Sepsis-associated acute kidney injury in the intensive care unit: Incidence, Patient Characteristics, Timing, Trajectory, Treatment, and Associated Outcomes. A multicenter, observational study.

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Abstract

Purpose The Acute Disease Quality Initiative (ADQI) Workgroup recently released a consensus definition of sepsis-associated acute kidney injury (SA-AKI), combining Sepsis-3 and Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria. This study aims to described the epidemiology of SA-AKI.

Methods Retrospective cohort study in 12 intensive care units (ICU) from 2015 to 2021. We studied the incidence, patient characteristics, timing, trajectory, treatment, and associated outcomes of the ADQI SA-AKI definition.

Results Of 84,831 admissions, 15,549 met the SA-AKI criteria with its incidence peaking at > 20% in 2021. SA-AKI patients were typically admitted from home via the emergency department (ED) with median time to SA-AKI diagnosis of one day (IQR 1–1) from ICU admission. At diagnosis, most SA-AKI patients had a stage 1 (55%) AKI, mostly due to the low urinary output (UO) criterion only (67%). Compared to diagnosis by creatinine alone, or both UO and creatinine criteria, patients diagnosed by UO alone had lower RRT requirement (3.3% vs 19% vs 51%; $p < 0.001$), which was consistent across all stages of AKI. SA-AKI hospital mortality was 19% and SA-AKI was independently associated with increased mortality. However, diagnosis by low UO only carried an odds ratio of 0.37 (95% CI, 0.34–0.39) for mortality.

Conclusion SA-AKI occurs in one in five ICU patients, is diagnosed on day one, and carries significant morbidity and mortality risk with patients mostly admitted from home via the ED. However, most SA-AKI is stage 1 and mostly due to low UO, which carries much lower risk than diagnosis by other criteria.

Take Home Message

SA-AKI is a common, increasing prevalence problem in ICU which predominantly occurs patients admitted from ED and is usually diagnosed within a day of ICU admission. Most patients with SA-AKI had stage 1 AKI and were diagnosied by low UO alone, a group in which deterioration in renal function was uncommon.

Introduction

Sepsis is a common cause of critical illness and is associated with high morbidity and mortality[1–3] and, often, with acute kidney injury (AKI). When AKI occurs in this setting, it is referred to as sepsis-associated acute kidney injury (SA-AKI) [4, 5]. The association between sepsis and AKI has been studied previously [6, 7]; however, the lack of a reproducible and standardized consensus definition has limited the interpretability of available knowledge.

Given its importance, a definition of sepsis-associated acute kidney injury (SA-AKI) was recently produced by the Acute Disease Quality Initiative (ADQI) 28 Workgroup [8]. This definition combines the presence of sepsis, defined by the Sepsis-3 criteria [9], with the presence of AKI, defined by the KDIGO criteria [10], occurring within 7 days of the diagnosis of sepsis.

The epidemiology of SA-AKI in the critically ill, based on this standardised consensus definition, remains unknown. Furthermore, the incidence, patient characteristics, timing, trajectory, treatment, and associated outcomes of SA-AKI have not been studied. Guided by the ADQI 28 Workgroup's consensus definition and research priorities, we analyzed a large, granular, multicentre database of routinely collected Electronic Medical Record (EMR) data to assess SA-AKI.

We aimed to test the primary hypothesis that SA-AKI admitted to the ICU would affect more than one in five ICU patients. We also intended to test the secondary hypothesis that most SA-AKI is not a disease of intensive care, but rather a disease that develops outside intensive care and triggers intensive care admission.

Methods

Study design

Large, multicentre, retrospective cohort study of granular, routinely collected, EMR-based clinical data.

Study Sites

The study sites were 12 closed-model ICUs located in Queensland, Australia. The ICUs included five tertiary ICUs, three outer metropolitan ICUs, and four regional ICUs. The centres comprise most of the entire state-wide ICU capacity and include all the state-wide referral centres for cardiothoracic, neurosurgical, obstetric, and trauma patients, as well as outer metropolitan and regionals ICUs. We evaluated all adult patients admitted between January 1st, 2015, and December 31st, 2021. All patients were eligible if their electronic medical records were retrievable. We excluded patients with advanced chronic kidney disease requiring chronic dialysis, patients admitted with palliative intent, and patients transferred from another participating ICU. We did not exclude readmission episodes within the same hospital admission.

