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ORIGINAL ARTICLE

Early and late acute kidney injury: temporal profile in the critically ill pediatric patient

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ABSTRACT

Background. Increasing AKI diagnosis precision to refine the understanding of associated epidemiology and outcomes is a focus of recent critical care nephrology research. Timing of onset of acute kidney injury (AKI) during pediatric critical illness and impact on outcomes has not been fully explored.

Methods. This was a secondary analysis of the Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology (AWARE) database. AKI was defined as per Kidney Disease: Improving Global Outcomes criteria. Early AKI was defined as diagnosed at ≤48 h after intensive care unit (ICU) admission, with any diagnosis >48 h denoted as late AKI. Transient AKI was defined as return to baseline serum creatinine ≤48 h of onset, and those without recovery fell into the persistent category. A second incidence of AKI ≥48 h after recovery was denoted as recurrent. Patients were subsequently sorted into distinct phenotypes as early-transient, late-transient, early-persistent, late-persistent and recurrent. Primary outcome was major adverse kidney events (MAKE) at 28 days (MAKE28) or at study exit, with secondary outcomes including AKI-free days, ICU length of stay and inpatient renal replacement therapy.

Results. A total of 1262 patients had AKI and were included. Overall mortality rate was 6.4% ($n = 81$), with 34.2% ($n = 432$) fulfilling at least one MAKE28 criteria. The majority of patients fell in the early-transient cohort ($n = 704$, 55.8%). The early-persistent phenotype had the highest odds of MAKE28 (odds ratio 7.84, 95% confidence interval 5.45–11.3), and the highest mortality rate (18.8%). Oncologic and nephrologic/urologic comorbidities at AKI diagnosis were associated with MAKE28.

Conclusion. Temporal nature and trajectory of AKI during a critical care course are significantly associated with patient outcomes, with several subtypes at higher risk for poorer outcomes. Stratification of pediatric critical care-associated AKI into distinct phenotypes is possible and may become an important prognostic tool.

Keywords: acute kidney injury, outcome, pediatric critical care, prognostication, renal recovery

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INTRODUCTION

Evidence has demonstrated the association of acute kidney injury (AKI) with higher morbidity and mortality in both hospitalized and critically ill populations [1, 2], but has largely focused on peak injury. Epidemiological studies have shown that AKI is common in the pediatric intensive care unit (PICU), with prevalence ranging from 10% to 82% [3–6]. This foundational work has been limited in exploring the components covered under the umbrella of AKI, making our understanding of AKI phenotypes incomplete, particularly in terms of temporal course and trajectory.

To optimize efforts to prevent AKI occurrence and modify the disease course, we need to understand whether different phenotypes of AKI exist and study associated risk factors to explore intervention opportunities. Much of our knowledge on pediatric AKI has been derived from the somewhat artificial construct of 'AKI peak'. As timeline has been poorly characterized, it is as yet unknown whether AKI that develops after 48 h represents a different phenotype than that diagnosed within 48 h of ICU admission, paralleling the worse morbidity and mortality of progressive or sequential multiple organ dysfunction syndrome (MODS) [7], and how AKI trajectory during an ICU stay may impact outcome.

We present a secondary analysis of the AWARE (Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology) cohort to investigate the temporal phenotypes of AKI based on the time course of AKI evolution. The landmark paper from the AWARE database evaluated 4683 patients and found AKI in 26.9% of patients (11.6% severe AKI) [5]. The aim of our study is to understand the epidemiology, and the impact of the timing of AKI onset (early/late) and AKI course (transient/persistent) might have on different outcome implications, specifically mortality and discharge renal function. We hypothesized that timing of onset, rapid reversibility and progression of AKI will have distinct clinical courses and impact on major adverse kidney event (MAKE) outcomes.

MATERIALS AND METHODS

The AWARE study was a prospective, observational study that recruited patients from 32 international PICUs as previously described [4]. All patients aged between 3 months and 25 years with a predicted ICU stay of at least 48 h were eligible. Data were collected daily for the first 8 days of ICU admission (Day 0 to Day 7), with an additional outcome assessment point at Day 28 or study exit, whichever came first. If patients were discharged prior to Day 28, the data point closest to 28 days was captured. Baseline serum creatinine (SCr) recorded was the lowest within 3 months prior to ICU admission if available. Those without a baseline SCr had it imputed to an estimated creatinine clearance of 120 mL/min/1.73 m^2, as previously validated [5, 8]. Outcomes were censored on Day 28 or study exit, whichever came first. For this analysis, all patients in the AWARE database who met Kidney Disease: Improving Global Outcomes (KDIGO) AKI criteria on ICU Day 0 up to ICU Day 6 either by SCr or urine output (UOP) were included.

Definition of AKI phenotype

Early AKI was defined as AKI at ≤48 h of ICU admission. Any AKI occurring after 48 h was termed late AKI. Patients who no longer fulfilled either AKI diagnostic criterion within 48 h of diagnosis and with no further AKI episodes during their admission were categorized as transient AKI. Those who still fulfilled KDIGO criteria beyond 48 h or died were considered to have persistent AKI.

Another AKI phenotype was defined as recurrent phenotype. Patients were categorized as such if they developed two distinct AKI events during study period. These patients recovered (no longer defined as AKI by KDIGO criteria) after their initial diagnosis but developed a second AKI episode at least 48 h after recovery.

