did not receive KRT, AKI predicted death, with hazard ratios of 2.62 (95% CI, 2.19-3.13), 2.81 (95% CI, 2.27-3.47), and 4.18 (95% CI, 3.43-5.09) for those with 1, 2, and 3 or more AKI episodes, respectively; $P < 0.001$ each (Table 5, model 2). The hazard ratio of patients with AKI with 3 or more episodes relative to those without AKI for all KRT was 2.20 (95% CI, 1.73-2.79); $P < 0.001$. The hazard ratio of patients with AKI with 3 or more episodes for converting to a maintenance dialysis program relative to those without AKI was 1.93 (95% CI, 1.45-2.57); $P < 0.001$ each (Table 5, model 2).

Costs of Patients With AKI Versus Those With No AKI

Mean hospital total cost in patients with AKI was A \$93,042 compared to that of A \$30,779 in the cohort with no AKI ($P < 0.001$). When excluding the cost for KRT, the total cost in the AKI cohort was A \$85,094 compared to A \$25,049 in the no-AKI cohort ($P < 0.001$). Compared with hospital costs in the cohort with no AKI of A \$30,779, costs of patients with 1, 2, and more than 3 AKI admissions were A \$63,082, A \$91,738, and A \$154,729, respectively, all $P < 0.001$ (Fig 5). After excluding the costs of dialysis, hospital costs were A \$25,049, A \$56,407, A \$83,253, and A \$144,742, respectively, for participants with no AKI admissions and with 1, 2, and 3 or more admissions, respectively; all $P < 0.001$ (Fig 6).

DISCUSSION

This study of 6,365 participants with preterminal CKD from the CKD.QLD Registry found at least 1 episode of AKI in 34.5% of the cohort during a follow-up of up to 5.4 years. People with CKD who were more likely to be admitted to the hospital with a diagnosis of AKI tended to

Table 3. Study End Points According to Occurrence of AKI

Characteristics	Total	With AKI	Without AKI	P
All death				<0.001
No death	5,416 (85.1%)	1,572 (71.5%)	3,844 (92.3%)	
Death	949 (14.9%)	627 (28.5%)	322 (7.7%)	
Death without KRT				<0.001
No death	5,529 (86.9%)	1,645 (74.8%)	3,884 (93.2%)	
Death	836 (13.1%)	554 (25.2%)	282 (6.8%)	
All KRT				<0.001
No KRT	5,765 (90.6%)	1,914 (87.0%)	3,851 (92.4%)	
KRT	600 (9.4%)	285 (13.0%)	315 (7.6%)	
Maintenance KRT				<0.001
No KRT	5,943 (93.4%)	2,009 (91.4%)	3,934 (94.4%)	
KRT	422 (6.6%)	190 (8.6%)	232 (5.6%)	

Note: Values expressed as number (percent). n = 6,365.

Abbreviations: AKI, acute kidney injury; KRT, kidney replacement therapy.

be older than 65 years, had more advanced stages of CKD, and more often had a vascular-related cause of kidney disease, diabetic nephropathy, and renovascular diseases. Men were more often admitted with AKI than women, which is similar to our national data set.⁹ People with CKD who were admitted to the hospital with a diagnosis of AKI stayed in the hospital longer, consumed more hospital resources, were more likely to transition onto maintenance KRT, and had a higher mortality rate. These findings were consistent with our national report⁹ and other overseas studies.^{12,14,15,26-29}

All end points (all deaths, death without KRT, and starting KRT) had similar relationships to AKI, adjusted for sex, age group, CKD stage, and primary renal diagnosis. Not surprisingly, participants who sustained multiple episodes of AKI compared to a single episode of AKI had higher likelihoods of death and KRT. Thakar et al³⁰ observed an association of cumulative risk between episodes of in-hospital AKI and the development of advanced CKD over multiple hospitalizations among diabetic

patients. Furthermore, associations between cumulative episodes of AKI and death or KRT appeared stronger after adjusting for all other significant factors. We found that the hazard ratio of conversion to maintenance (as opposed to acute) KRT was not statistically significant between the AKI and no-AKI cohorts. All the significance in the differences in KRT was explained by differences in acute dialysis.