Identification of Sepsis

Sepsis was defined according to the Third International Consensus definitions for sepsis and septic shock [9]. According to the SEPSIS-3 definition, we identified patients with an increase in Sequential Organ Failure Assessment (SOFA) score by two points with proven or suspected infection [9]. We assumed that the SOFA score was zero prior to admission to ICU, and, where individual components of SOFA were missing, no contribution was made to the total score [11]. The daily total SOFA score was calculated and an increase in two points over 24 hours was identified. Given the challenges interpreting neurological SOFA with concurrent sedation it was not included in the total SOFA [12]. Proven or suspected infection was defined as the commencement or escalation of antimicrobial therapy and microbiological sampling within one day of SOFA score increase [13]. An escalation of antimicrobials was defined as an increase in antimicrobial 'rank' within 1 day of diagnosis of sepsis [14, 15]. As demonstrated in Online Supplement, **Table S1**, ranking corresponds to the spectrum of activity with the

rank one indicating the lowest spectrum, such as first-generation cephalosporin, and rank four the highest spectrum, such as carbapenems or tigecycline [15].

Elective surgical patients were assumed to be receiving antibiotic prophylaxis in the first 2 days of admission. Thus, they were not classified as having sepsis regardless of their SOFA score. Septic shock was defined as the administration of a vasopressor medication and at least one blood lactate greater than 2 mmol/L on the day of sepsis diagnosis [16]. Futhermore, the dosage of vasopressor was converted to norepinephrine equivalent, with conversion method shown in Online Supplement (**Table S2**) [17].

Identification of Acute Kidney Injury

AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) AKI definition, with daily serum creatinine and hourly urine output data [10]. In order to manage absent hourly urine output measurements secondary to absence of indwelling catheter or transfer outside of ICU we performed imputation of hourly urine output as described in the Online Supplement, **Table S3.** Hourly urine output per kilogram of body weight was assessed on a rolling basis to identify patients who met AKI urine output criteria. Every sliding six, 12, and 24-hour window of urine output was assessed against AKI thresholds. In the absence of pre-ICU creatinine data, the baseline creatinine was estimated using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation [18, 19]. Daily serum creatinine was compared to estimated baseline creatinine and values meeting definition of AKI were recorded. Urine output-based or creatinine-based criteria or both were used to identify whether a patient met the KDIGO criteria for AKI.

Identification of Sepsis Associated-Acute Kidney Injury

After individually identifying episodes of sepsis and AKI, we applied the ADQI 28 Workgroup SA-AKI definition. We compared the day of sepsis diagnosis to the day of AKI diagnosis. If AKI occurred between day 1 and 7 after sepsis diagnosis, then these patients were classified as SA-AKI according to the ADQI SA-AKI criteria.

Data Sources

Routinely collected data were obtained from all centres using the eCritical MetaVision™ (iMDsoft, Boston, MA, USA) clinical information systems. This included daily laboratory data, daily medications, daily microbiology, as well as hourly haemodynamic and hourly fluid balance data. Information on baseline demographics, admission diagnosis, severity of illness and outcomes were extracted from the Australia and Zealand Intensive Care Society (ANZICS) Centre for Outcome and Resource Evaluation (CORE) Adult Patient Database (APD) [11, 20–22].

Outcomes

The primary outcome was the incidence of SA-AKI. The secondary outcomes were AKI severity, timing of AKI, requirement for RRT, ICU and hospital length of stay, and ICU and hospital mortality.

Statistical analysis

Descriptive statistics were expressed as frequencies and proportions for categorical variables and medians with interquartile ranges (IQR) or means with standard deviations depending on their parametric or non-parametric distribution. The Fisher's exact test was used to compare categorical data. A mixed-effect logistic regression model, including hospitals as random effect, was developed to examine factors associated with hospital mortality and major adverse kidney events at day 30 (MAKE-30). The variables used for analysis were determined a priori and reflected the clinical utility of available data. The results of the multivariable analysis were reported as odds ratios (OR) with 95% confidence intervals (95% CI). Given the large data set a two-sided p value of < 0.01 was considered statistically significant. Statistical analyses were performed using R v.4.0.3.

Results

Incidence of SA-AKI

From January 1st, 2015, to December 31st, 2021, 89,776 patients were admitted to the participating ICUs. We excluded 1,950 patients with end-stage kidney disease, 547 patients admitted with palliative intent, and 2,507 patients transferred between facilities. Of the remaining 84,831 patients, 15,459 met the criteria for SA-AKI during their ICU admission. As demonstrated in Online Supplement, **Figure S1**, the percentage of admissions that met SA-AKI criteria increased over time from 16% in 2015 to greater than 20% in 2021.