The cumulative number of days with AKI was computed for all the subgroups. The different phenotypes of AKI were further analyzed in groups as such: early-transient, early-persistent, late-transient, late-persistent and recurrent.

Outcomes definitions

The primary outcome was MAKE at study exit. MAKE was modeled after MAKE30, which is a composite score of persistent renal dysfunction (meeting any KDIGO AKI criteria at last datapoint available), in-hospital mortality and new renal replacement therapy (RRT). However, as AWARE data collection stopped at 28 days, we computed MAKE at either 28 days or study exit (MAKE28). Secondary outcomes include AKI-free days, mechanical ventilation free (MV-free) days, 28-day ICU discharge, ICU and hospital length of stay (LOS), and receipt of RRT. Severity of illness (SOI) scores such as the Pediatric Index of Mortality-2 (PIM-2), Pediatric Risk of Mortality Score (PRISM) and PELOD (Pediatric Logistic Organ Dysfunction) score were collected when available. Patients were flagged as having a high SOI score if any score was >75th percentile for the relevant score. As a surrogate of severity of illness at the point of AKI diagnosis, the use of inotropic support was collected.

Percent fluid overload (%FO) was calculated as previously described [9] and median cumulative value of %FO reported at the time of AKI diagnosis. With regard to use of nephrotoxic agents, we analyzed receipt of nonsteroidal anti-inflammatory drugs and other nephrotoxins (specifically vancomycin, aminoglycosides, amphotericin administration and radiocontrast exposure) administered in the ICU pre-AKI diagnosis.

Missing data

A proportion of our patients qualified solely on KDIGO UOP criterion ($n = 443$, 35.1%) with no available SCr. As these patients could not be evaluated for renal recovery based on the SCr criterion of KDIGO, they were conservatively adjudicated as 'renal recovery' in analyses. A further 23 patients had no follow-up SCr values after their initial, hence the number of patients adjudicated to renal recovery totaled 466. It was decided *a priori* to conduct a sensitivity analysis for this cohort who qualified via the UOP criterion only, as they potentially represent a distinct subpopulation.

Statistical analysis

Patient demographics, clinical characteristics and outcomes were summarized overall and by AKI phenotype combinations (early-transient, early-persistent, late-transient, late-persistent and recurrent) using medians and interquartile ranges (IQR) for continuous variables, and frequencies and percentages for discrete characteristics. Bivariable and multivariable logistic

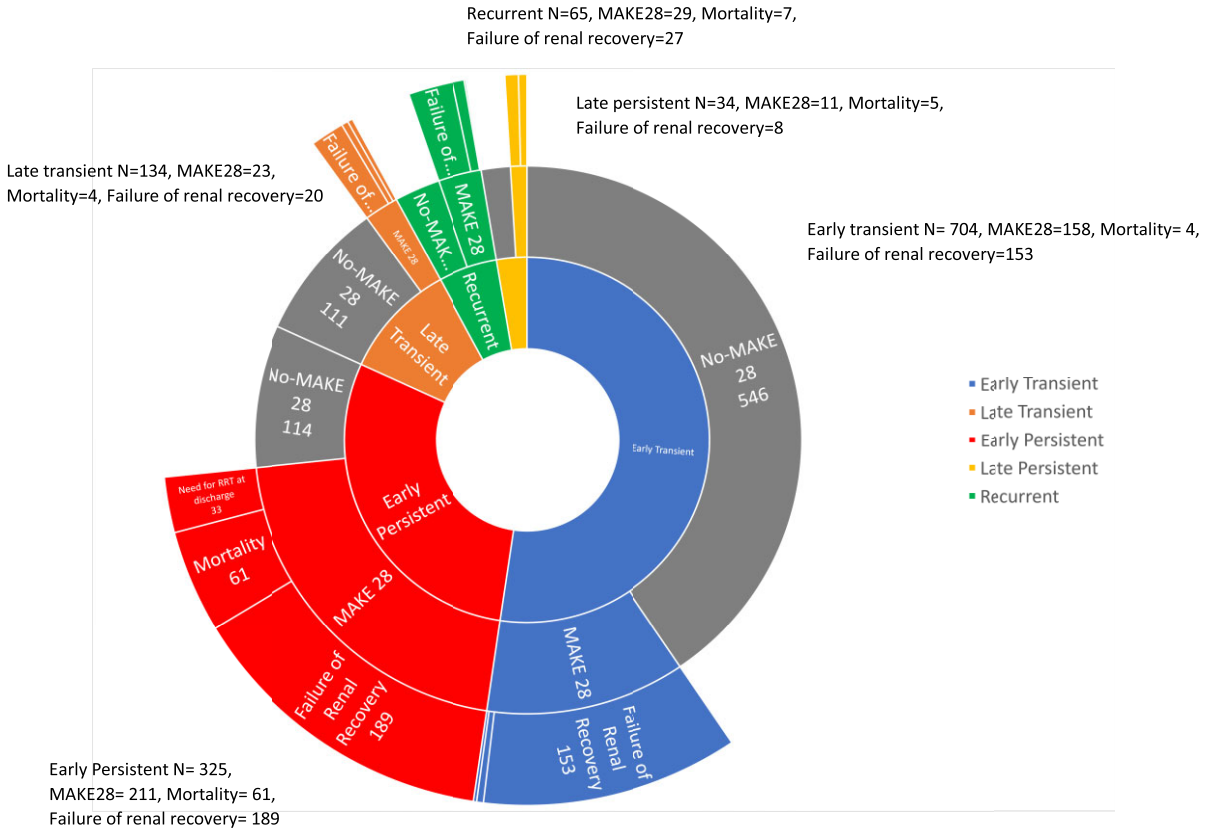

FIGURE 1: Breakdown of MAKE28 by phenotype.