However, significant differences in maintenance KRT emerge when the AKI cohort is stratified as Thakar et al did into number of episodes of AKI. Those with 3 and more AKI episodes were more likely to convert to maintenance KRT. This relationship held even when those who required acute (ie, start) KRT were excluded. Almost 90% of AKI admissions were through the emergency department. For the majority of hospitalizations in which AKI was recorded, it was listed as an associated or additional diagnosis. AKI was recorded as a principal diagnosis in only 17% of AKI hospitalizations, which is similar to the national data that record 14% of AKI hospitalizations as a principal

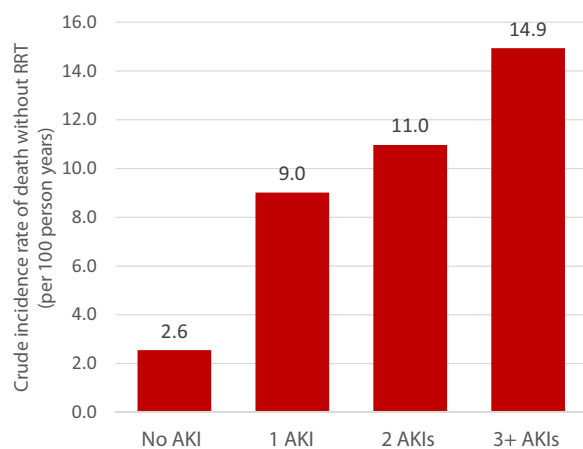


Figure 3. Crude incidence rate of death without kidney replacement therapy (KRT) by number of acute kidney injury (AKI) episodes.

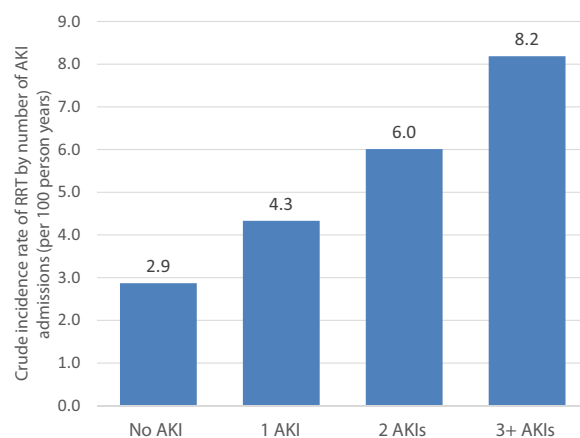


Figure 4. Crude incidence rate of renal replacement therapy (RRT) by number of AKI episodes.