Patient Characteristics

The overall patient characteristics, inclusive of both non-SA-AKI and SA-AKI patients, are shown in Table 1. The median age was 61 years, 39% were female, and the median body mass index (BMI) was 27.8. Severity of illness as measured by the median APACHE III score was 50 and the most common source of admission was the operating room followed by the emergency department.

Table 1
Baseline Characteristics

	SA-AKI		
Variable	**Yes**, N = 15,459[1]	**No**, N = 69,372[1]	p value[2]
Age (years)	63.00 (50.00, 73.00)	60.00 (46.00, 71.00)	< 0.001
Female	6,187 (40%)	26,834 (39%)	0.002
Body Mass Index	27.78 (25.39, 34.11)	27.68 (24.42, 31.24)	< 0.001
Co-morbidities			
Respiratory	1,042 (6.7%)	2,031 (2.9%)	< 0.001
Cardiovascular	641 (4.1%)	1,895 (2.7%)	< 0.001
Cirrhosis	713 (4.6%)	1,038 (1.5%)	< 0.001
Hematological Malignancy	332 (2.1%)	524 (0.8%)	< 0.001
Metastatic Cancer	409 (2.6%)	2,280 (3.3%)	< 0.001
Immunosuppressed	1,802 (12%)	4,947 (7.1%)	< 0.001
Diabetes Mellitus	725 (4.7%)	2,258 (3.3%)	< 0.001
No Co-morbidities	11,036 (71%)	57,432 (83%)	< 0.001
APACHE Diagnosis Group			< 0.001
Cardiovascular	2,321 (15%)	23,148 (33%)	
Gastrointestinal	2,249 (15%)	9,001 (13%)	
Genitourinary	695 (4.5%)	2,533 (3.7%)	
Hematological	86 (0.6%)	122 (0.2%)	
Metabolic	846 (5.5%)	5,912 (8.5%)	
Neurological	1,035 (6.7%)	10,543 (15%)	
Other	485 (3.1%)	2,019 (2.9%)	
Respiratory	2,669 (17%)	7,461 (11%)	
Sepsis	4,066 (26%)	2,974 (4.3%)	
Trauma	1,007 (6.5%)	5,659 (8.2%)	
Admission Circumstances			
Post Elective Surgery	88 (0.6%)	33,300 (48%)	< 0.001

	SA-AKI		
Post Rapid Response	3,163 (21%)	4,856 (7.1%)	< 0.001
Post Cardiac Arrest	957 (6.2%)	2,734 (3.9%)	< 0.001
Readmission	1,135 (7.3%)	2,879 (4.2%)	< 0.001
LOS in Hospital before ICU (hours)	7.98 (3.20, 37.03)	12.68 (5.23, 43.93)	< 0.001
Severity of Illness			
APACHE 2 Score	21.00 (16.00, 27.00)	14.00 (10.00, 18.00)	< 0.001
APACHE 3 Score	71.00 (55.00, 90.00)	47.00 (35.00, 61.00)	< 0.001
APACHE 3 Risk of Death	0.22 (0.09, 0.47)	0.04 (0.02, 0.11)	< 0.001
Day of Admission			
Any Ventilation	9,011 (58%)	37,334 (54%)	< 0.001
Invasive Ventilation	8,534 (55%)	36,448 (53%)	< 0.001
Non-invasive Ventilation	477 (3.1%)	886 (1.3%)	< 0.001
Urine Output (mL/kg/h)	0.62 (0.31, 1.13)	0.98 (0.61, 1.59)	< 0.001
Diuretics	1,766 (11%)	2,532 (3.6%)	< 0.001
Maximum Creatinine (µmol/L)	130.00 (80.00, 204.00)	76.00 (60.00, 97.00)	< 0.001
AKI Stage			< 0.001
0	7,172 (46%)	61,017 (88%)	
1	3,803 (25%)	5,843 (8.4%)	
2	2,265 (15%)	1,264 (1.8%)	
3	2,219 (14%)	1,248 (1.8%)	
RRT	1,276 (8.3%)	666 (1.0%)	< 0.001
Vasopressors	9,254 (60%)	27,291 (39%)	< 0.001
NEE Score (µg/kg/min)	0.06 (0.02, 0.18)	0.03 (0.01, 0.14)	< 0.001
Mean MAP (mmHg)	75.33 (70.22, 83.00)	78.00 (71.67, 87.67)	< 0.001
Maximum SOFA Score	7.00 (4.00, 9.00)	4.00 (2.00, 6.00)	< 0.001
Maximum Lactate (mmol/L)	2.40 (1.50, 4.50)	1.70 (1.20, 2.80)	< 0.001
ICU Level			< 0.001
Tertiary	8,776 (57%)	54,686 (79%)	