regression considered the odds of MAKE28 by groups of AKI phenotypes, unadjusted and adjusted for patient covariates. Age at ICU admission, gender, need for mechanical ventilation and inotropic support use were included as adjustors in the multivariable model, irrespective of statistical significance. Additional covariates were added using backward selection and retained if the corresponding P-values were <0.05. Results are presented as odds ratios with 95% confidence intervals (CI), using early-transient as reference. Incidence of any of the following: (i) mortality, (ii) need for RRT at discharge or (iii) failure of renal recovery at 28 days, constituted a MAKE28 event.

For all analyses, missing data for mortality and need for RRT at discharge were assumed 'no' (thus all patients had MAKE adjudicated).

For failure of renal recovery at study exit or 28 days, missing data were practically treated as 'no' for MAKE28 but removed from the denominator for descriptive reporting and hypothesis testing.

For the secondary outcome time until 28-day ICU discharge, competing risks analysis was performed to model the probability over time for two mutually exclusive endpoints: ICU discharge and mortality; the remaining patients were alive without ICU discharge. As with the primary aim, models principally considered the association with AKI phenotypes and assessed the relationship unadjusted and adjusted for patient covariates. Results are presented as hazard ratios (HR) with 95% CI using early-transient as reference. Results from these analyses are visually plotted using cumulative incidence curves. AKI phenotype differences between cumulative incidence curves for each endpoint were tested using Gray's tests, with pairwise analyses adjusted for multiple comparisons using Holm's procedure. For each outcome analysis, SOI scores were considered as bivariable predictors by pooling across the PRISM-III, PIM-2 and PELOD measures, and calculating an overall indicator variable. Since SOI scores were only available in 42.2% (532/1262) of the sample, these metrics were not included in the primary multivariable analysis due to listwise deletion. All analyses were performed in SAS v.9.4 (Cary, NC, USA) and CRAN R v.4.0 (Vienna, Austria), and statistical significance was assessed at the 0.05 level.

RESULTS

Demographics and population breakdown

Overall, 1262 patients met our inclusion criteria. The majority had early transient AKI ($n = 704$, 55.8%), with late persistent AKI comprising the smallest group ($n = 34$, 2.7%) (Figure 1). The most common primary diagnosis was respiratory, followed by shock. Mortality was 6.4% ($n = 81$) in the cohort, with 34.2% ($n = 432$) fulfilling at least one criterion in the MAKE28. While a significant portion of the cohort required mechanical ventilation (39.4%, $n = 497$), only a small number required RRT during ICU stay (5%, $n = 63$). The median cumulative AKI days of the cohort was 1 day (IQR 1–3).

Median %FO at AKI diagnosis was 3.6% (IQR 1–7.5%), and this was highest in the late-persistent phenotype (9.1%, IQR 4.9–13.9%) (Table 1).