Table 4. Cox Regression Analysis of Prediction of Death by AKI

Predictors	All Death		Death Without KRT	
	HR (95% CI)	P	HR (95% CI)	P
Model 1				
AKI				
No AKI	1.00		1.00	
AKI	2.95 (2.56-3.39)	<0.001	3.02 (2.60-3.51)	<0.001
Sex				
Male	1.00		1.00	
Female	0.78 (0.68-0.89)	<0.001	0.79 (0.69-0.91)	<0.001
Age group				
<55 y	1.00		1.00	
55-64 y	1.70 (1.22-2.37)	0.002	2.33 (1.56-3.48)	<0.001
65-74 y	2.00 (1.48-2.72)	<0.001	2.89 (1.99-4.21)	<0.001
≥75 y	3.48 (2.59-4.68)	<0.001	5.51 (3.81-7.96)	<0.001
CKD stage				
1	1.00		1.00	
2	1.45 (0.64-3.32)	0.4	1.47 (0.61-3.56)	0.4
3A	1.30 (0.59-2.86)	0.5	1.20 (0.51-2.81)	0.7
3B	1.97 (0.91-4.26)	0.08	1.76 (0.77-4.05)	0.2
4	3.97 (1.84-8.54)	<0.001	3.26 (1.42-7.46)	0.005
5	12.94 (5.96-28.09)	<0.001	7.86 (3.38-18.27)	<0.001
Primary renal diagnosis				
Glomerulonephritis	1.00		1.00	
Genetic renal disease	0.72 (0.40-1.30)	0.3	0.91 (0.48-1.71)	0.8
Diabetic nephropathy	2.06 (1.52-2.81)	<0.001	2.08 (1.47-2.93)	<0.001
Renovascular	1.86 (1.37-2.53)	<0.001	1.88 (1.34-2.65)	<0.001
Uncertain	2.11 (1.44-3.10)	<0.001	2.39 (1.59-3.61)	<0.001
Others	1.59 (1.15-2.20)	0.005	1.70 (1.19-2.44)	0.003
Model 2				
AKI episodes				
No AKI	1.00		1.00	
1 AKI	2.46 (2.07-2.91)	<0.001	2.62 (2.19-3.13)	<0.001
2 AKIs	3.00 (2.48-3.64)	<0.001	2.81 (2.27-3.47)	<0.001
≥3 AKIs	3.99 (3.31-4.80)	<0.001	4.18 (3.43-5.09)	<0.001
Sex				
Male	1.00		1.00	
Female	0.78 (0.68-0.89)	<0.001	0.79 (0.69-0.91)	<0.001
Age group				
<55 y	1.00		1.00	
55-64 y	1.71 (1.23-2.38)	<0.001	2.33 (1.56-3.49)	<0.001
65-74 y	2.00 (1.47-2.71)	<0.001	2.89 (1.98-4.20)	<0.001
≥75 y	3.51 (2.61-4.72)	<0.001	5.58 (3.86-8.06)	<0.001
CKD stage				
1	1.00		1.00	
2	1.45 (0.64-3.31)	0.4	1.47 (0.61-3.55)	0.4
3A	1.30 (0.59-2.87)	0.5	1.20 (0.51-2.81)	0.7
3B	1.96 (0.91-4.24)	0.09	1.75 (0.76-4.03)	0.2
4	3.88 (1.80-8.36)	<0.001	3.18 (1.39-7.28)	0.006
5	13.04 (6.01-28.31)	<0.001	7.88 (3.39-18.31)	<0.001
Primary renal diagnosis				
Glomerulonephritis	1.00		1.00	
Genetic renal disease	0.71 (0.39-1.29)	0.3	0.91 (0.48-1.71)	0.8
Diabetic nephropathy	2.00 (1.47-2.72)	<0.001	2.03 (1.44-2.86)	<0.001
Renovascular	1.82 (1.34-2.48)	<0.001	1.85 (1.32-2.60)	<0.001
Uncertain	2.09 (1.42-3.06)	<0.001	2.39 (1.58-3.60)	<0.001
Others	1.56 (1.13-2.15)	0.007	1.67 (1.17-2.39)	0.005

Note: Models adjusted for sex, age group, CKD stage, and primary renal diagnosis.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; KRT, kidney replacement therapy.