	SA-AKI		
Outer Metropolitan	2,618 (17%)	4,979 (7.2%)	
Regional	3,932 (26%)	9,479 (14%)	
Source of Hospital Admission			< 0.001
High Care Facility	108 (0.7%)	224 (0.3%)	
Home	11,266 (73%)	53,978 (78%)	
Low Acuity Facility	40 (0.3%)	104 (0.1%)	
Other Hospital	4,045 (26%)	15,066 (22%)	
Source of ICU Admission			
Emergency department	6,747 (44%)	16,883 (24%)	
Operating Theatre	3,645 (24%)	42,807 (62%)	
Other hospital	1,069 (6.9%)	2,687 (3.9%)	
Unknown	5 (< 0.1%)	10 (< 0.1%)	
Ward	3,993 (26%)	6,985 (10%)	
Treatment Goals on Admission			< 0.001
Full active treatment	13,594 (88%)	66,583 (96%)	
Missing	1 (< 0.1%)	4 (< 0.1%)	
Treatment limitation order	1,864 (12%)	2,785 (4.0%)	
[1]Median (IQR) or Frequency (%)			
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test			
Abbreviations: SA-AKI = sepsis-associated acute kidney injury; LOS = length of stay; AKI = acute kidney injury; RRT = renal replacement therapy; NEE = norepinephrine equivalent			

Compared to the entire ICU cohort, patients with SA-AKI had a higher APACHE 3 score, were more likely to be admitted to ICU from the emergency department or a hospital ward and had a higher risk of death. Though statistically different, the SA-AKI group had a numerically similar age, sex distribution, and body mass index to the entire cohort.

On the day of admission to ICU, more than half of SA-AKI patients required invasive ventilation, almost half received at least one hour of vasopressor therapy and almost one in ten required RRT. However, diuretic therapy was rarely used.

Timing and Characterisitcs of SA-AKI Diagnosis

As shown in Table 2, the median day of sepsis diagnosis was the day of ICU admission, or day 1 (IQR 1–1). At the time of SA-AKI diagnosis, over a third (40%) of patients had septic shock and the median SOFA score at sepsis diagnosis of 7 (IQR 4–9). Most patients met AKI criteria on the same day as sepsis criteria, with a median time from sepsis to AKI of 0 days (IQR 0–1). Most patients (46%), were diagnosed with AKI based on urine output (UO) alone, whereas 32% and 21% met creatinine criteria alone or both UO and creatinine criteria, respectively. At AKI diagnosis, the majority (55%) had stage 1 AKI, whereas only 25% and 20% had stage 2 and stage 3 AKI, respectively. Moreover 10% of patients received RRT on the day of SA-AKI diagnosis. As demonstrated in Online Supplement, **Table S4**, 67% (5,700) of SA-AKI patients with stage1 AKI were diagnosed by urine output alone, representing 37% of the entire SA-AKI cohort.

Table 2
Characteristics at SA-AKI Diagnosis

	SA-AKI
Variable	N = 15,459[1]
Day of Sepsis Diagnosis [2]	1.00 (1.00, 1.00)
Day of AKI Diagnosis	1.00 (1.00, 2.00)
Septic Shock at Sepsis Diagnosis	6,535 (42%)
Days from Sepsis to AKI Diagnosis	0.00 (0.00, 1.00)
SOFA Score	7.00 (4.00, 9.00)
Lactate (mmol/L)	2.40 (1.50, 4.50)
Antibiotic Rank [3]	
1	1,743 (11%)
2	3,672 (24%)
3	7,464 (48%)
4	2,580 (17%)
Any Ventilation	9,109 (59%)
Vasopressors	9,481 (61%)
NEE Score (µg/kg/min)	0.06 (0.02, 0.18)
AKI Stage	
1	8,528 (55%)
2	3,857 (25%)
3	3,074 (20%)
AKI Diagnostic Criteria	
Urine Output Only	7,180 (46%)
Creatinine Only	4,999 (32%)
Both	3,280 (21%)
Daily Urine Output (mL)	825.00 (355.50, 1,400.00)
Creatinine (µmol/L)	136.00 (79.00, 206.00)
RRT	1,614 (10%)

	SA-AKI
Diuretic Therapy	2,784 (18%)
Cumulative FB (mL)	335.90 (-170.75, 1,285.50)
[1]Median (IQR) or Frequency (%) [2]Corresponds ICU admission day [3] Braykov NP, Morgan DJ, Schweizer ML, Uslan DZ, et al. Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study. Lancet Infect Dis. 2014;14(12):1220–7.	
Abbreviations: SA-AKI = sepsis-associated acute kidney injury; AKI = acute kidney injury; RRT = renal replacement therapy; NEE = norepinephrine equivalent; FB = fluid balance	