Table 1. Demographics and characteristics of AKI phenotypes

Characteristics, *n* (%)	Overall, *n* = 1262	Early-transient, *n* = 704 (55.8%)	Early-persistent, *n* = 325 (25.8%)	Late-transient, *n* = 134 (10.6%)	Late-persistent, *n* = 34 (2.7%)	Recurrent, *n* = 65 (5.2%)	P-value (ES)
Age, years	6 (1.3, 13.6)	6.9 (1.5, 14)	4.8 (1, 13.6)	4.9 (1.4, 12.4)	4.2 (1.9, 12.5)	4.3 (0.7, 12.9)	0.143 (0.130)
Male gender	700 (55.5)	395 (56.1)	176 (54.2)	70 (52.2)	20 (58.8)	39 (60)	0.803 (0.082)
Primary diagnosis group							
Cardiovascular	70 (5.6)	28 (4)	29 (8.9)	7 (5.2)	1 (2.9)	5 (7.7)	**0.025** (0.135)
Respiratory	519 (41.1)	227 (32.2)	163 (50.2)	69 (51.5)	22 (64.7)	38 (58.5)	**<0.001** (0.303)
Surgical or trauma	280 (22.2)	182 (25.9)	55 (16.9)	28 (20.9)	4 (11.8)	11 (16.9)	**0.009** (0.167)
Neurologic	217 (17.2)	133 (18.9)	52 (16)	20 (14.9)	4 (11.8)	8 (12.3)	0.403 (0.101)
Shock	429 (34)	221 (31.4)	152 (46.8)	32 (23.9)	10 (29.4)	14 (21.5)	**<0.001** (0.253)
Pain	34 (2.7)	21 (3)	8 (2.5)	3 (2.2)	1 (2.9)	1 (1.5)	0.952 (0.048)
Comorbidities							
Cardiovascular	213 (16.9)	101 (14.4)	69 (21.2)	20 (14.9)	7 (20.6)	16 (24.6)	**0.021** (0.137)
Pulmonary	468 (37.1)	250 (35.5)	124 (38.2)	52 (38.8)	13 (38.2)	29 (44.6)	0.615 (0.077)
Neurologic	428 (33.9)	245 (34.8)	92 (28.3)	47 (35.1)	15 (44.1)	29 (44.6)	**0.040** (0.175)
Hepato-intestinal	320 (25.4)	154 (21.9)	105 (32.3)	35 (26.1)	6 (17.7)	20 (30.8)	**0.006** (0.178)
Hematologic	132 (10.5)	61 (8.7)	42 (12.9)	14 (10.5)	3 (8.8)	12 (18.5)	0.061 (0.142)
Oncologic	143 (11.3)	76 (10.8)	51 (15.7)	6 (4.5)	3 (8.8)	7 (10.8)	**0.012** (0.167)
Immunologic	48 (3.8)	25 (3.6)	18 (5.5)	4 (3)	1 (2.9)	0 (0)	0.215 (0.153)
Infectious disease	134 (10.6)	57 (8.1)	47 (14.5)	17 (12.7)	2 (5.9)	11 (16.9)	**0.009** (0.182)
Rheumatologic	17 (1.4)	7 (1)	8 (2.5)	1 (0.8)	1 (2.9)	0 (0)	0.213 (0.135)
Neuromuscular	176 (14)	93 (13.2)	42 (12.9)	17 (12.7)	9 (26.5)	15 (23.1)	**0.044** (0.194)
Metabolic	192 (15.2)	116 (16.5)	51 (15.7)	12 (9)	2 (5.9)	11 (16.9)	0.109 (0.187)
Nephrologic/urologic	129 (10.2)	55 (7.8)	52 (16)	14 (10.5)	3 (8.8)	5 (7.7)	**0.003** (0.122)
% Fluid overload, at AKI diagnosis[a]	3.6 (1, 7.5)	3.1 (0.8, 6.2)	3.3 (0.9, 7.7)	7.5 (3.1, 14.5)	9.1 (4.9, 13.9)	4.6 (1.6, 9.9)	**<0.001** (0.411)
Severity of illness[a]							
PRISM-III	5 (0, 9)	3 (0, 7)	9.5 (5, 16)	3 (0, 6)	3 (0, 9)	3.5 (1.0, 10.0)	**<0.001** (0.477)
PIM-2	1 (1, 4)	1 (0, 3)	3 (1, 10)	2 (1, 4)	1 (1, 3)	1.5 (1.0, 5.0)	**<0.001** (0.446)
PELOD-R	10, (1, 12)	10 (1, 11)	11.5 (10, 20)	10 (1, 12)	5.5 (0.5, 11)	11.0 (2.0, 11.0)	**<0.001** (0.463)
Any severity score >75th percentile[a]	159 (29.9)	55 (19.2)	75 (53.6)	16 (23.9)	3 (20)	10 (41.7)	**<0.001** (0.398)
Inotropic support, at AKI diagnosis	222 (17.6)	82 (11.7)	113 (34.8)	12 (9)	4 (11.8)	11 (16.9)	**<0.001** (0.293)
Exposure to nephrotoxins pre-AKI[a]							
NSAIDs	96 (13.3)	55 (13.3)	13 (12.4)	16 (11.9)	8 (23.5)	4 (11.4)	0.482 (0.137)
Other[b]	220 (30.5)	91 (22)	47 (44.8)	55 (41)	16 (47.1)	11 (31.4)	**<0.001** (0.272)

Where data are not presented as n (%), they are median (IQR). Values in bold denote statistical significance. NSAIDs, non-steroidal anti-inflammatory drugs; ES = effect size, interpreted using Cohen's *f* as small (0.1), moderate (0.25) and large (0.4).
[a]Reduced sample sizes: % fluid overload (*n* = 1240), PRISM (*n* = 405), PIM (*n* = 365), PELOD (*n* = 189), any SS >75th percentile (*n* = 532), NSAIDs (*n* = 722), other (*n* = 722).
[b]Other nephrotoxins: vancomycin, amphotericin, aminoglycosides and radiocontrast exposure.

Factors associated with MAKE28

On bivariate analysis, cardiovascular, respiratory and shock admitting diagnoses were associated with MAKE28 (Table 3). Having any severity score >75th percentile, need for inotropic support at AKI diagnosis and mechanical ventilation were similarly associated with MAKE28. Older patients had lower odds of having a MAKE28 outcome [odds ratio (OR) 0.74, 95% CI 0.67–0.81].

On multivariable analysis, the associations with MAKE28 held for hepato-intestinal, oncologic and nephrologic/urologic comorbidities. Metabolic comorbidity also was found to have significant association.

AKI phenotypes and outcomes

Among the subgroups, the early-persistent AKI phenotype had the worst outcome overall with the highest mortality rate (18.8%), highest percentage of patients requiring RRT during admission (15.1%) and the lowest 28-day MV-free days (19 days, IQR 0–24). At discharge, this phenotype also had the highest percentage of patients with failure of renal recovery (58.2%, 189/325) (Table 2).