Table 5. Cox Regression Analysis of Prediction of Starting KRT by AKI

Predictors	All KRT		Maintenance KRT	
	HR (95% CI)	P	HR (95% CI)	P
Model 1				
AKI				
No AKI	1.00			
AKI	1.40 (1.18-1.66)	<0.001	1.21 (0.98-1.48)	0.07
Sex				
Male	1.00			
Female	0.75 (0.64-0.90)	<0.001	0.65 (0.53-0.80)	<0.001
Age group				
<55 y	1.00			
55-64 y	0.69 (0.55-0.87)	<0.001	0.59 (0.45-0.77)	<0.001
65-74 y	0.38 (0.30-0.47)	<0.001	0.34 (0.26-0.44)	<0.001
≥75 y	0.17 (0.12-0.22)	<0.001	0.12 (0.08-0.17)	<0.001
CKD stage				
1	1.00			
2	1.94 (0.62-6.12)	0.3	1.19 (0.28-5.00)	0.8
3A	2.35 (0.80-6.94)	0.1	1.22 (0.31-4.73)	0.8
3B	6.70 (2.43-18.5)	<0.001	5.32 (1.63-17.38)	0.006
4	28.64 (10.57-77.64)	<0.001	28.01 (8.85-88.66)	<0.001
5	196.08 (72.41-530.91)	<0.001	218.19 (69.16-688.4)	<0.001
Primary renal diagnosis				
Glomerulonephritis	1.00		1.00	
Genetic renal disease	0.88 (0.63-1.24)	0.5	1.03 (0.70-1.52)	0.9
Diabetic nephropathy	1.12 (0.87-1.44)	0.4	1.27 (0.94-1.73)	0.1
Renovascular	0.90 (0.68-1.20)	0.5	0.99 (0.70-1.41)	0.9
Uncertain	0.54 (0.32-0.91)	0.02	0.65 (0.35-1.18)	0.1
Others	0.71 (0.53-0.96)	0.02	0.77 (0.53-1.10)	0.2
Model 2				
AKI episodes				
No AKI	1.00			
1 AKI	1.11 (0.89-1.40)	0.4	0.98 (0.75-1.29)	0.9
2 AKIs	1.28 (0.98-1.69)	0.07	1.02 (0.73-1.43)	0.9
≥3 AKIs	2.20 (1.73-2.79)	<0.001	1.93 (1.45-2.57)	<0.001
Sex				
Male	1.00			
Female	0.76 (0.64-0.91)	0.002	0.66 (0.53-0.81)	<0.001
Age group				
<55 y	1.00			
55-64 y	0.70 (0.56-0.87)	0.002	0.57 (0.45-0.76)	<0.001
65-74 y	0.37 (0.30-0.46)	<0.001	0.33 (0.25-0.43)	<0.001
≥75 y	0.17 (0.12-0.22)	<0.001	0.11 (0.08-0.17)	<0.001
CKD stage				
1	1.00		1.00	
2	1.93 (0.61-6.08)	0.3	1.18 (0.28-4.96)	0.8
3A	2.34 (0.79-6.91)	0.1	1.21 (0.31-4.68)	0.8
3B	6.65 (2.41-18.37)	<0.001	5.27 (1.61-17.22)	0.006
4	28.26 (10.42-76.61)	<0.001	27.65 (8.74-87.54)	<0.001
5	199.05 (73.50-539.06)	<0.001	221.88 (70.31-700.24)	<0.001
Primary renal diagnosis				
Glomerulonephritis	1.00			
Genetic renal disease	0.86 (0.61-1.21)	0.4	1.00 (0.68-1.48)	0.9
Diabetic nephropathy	1.10 (0.85-1.42)	0.5	1.27 (0.93-1.72)	0.1
Renovascular	0.91 (0.68-1.21)	0.5	1.01 (0.71-1.45)	0.9
Uncertain	0.54 (0.32-0.91)	0.02	0.65 (0.36-1.19)	0.2
Others	0.72 (0.53-0.97)	0.03	0.79 (0.55-1.14)	0.2

Note: Models adjusted for sex, age group, CKD stage, and primary diagnosis.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; KRT, kidney replacement therapy.

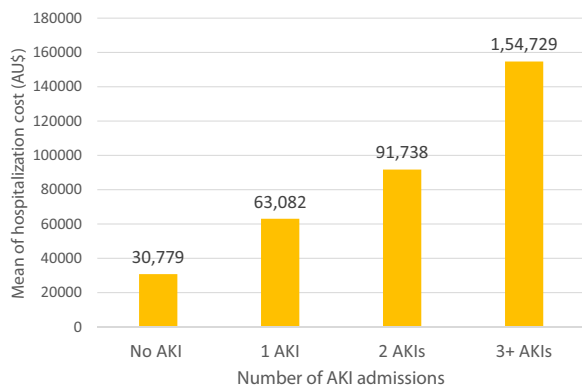


Figure 5. Mean of hospitalization cost by number of acute kidney injury (AKI) admissions.

diagnosis.⁹ It is unclear why a diagnosis with the high risk for poor outcomes was underweighted by coders in both national data and our data. Our study indicated that congestive heart failure, urinary tract infection, pneumonia, myocardial infarction, and chronic obstructive pulmonary disease with infection were the top 5 leading additional diagnoses when AKI was the principal diagnosis. When AKI was an additional condition, the 5 leading principal diagnoses (essential hypertension, type 2 diabetes with nephropathy and complications, CKD stages 3-4, and volume depletion) were all predisposing risk factors or conditions. Thus, these common conditions are frequently complicated by AKI, a potentially catastrophic development.¹² However, we cannot comment about whether AKI ought to have been the principal diagnosis.

Mean total hospital costs in those with AKI were more than triple those of patients with no AKI. Costs increase with more episodes of AKI, underscoring the argument for weighting AKI diagnoses as primary. Chertow et al²⁷ also found that AKI was associated with significantly increased costs among hospitalized patients with decreased kidney function in Boston, MA.