Trajectory of SA-AKI

We examined the trajectory of SA-AKI patients by daily serum creatinine and hourly UO over 14 days. The mean serum creatinine of all SA-AKI patients stabilised at day six of admission at a mean of 130 µmol/L from a peak of > 170 µmol/L in survivors and at a mean of 155 µmol/L from a peak of 180 µmol/L in patients who died in hospital (Online Supplement, **Figure S2)**. Patients with stage 1 and stage 2 AKI did not have major fluctuations in mean serum creatinine over time, whereas the mean serum creatinine of patients with Stage 3 AKI stabilised at day six at 200 µmol/L from a peak > 340 µmol/L (Online Supplement, **Figure S3**). Given that most patients were diagnosed with AKI by UO alone, we examined serum creatinine over time by AKI diagnostic criteria. In patients diagnosed by UO alone the mean serum creatinine remained unchanged and within normal range throughout the ICU admission (Fig. 1). These findings were consistent across each stage of AKI (**Figure S4-S6**). Furthermore, among patients diagnosed by urine output alone, the hourly UO data for all AKI stages demonstrates that normalisation of urine output was typical and occurred with 24–48 hours of admission to ICU (Online Supplement, **Figure S7-S9)**.

In contrast, patients diagnosed with AKI by both urine output and creatinine had a persistently lower urine output and elevated serum creatinine. In this group, the mean hourly urine output never increased above 1 mL/kg/h (Online Supplement, **Figures S9**), and the serum creatinine remained elevated at greater than 200 µmol/L (Online Supplement, **Figures S10**).

A summary of the trajectory of AKI stages over time for the entire SA-AKI cohort is shown in Online Supplement, **Figure S11**, demonstrating patients who had a stage 1 or stage 2 AKI diagnosis decreased in number with resolution of AKI, whereas, patients diagnosed with stage 3 AKI maintained their severe AKI throughout the ICU admission. The trajectory of SA-AKI patients diagnosed with AKI by UO alone is shown in Online Supplement, **Figure S12**, demonstrating rapid resolution of AKI in the majority of patients with few progressing to more severe stages of AKI.

Treatment During First 7 Days of ICU Admission

ICU therapies were examined during the first seven days of ICU admission, a duration which represents the top quartile of ICU length of stay. Compared to patients diagnosed by creatinine alone or both urine output and creatinine, patients who were diagnosed with SA-AKI by UO alone were more likely to receive ventilation, but were significantly less likely to require vasopressors and RRT (Table 3). These findings were consistent across all stages of AKI severity (Online Supplement, **Table S5-S7**).

Table 3
Treatment during First 7 Days by AKI Diagnostic Criteria in SA-AKI Patients

	AKI Diagnostic Criteria			
Variable	**Urine Output Only**, N = 7,180[1]	**Creatinine Only**, N = 4,999[1]	**Both**, N = 3,280[1]	p value[2]
Any				
Ventilation	5,199 (72%)	2,790 (56%)	2,305 (70%)	< 0.001
Invasive ventilation	5,016 (70%)	2,619 (52%)	2,208 (67%)	< 0.001
Non-invasive ventilation	387 (5.4%)	304 (6.1%)	175 (5.3%)	0.2
Vasopressors	4,639 (65%)	3,786 (76%)	2,816 (86%)	< 0.001
Diuretics	3,556 (50%)	2,289 (46%)	1,603 (49%)	< 0.001
RRT	186 (2.6%)	912 (18%)	1,626 (50%)	< 0.001
Nephrotoxic Antibiotics	1,928 (27%)	1,784 (36%)	1,422 (43%)	< 0.001
Days of Intervention				
Ventilation	2 (0, 5)	1 (0, 4)	2 (0, 6)	< 0.001
Invasive ventilation	2 (0, 5)	1 (0, 4)	2 (0, 6)	< 0.001
Non-invasive ventilation	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.2
Vasopressors	2 (0, 5)	1 (0, 4)	2 (0, 6)	< 0.001
RRT	2 (0, 3)	2 (1, 3)	3 (1, 5)	< 0.001
Diuretic	0 (0, 2)	0 (0, 2)	0 (0, 2)	< 0.001
Mean Daily				
Fluid Balance (mL)	132.71 (-434.85, 697.87)	-139.20 (-877.79, 547.51)	420.04 (-294.09, 1,188.55)	< 0.001