MAKE28 outcomes. The early-persistent phenotype had the highest percentage of patients meeting a MAKE28 criteria (64.9%, *n* = 211). Under bivariate analysis, and relative to early-transient patients, this group carried the highest odds of having MAKE28 (OR 6.40, 95% CI 4.79–8.54), followed by the recurrent phenotype (OR 2.78, 95% CI 1.66–4.68).

In the multivariable logistic regression model, our findings remained consistent with the early-persistent phenotype retaining the strongest association with MAKE28 (OR 7.84, 95% CI 5.45–11.3), followed by the recurrent phenotype (OR 3.82, 95% CI 2.07–7.06) (Table 3).

28-Day discharge modeling. In this model where lower HR indicate a lower likelihood of ICU discharge, relative to early-transient and accounting for death as a competing risk, patients with the late-persistent AKI phenotype had the least desirable outcome with an HR of 0.30 (95% CI 0.22–0.42), followed by those

Table 2. Outcomes

Characteristics, *n* (%)	Overall, *n* = 1262	Early-transient, *n* = 704 (55.8%)	Early-persistent, *n* = 325 (25.8%)	Late-transient, *n* = 134 (10.6%)	Late-persistent, *n* = 34 (2.7%)	Recurrent, *n* = 65 (5.2%)	P-value (ES)
MAKE28[a]	432 (34.2)	158 (22.4)	211 (64.9)	23 (17.2)	11 (32.4)	29 (44.6)	**<0.001** (0.524)
Mortality	81 (6.4)	4 (0.6)	61 (18.8)	4 (3)	5 (14.7)	7 (10.8)	**<0.001** (0.355)
Need for RRT at discharge	39 (3.1)	2 (0.3)	33 (10.2)	3 (2.2)	0 (0)	1 (1.5)	**<0.001** (0.246)
Failure of renal recovery[b]	397 (49.9)	153 (39.8)	189 (62.8)	20 (41.7)	8 (44.4)	27 (60)	**<0.001** (0.262)
ICU length of stay[b]	5 (3, 8)	3 (2, 5)	7 (4, 13)	6 (5, 9)	8 (8, 11)	10 (8, 15)	**<0.001** (0.621)
28-Day ICU-free days[b]	23 (18, 25)	25 (23, 26)	18 (6, 22)	22 (19, 23)	18 (13, 20)	18 (9, 20)	**<0.001** (0.682)
Receipt of MV[a]	497 (40.4)	192 (28.4)	186 (57.6)	68 (50.8)	13 (38.2)	38 (58.5)	**<0.001** (0.330)
Length of MV[b]	4 (2, 9)	3 (1, 5)	6 (3, 11)	5 (3, 7)	7 (5, 9)	8 (5, 14)	**<0.001** (0.348)
28-Day MV-free days[b]	23 (15, 26)	25 (23, 27)	19 (0, 24)	23 (21, 25)	21 (14, 23)	20 (0, 23)	**<0.001** (0.533)
RRT during admission	63 (5)	7 (1)	49 (15.1)	3 (2.2)	1 (2.9)	3 (4.6)	**<0.001** (0.252)
Total AKI days	1 (1, 3)	1 (1, 1)	4 (3, 6)	1 (1, 1)	3 (2, 4)	3 (2, 4)	**<0.001** (1.512)

Where data are not presented as n (%), they are median (IQR). Values in bold denote statistical significance. ES, effect size, interpreted using Cohen's *f* as small (0.1), moderate (0.25), and large (0.4).

[a]MAKE28 calculated by any of three events: mortality, need for RRT at discharge, failure of renal recovery at study exit or 28 days. For missing data, components of the MAKE28 definition were adjudicated as 'no'.

[b]Reduced sample sizes: ICU LOS and 28 ICU-free days (*n* = 1 178), receipt of MV (*n* = 1231), length of MV and 28-day MV-free days (*n* = 493/497 with MV), failure of renal recovery is at study exit or 28 days (*n* = 796).

in the recurrent phenotype (HR 0.33, CI 0.27–0.42), after adjustment (Table 4) (Figure 2).

Sensitivity analysis

Patients who met inclusion criteria solely based on UOP (443/1262) were analyzed separately and conservatively assumed to have renal recovery for statistical purposes. Comparing them to patients who had both SCr and UOP available, patients qualifying on UOP appeared to be less severely ill, with only a 2% mortality rate (versus 19%) and one patient (0.2% versus 17.2%) needing RRT at discharge (Supplementary data).

DISCUSSION

To our knowledge, this report is one of the first to study the timing of AKI as it relates to outcomes in critically ill children. While intuitively it seems that the timing of AKI onset would affect outcomes, we found that the trajectory of the resolution of AKI is a more significant predictor, with early-persistent AKI strongly associated with poorer outcomes. A surprising finding was the recurrent phenotype, where a second onset of AKI seemed to be a strong signal of poor prognosis.

It is well established that AKI during a pediatric ICU admission is an independent predictor for mortality and morbidity, and much recent work has illuminated the need for more sophisticated stratifications of cohorts with pediatric critical care illness-related AKI. Our findings show that delineating the temporal nature and trajectory of AKI in a pediatric critical illness course carries a significant impact on patient outcomes.