This study has several strengths worthy of mention. We describe characteristics of participants with AKI among those with preterminal CKD and examined whether AKI is an independent risk factor for the adverse outcomes of mortality and starting KRT, filling some of the gaps in the literature. The linked data approach we used produced comprehensive cross-jurisdictional data sets of hospital service utilization and costs across public and private health sectors during a follow-up of up to 5.4 years. The comprehensive data sets allowed us to test putative factors, including age, sex, CKD stage, and primary diagnosis at consent, as potential confounders in the relationship between AKI and the end points to reduce confounding bias. Both the death and death without KRT end points were examined for their relationships with the patterns of AKI. KRT with conversion to maintenance dialysis as the outcome was also examined. Furthermore, we have compared the total

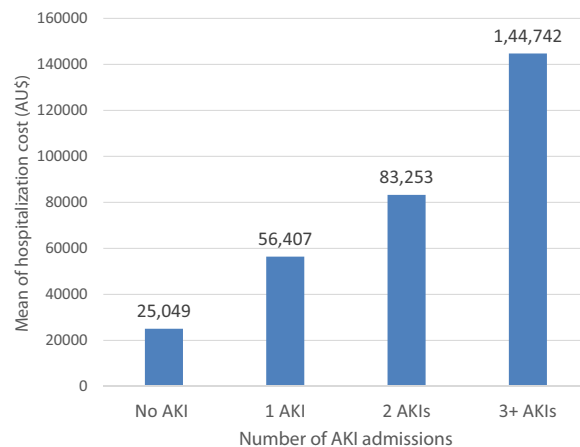


Figure 6. Mean of hospitalization cost (excluding cost for dialysis) by number of acute kidney injury (AKI) admissions.

hospital cost between AKI and no AKI, and in greater granularity by the number of AKI admissions, which we believe are the first empirical data in this area.

There are some limitations to this study. The linked data were limited to the CKD.QLD Registry patients from major public renal services in Queensland. It may not be generalizable to other CKD populations from other health environments such as community care and people not admitted to hospitals. Because AKI was identified from ICD-10-AM codes in this study, there was no opportunity to assess the association between severity of AKI, classified accordingly to the KDIGO definition, and mortality or starting KRT,³¹ noting that some studies have found a relationship between severity of AKI and death.^{14,15} We may have this opportunity in the future because our data sets are extracted from clinical records that are migrating to digital platforms. AKI from ICD-10-AM codes might be underreported because the ICD-10-AM codes have changed according to changes in the definition for AKI within recent years.^{2,9,29} Thus, it may cause some information bias and “poor sensitivity,”⁴ so that we have analyzed AKI in the Cox regression modelings. Furthermore, there might be other residual confounders because the models were adjusting for a very limited set of covariates. Notwithstanding this caveat, we found that AKI was an important risk factor associated with heightened mortality, starting KRT, and excessive hospital resource consumption in the CKD cohort.

The goal set out by the International Society of Nephrology is “zero preventable deaths by 2025” for AKI, or “0by25,” which means that no one should die of untreated AKI in low-resource regions by 2025. The initiative aims to eliminate preventable deaths from AKI by calling for global strategies that permit timely diagnosis and treatment.⁶ These initiatives are equally powerful in the CKD.QLD Registry cohort of preterminal CKD, a group at high risk for AKI.

In conclusion, this study shows that AKI is a common cause of hospitalization of patients with CKD in the Queensland public renal services. They enter the acute hospital sector through predominantly unplanned emergency admissions. These people are at greater risk for death and start-up of KRT and consumed more hospital resources than patients with CKD who were hospitalized without AKI. However, the powerful flag of AKI is not accorded primacy in the ICD-10-AM coding processes, and the cause of sex differences in AKI hospitalizations needs to be explored in future study.

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Support: This study has been supported in part from the National Health and Medical Research Council under the Centre of Research Excellence (APP1079502). The funders had no role in study design; data collection, analysis, or reporting; or the decision to submit for publication.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: We thank the clinical and academic teams that have enabled the linkage study; all the people who are participating in the CKD.QLD Registry Study; the Queensland Health data custodians for providing the linked data; and data

linkage officers from the Statistical Analysis and Linkage Team of Queensland Health for conducting the data linkage.

Peer Review: Received December 18, 2018. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form June 14, 2019.

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