	AKI Diagnostic Criteria			
NEE Score (µg/kg/min)	0.04 (0.01, 0.08)	0.05 (0.02, 0.13)	0.08 (0.03, 0.23)	< 0.001
Furosemide Dose (mg)	40.00 (20.00, 60.00)	40.00 (26.67, 74.24)	51.21 (33.33, 91.06)	< 0.001
[1]Median (IQR) or Frequency (%)				
[2]Pearson's Chi-squared test; Kruskal-Wallis rank sum test				
Abbreviations: SA-AKI = sepsis-associated acute kidney injury; RRT = renal replacement therapy; NEE = norepinephrine equivalent				

In SA-AKI patients, when compared to stage 1 and stage 2, patients with stage 3 were less likely to receive ventilation, received fewer days of vasopressor, and were more likely to require RRT (Online Supplement, **Table S8**), which may represent a possible interaction with chronic kidney disease (CKD), which was not available in the data. For the entire cohort, patients with SA-AKI were more likely to require ventilation, vasopressors, and RRT (Online Supplement, **Table S9**).

Associated Outcomes

As shown in Table 4, we examined outcomes based on the AKI diagnostic criteria met (urine output alone, creatinine along, or both). Patients diagnosed with AKI only due to low urine output, had lower severity of maximum AKI, less need for RRT, a shorter LOS, and a lower mortality, when compared to diagnosis with both, or serum creatinine alone. To further determine the impact of severity of AKI at diagnosis, we compared outcomes for AKI diagnostic criteria met in each AKI severity group. In stage 1 AKI, when compared to creatinine alone or both, low UO consistently had lower severity of AKI, a much lower RRT requirement, a lower mortality, and a MAKE-30 demonstrating few adverse renal outcomes (Online Supplement, **Table S10**). The relatively low requirement for RRT, low mortality and almost absence of adverse renal outcomes in patients diagnosed by urine output alone was consistent in stage 2 and stage 3 AKI (Online Supplement, **Tables S11 – S12**).

Table 4
Outcomes in all SA-AKI patients by AKI Diagnostic Criteria

	AKI Diagnostic Criteria			
Variable	**Urine Output Only**, N = 7,180[1]	**Creatinine Only**, N = 4,999[1]	**Both**, N = 3,280[1]	p value[2]
Maximum AKI Stage in ICU				< 0.001
1	4,076 (57%)	1,576 (32%)	272 (8.3%)	
2	1,909 (27%)	1,461 (29%)	713 (22%)	
3	1,195 (17%)	1,962 (39%)	2,295 (70%)	
Any RRT	237 (3.3%)	949 (19%)	1,657 (51%)	< 0.001
ICU LOS (hours)	87 (47, 158)	73 (41, 141)	95 (47, 200)	< 0.001
Hospital LOS (hours)	291 (157, 548)	283 (158, 559)	347 (160, 654)	< 0.001
ICU Mortality	714 (9.9%)	569 (11%)	889 (27%)	< 0.001
Hospital Mortality	1,016 (14%)	843 (17%)	1,147 (35%)	< 0.001
MAKE-30	1,110 (15%)	1,448 (29%)	2,085 (64%)	< 0.001
[1]Median (IQR) or Frequency (%)				
[2]Pearson's Chi-squared test; Kruskal-Wallis rank sum test				
Abbreviations: AKI = acute kidney injury; RRT = renal replacement therapy; ICU = intensive care unit; LOS = length of stay; MAKE-30 = major adverse kidney events at day 30				

For patients with SA-AKI, we created a multivariable logistic regression model for MAKE-30 (major adverse kidney events at day 30), defined as mortality, RRT, or doubling of creatinine at day 30, censored at discharge (Online Supplement, **Table S13**). When controlling for patient characteristics and severity of illness, an AKI diagnosis by urine output criteria alone (OR 0.37; 95% CI 0.34–0.39; $p < 0.001$) was associated with a significant decrease in MAKE-30 when compared to both criteria.

Discussion

Key Findings

In this multicentre study, we examined granular data of all ICU admissions at participating hospitals to determine the epidemiology of SA-AKI. We investigated close to 90,000 critically ill patients and found that SA-AKI occurred in one sixth of all ICU admissions, that four out of ten such patients were emergency admissions from the community and one in four from the hospital wards. Furthermore, the proportion of ICU admissions diagnosed with SA-AKI has increased year on year. When compared to other ICU admissions, patients with SA-AKI had a higher severity of illness, despite being more likely to be admitted from the community, and received more organ support therapies.