Recent consensus definitions for AKI have increasingly recommended inclusion of the temporal characteristics of AKI [10, 11]. However, the definitions of timing have so far have been widely variable, with some studies framing early AKI as present at admission versus up to a week into the hospital stay [12, 13]. The original KDIGO definition stipulates a timeline (a 0.3 mg/dL increase in SCr within 48 h or 1.5× SCr within 7 days), yet this time-sensitive aspect of the definition has frequently been ignored in the pediatric literature [8]. Available adult data actually show that many AKI events occur >48 h after ICU admission [14, 15].

More data are emerging—one recent paper exploring the effects of FO on AKI patients found that delineating distinct phenotypes within their cohort had implications for outcomes [16]. Another potentially illustrative analog is the work investigating the MODS population. While existing data show patients with Day 1 MODS have worse outcomes compared with those without [17], a recent study of septic pediatric patients showed the subsets of population whose MODS progressed and those who developed new MODS had worse morbidity and mortality [7]. One unique phenotype we introduced was the recurrent subgroup; while they comprise a small percentage of patients, their outcomes were significantly worse. This raises a question of a 'second-hit' theory (parallel to the findings in new and progressive MODS), in which some ICU patients who recovered from their initial AKI suffered another complication and worsening of their underlying diagnosis, versus underrecognition and undertreatment of subtle but ongoing AKI. While sparse, data in the surgical cardiac population suggest that a first episode of AKI may portend a worse episode later, potentially due to lower renal reserve [18]. Another possibility that would be challenging to differentiate is that the second onset of AKI is simply a marker of the underlying severity of illness. Nevertheless, whichever the underlying pathophysiology happens to be, the signal remains clear that this pattern of AKI represents a distinctive subset of patients, consistent with emerging literature [19, 20].

In 2015, Perinel *et al.* [21] examined critically ill adult patients and found that those with persistent AKI had a higher rate of mortality compared with those with transient AKI. An additional paper by Sanchez-Pinto *et al.* [22] examined the association of AKI progression in critically ill children with mortality, and found that patients whose AKI worsened from admission to peak and reached an AKI stage of 2 or 3 had higher mortality than patients without AKI and those whose AKI remained at stage 1. Of note, this study also found that despite AKI resolution, patients with stage 1 AKI still had increased mortality compared with those without. Since then, there has been no further pediatric study done on how the course of AKI during an ICU admission correlates with outcomes, but these findings

Table 3. Bivariable and multivariable logistic regression models for risk of MAKE28

Characteristic, *n* (column %)	No MAKE28, *n* = 830 (65.8%)	MAKE28, *n* = 432 (34.2%)	Bivariable OR (95% CI)	Multivariable[a] OR (95% CI)
Recurrent	36 (4.3)	29 (6.7)	2.78 (1.66, 4.68)	3.82 (2.07, 7.06)
Late-persistent	23 (2.8)	11 (2.5)	1.65 (0.79, 3.46)	2.60 (1.16, 5.83)
Late-transient	111 (13.4)	23 (5.3)	0.72 (0.44, 1.16)	0.78 (0.46, 1.34)
Early-persistent	114 (13.7)	211 (48.8)	6.40 (4.79, 8.54)	7.84 (5.45, 11.3)
Early-transient	546 (65.8)	158 (36.6)	Reference	Reference
Age, years[b]	7.5 (2.1, 14.4)	2.8 (0.8, 11.2)	0.74 (0.67, 0.81)	0.64 (0.57, 0.72)
Male gender	455 (54.8)	245 (56.7)	1.08 (0.85, 1.36)	0.99 (0.75, 1.31)
Primary diagnosis group				
Cardiovascular	37 (4.5)	33 (7.6)	1.77 (1.09, 2.88)	
Respiratory	316 (38.1)	203 (47)	1.44 (1.14, 1.82)	
Surgical or trauma	200 (24.1)	80 (18.5)	0.72 (0.54, 0.96)	
Neurologic	140 (16.9)	77 (17.8)	1.07 (0.79, 1.45)	
Shock	258 (31.1)	171 (39.6)	1.45 (1.14, 1.85)	
Pain	25 (3)	9 (2.1)	0.69 (0.32, 1.48)	
Comorbidities				
Cardiovascular	134 (16.1)	79 (18.3)	1.16 (0.86, 1.58)	
Pulmonary	304 (36.6)	164 (38)	1.06 (0.83, 1.35)	
Neurologic	292 (35.2)	136 (31.5)	0.85 (0.66, 1.09)	
Hepato-intestinal	182 (21.9)	138 (31.9)	1.67 (1.29, 2.17)	1.39 (1.02, 1.90)
Hematologic	76 (9.2)	56 (13)	1.48 (1.02, 2.13)	1.62 (1.03, 2.54)
Oncologic	81 (9.8)	62 (14.4)	1.55 (1.09, 2.21)	1.58 (1.04, 2.40)
Immunologic	25 (3)	23 (5.3)	1.81 (1.02, 3.23)	
Infectious disease	81 (9.8)	53 (12.3)	1.29 (0.89, 1.87)	
Rheumatologic	13 (1.6)	4 (0.9)	0.59 (0.19, 1.81)	
Neuromuscular	124 (14.9)	52 (12)	0.78 (0.55, 1.10)	
Metabolic	122 (14.7)	70 (16.2)	1.12 (0.81, 1.54)	1.50 (1.02, 2.22)
Nephrologic/urologic	63 (7.6)	66 (15.3)	2.19 (1.52, 3.17)	1.86 (1.20, 2.88)
% FO, at AKI diagnosis	3.7 (1.1, 7.4)	3.5 (1.0, 7.9)	1.00 (0.99, 1.02)	
Severity of illness				
PRISM-III	3 (0, 7)	7 (3, 13)	1.10 (1.06, 1.14)	
PIM-2	1 (1, 3)	3 (1, 11.5)	1.06 (1.03, 1.09)	
PELOD-R	10 (1, 11)	11 (1, 20)	1.05 (1.01, 1.09)	
Any severity score >75th percentile	77 (21.5)	82 (47.1)	3.25 (2.20, 4.81)	
Inotropic support, at AKI diagnosis	115 (13.9)	107 (24.8)	2.05 (1.52, 2.75)	1.30 (0.89, 1.90)
Nephrotoxins pre-AKI diagnosis				
NSAIDs	85 (14.7)	11 (7.6)	0.47 (0.25, 0.92)	
Other[c]	156 (27)	64 (44.1)	2.13 (1.46, 3.11)	
ICU LOS, days	5 (3, 8)	5 (3, 9)	1.01 (0.99, 1.03)	
Receipt of MV	308 (38.1)	189 (44.7)	1.31 (1.03, 1.66)	0.98 (0.72, 1.34)
MV duration	4 (2, 7)	6 (2, 11)	1.04 (1.01, 1.06)	
Total AKI days	1 (1, 2)	2 (1, 5)	1.56 (1.45, 1.67)	