SA-AKI predominantly occurred within 24 hours of ICU admission and furthermore, the diagnosis of sepsis and AKI were essentially simultaneous. At diagnosis, however, most patients had stage 1 AKI due to low urine output (UO) and relatively low serum creatinine. This cohort typically had early normalisation of UO with resolution of AKI. Overall, patients with SA-AKI who met AKI diagnostic criteria by low UO alone had had a shorter length of stay in the ICU and hospital, as well as lower mortality compared to the remainder of the SA-AKI patients, Finally, when adjusting for baseline characteristics and severity of illness, UO alone had significantly less MAKE-30 events.

Relationship to Literature

To our knowledge no other study has examined the epidemiology of SA-AKI in a large multicenter cohort of patients admitted to ICU utilising the recent consensus ADQI definition. Prior to such definition, previous research demonstrated significant heterogeneity in patient populations, with varying incidence and mortality [8]. Two previously published studies, however, used the SEPSIS-3 and KDIGO criteria to define SA-AKI [23, 24]. One was a single-center retrospective study, only included 351 SA-AKI patients, and reported a very low incidence of SA-AKI at 2.8%, limiting its external validity [23]. Another was a single-centre retrospective study of the association between obesity and AKI in a cohort of 456 patients and did not focus on the epidemiology of SA-AKI [24] Neither study examined the incidence, characteristics, timing, trajectory, treatment, and outcomes of SA-AKI in detail and in a multicentric setting involving a large population. No previous research has assessed the relationship between AKI diagnostic criteria and outcomes in SA-AKI patients.

Implications of the Study Findings

Our findings imply that that SA-AKI is a common and an increasingly prevalent condition in the ICU. Furthermore, they suggest that SA-AKI mostly occurs in patients admitted from the community who already present to the ICU with the combination of sepsis and AKI. In another significant proportion, however, it develops in the hospital wards and, as such, it may be a target for earlier intervention.

Furthermore, the rapid resolution, and rare deterioration, of renal function in SA-AKI patients diagnosed by UO alone suggests that in over half of such patients the presence of SA-AKI is of limited clinical importance. Thus a low urine output may represent a physiological response to sepsis more than a pathophysiological marker of incipient organ failure. These findings may also have significant future therapeutic and research implications as the current standard of care may be sufficient to manage most

cases of stage 1 SA-AKI and prevent adverse outcomes. Moreover, future trials of SA-AKI therapies are unlikely to have sufficient power to detect effects on RRT, MAKE-30, or mortality, if low UO alone SA-AKI patients are included.

Strengths and Limitations

Our study had several strengths. First, it was conducted on a large cohort with a wide array of ICU admissions from a state-wide ICU system encompassing a complete range of adult critical care. This broad patient population is representative of the general Australian population and likely representative of similar populations in resource-rich countries. Second, our study data was comprehensive with highly granular data, which was electronically extracted from a ubiquitous clinical information system. All data collected were clinically validated and had minimal missing data points. Moreover, given their collection by non-research staff they represent an unbiased sample. Third, although we utilised a novel standardised definition for SA-AKI, the definition is composed of the SEPSIS-3 and KDIGO AKI definitions, which are well establish in the literature. As such, we were able to leverage well recognised techniques to analyse large database to identify sepsis and AKI.

We acknowledge some limitations. First, the detection of sepsis and AKI, and therefore SA-AKI, was done electronically and patients may have been misclassified. Organ dysfunction detected by the analysis may not have been caused by infection with an alternative explanation for antibiotics administration and microbiological sampling. However, our very large cohort of patients likely limits the impact of these unusual circumstances. Second, we did not classify SA-AKI into phenotypes as suggested by the ADQI 28 Workgroup [8]. Thus, our cohort of SA-AKI patients may represent different groups with diverging risk factors and outcomes. We plan to focus future work on such phenotypes. Finally, we could not identify, which patients had chronic kidney disease (CKD) prior to presentation. Such patients with AKI on CKD are significant proportion of patients presenting to the ICU with AKI and have specific features and different outomes form those without CKD [25]. Investigation of such patients will require additional data acquisition in future studies.

Conclusion

In a large cohort of critically ill patients, we found that SA-AKI is common in patients admitted to the ICU from the ED, mainly occurs within the day of ICU admission, and with sepsis and AKI simultaneously present. Furthermore, most patients with SA-AKI were diagnosed with stage 1 AKI and by low UO alone, which was associated with infrequent deterioration in renal function, as defined by MAKE-30. These observations provide the necessary epidemiological basis for interventional trials, whilst highlightling the need to focus on specific subsets of all SA-AKI patients.