Where data are not presented as n (%), they are median (IQR). NSAIDs, non-steroidal anti-inflammatory drugs.
[a]Age at ICU admission, gender, mechanical ventilation and inotropic support included in model, regardless of statistical significance.
[b]OR for age at ICU admission increment in units of 5 years.
[c]Vancomycin, ambisome/amphotericin, aminoglycosides, radiocontrast exposure.

suggest that the progression of AKI may be a clinically significant signal.

While adult data on transient versus persistent AKI have so far been inconclusive, our study strengthens the assertion that rapid recovery of renal function is a favorable prognostic factor. Subtle differences in our definitions notwithstanding (adult studies have defined persistent AKI as ≥72 h, while we used a 48 h cut off), our study suggests that there are groups of patients—such as those with persistent AKI—who warrant additional attention in clinical practice, with the 'early-persistent' subgroup potentially a target for intervention. Certainly, our results seem in line with the evolving thought that AKI recovery pattern should acquire more importance in our prognostication [23–25] for both in-hospital and outpatient outcomes. In addition, we present a stratification framework that might be leveraged for interventional trials to fine-tune renal morbidity and selectively target at-risk patients expected to have worse outcomes for prognostic enrichment [26, 27].

Our study has several limitations arising from the retrospective nature of the analysis. As AWARE only collected data up to 7 days in the ICU, this created challenges for our follow-up, especially of the 'late-persistent' and the 'recurrent' subgroups whose second AKI incidences were diagnosed much later in the ICU stay. While this accounted for a small subset of our total cohort (168 patients in the 'late-persistent', 65 patients in the 'recurrent' category and only 13 patients whose AKI were diagnosed on Day 7 of ICU stay), data for potential renal recovery in this group is incomplete. We do not have enough granular follow-up data to ascertain precisely when late-persistent AKI resolved as their outcome data point was collected at Day 28 or