Declarations

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Statement of Ethics

This study was approved by the Metro South Hospital and Health Service Human Research Ethics Committee (HREC/2022/QMS/82024) with an individual waiver of consent granted.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The study conception and design (all authors); data acquisition (KW); analysis (AS, KW); interpretation of data (all authors); article drafting (KW), article revision for important intellectual content (all authors); final approval of the version submitted for publication (all authors); agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (KW, RB).

Data Availability Statement

Data cannot be shared publicly due to institutional ethics, privacy, and confidentiality regulations. Data release for the purposes of research under Sect. 280 of the Public Health Act 2005 requires application to the Director-General of Queensland Health (PHA@health.qld.gov.au).

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Figures

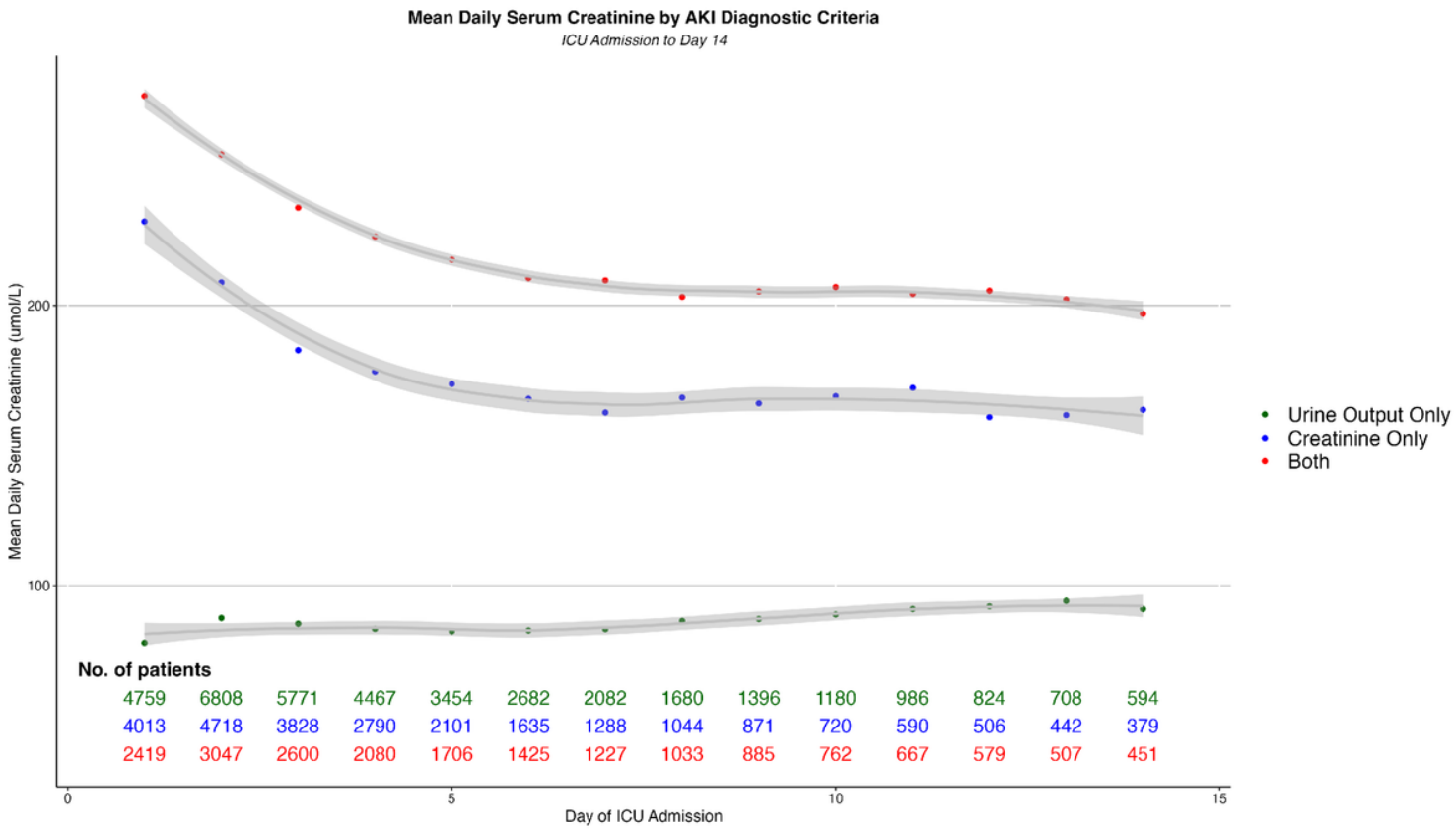

Figure 1

Legend not included with this version.

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