Table 4. Bivariable and multivariable CRA models for 28-day ICU discharge

Characteristic, *n* (column %)	No event, *n* = 95 (7.5%)	28-Day death, *n* = 74 (5.9%)	28-Day discharge, *n* = 1093 (86.6%)	Bivariable HR (95% CI)	Multivariable[a] HR (95% CI)
Recurrent	9 (9.5)	6 (8.1)	50 (4.6)	0.29 (0.24, 0.36)	0.33 (0.27, 0.42)
Late-persistent	3 (3.2)	4 (5.4)	27 (2.5)	0.31 (0.23, 0.41)	0.30 (0.22, 0.42)
Late-transient	15 (15.8)	4 (5.4)	115 (10.5)	0.50 (0.43, 0.58)	0.56 (0.48, 0.65)
Early-persistent	28 (29.5)	58 (78.4)	239 (21.9)	0.29 (0.25, 0.33)	0.38 (0.33, 0.45)
Early-transient	40 (42.1)	2 (2.7)	662 (60.5)	Reference	Reference
Age, years[b]	5.1 (0.7, 13)	4.7 (0.9, 11.8)	6.2 (1.4, 13.7)	1.05 (1.01, 1.09)	1.00 (0.99, 1.02)
Male gender	54 (56.8)	42 (56.8)	604 (55.3)	1.01 (0.91, 1.13)	1.01 (0.90, 1.14)
Primary diagnosis group					
Cardiovascular	6 (6.3)	15 (20.3)	49 (4.5)	0.57 (0.43, 0.75)	0.66 (0.49, 0.89)
Respiratory	46 (48.4)	43 (58.1)	430 (39.3)	0.70 (0.62, 0.78)	0.82 (0.72, 0.93)
Surgical or trauma	20 (21.1)	4 (5.4)	256 (23.4)	1.29 (1.15, 1.46)	
Neurologic	15 (15.8)	15 (20.3)	187 (17.1)	1.05 (0.90, 1.21)	0.82 (0.69, 0.96)
Shock	35 (36.8)	40 (54.1)	354 (32.4)	0.87 (0.77, 0.98)	
Pain	1 (1.1)	1 (1.4)	32 (2.9)	1.27 (0.93, 1.73)	
Comorbidities					
Cardiovascular	20 (21.1)	21 (28.4)	172 (15.7)	0.73 (0.63, 0.85)	
Pulmonary	42 (44.2)	28 (37.8)	398 (36.4)	0.91 (0.81, 1.02)	
Neurologic	36 (37.9)	21 (28.4)	371 (33.9)	1.03 (0.92, 1.16)	
Hepato-intestinal	21 (22.1)	19 (25.7)	280 (25.6)	0.92 (0.81, 1.03)	
Hematologic	10 (10.5)	19 (25.7)	103 (9.4)	0.74 (0.61, 0.90)	0.82 (0.68, 0.98)
Oncologic	6 (6.3)	11 (14.9)	126 (11.5)	0.94 (0.79, 1.12)	
Immunologic	6 (6.3)	6 (8.1)	36 (3.3)	0.86 (0.60, 1.24)	
Infectious disease	16 (16.8)	13 (17.6)	105 (9.6)	0.70 (0.59, 0.85)	0.75 (0.59, 0.97)
Rheumatologic	1 (1.1)	0 (0)	16 (1.5)	1.12 (0.84, 1.48)	
Neuromuscular	23 (24.2)	8 (10.8)	145 (13.3)	0.93 (0.80, 1.08)	
Metabolic	21 (22.1)	7 (9.5)	164 (15)	1.14 (0.97, 1.34)	
Nephrologic/urologic	10 (10.5)	9 (12.2)	110 (10.1)	0.91 (0.76, 1.08)	1.17 (1.00, 1.37)
% FO at AKI diagnosis	4.8 (1.7, 9.9)	6.8 (3.2, 10.8)	3.4 (0.9, 7.2)	0.97 (0.96, 0.98)	0.99 (0.98, 1.00)
Severity of illness					
PRISM-III	8 (4, 14)	14 (9, 22)	4 (0, 8)	0.94 (0.93, 0.96)	
PIM-2	3 (1, 16)	5 (3.5, 52)	1 (1, 3)	0.96 (0.95, 0.97)	
PELOD-R	11 (1, 13)	20 (10, 32)	10 (1, 11)	0.95 (0.93, 0.97)	
Any severity score >75th percentile	13 (52)	31 (77.5)	115 (24.6)	0.49 (0.40, 0.60)	
Inotropic support, at AKI diagnosis	23 (24.2)	41 (55.4)	158 (14.5)	0.50 (0.42, 0.58)	0.77 (0.65, 0.91)
Exposure to nephrotoxins, pre-AKI diagnosis					
NSAIDs	7 (14)	3 (10.3)	86 (13.4)	1.11 (0.90, 1.37)	
Other[c]	15 (30)	17 (58.6)	188 (29.2)	0.65 (0.55, 0.75)	
Receipt of MV	48 (75)	56 (75.7)	393 (36)	0.44 (0.39, 0.49)	0.51 (0.45, 0.59)
MV duration	24.5 (17, 28)	5 (2, 10)	4 (2, 7)	0.91 (0.89, 0.93)	
RRT during admission	12 (12.6)	21 (28.4)	30 (2.7)	0.29 (0.20, 0.41)	0.48 (0.35, 0.68)
Total AKI days	2 (1, 5)	2 (2, 5)	1 (1, 2)	0.82 (0.80, 0.84)	

Where data are not presented as n (%), they are median (IQR).
[a]Age at ICU admission, gender, mechanical ventilation and inotropic support included in model, regardless of statistical significance.
[b]HR for age at ICU admission increment in units of 5 years.
[c]Vancomycin, ambisome/amphotericin, aminoglycosides, radiocontrast exposure.

at hospital discharge. Therefore, it is likely that we have underestimated the median duration of AKI in the cohort. In addition, we had a subset of the population whose inclusion was based solely on UOP data without an SCr value, which could skew our results. However, recent literature has demonstrated that patients diagnosed with AKI by either the SCr or UOP criterion only are distinct from those diagnosed based on both SCr and UOP criteria, and that although their clinical characteristics may be different, those diagnosed through the UOP criterion alone had comparable outcomes to patients who qualified through SCr criterion [28]. While we are aware that UOP data collection could be imprecise, we believed that this cohort remained important to include as they potentially represent a distinct subpopulation with discrete patient outcomes. The sensitivity analysis we conducted on the cohort supported this assumption (Supplementary data). Finally, while we had patients with missing data, we decided *a priori* to adjudicate patients with missing data to more favorable outcomes (i.e. no continuous RRT, MAKE28) in order to conservatively bias us away from an effect.

CONCLUSION

We present a novel classification strategy of AKI in pediatric critical care illness. Our study shows that there are clear differences between subgroups outcomes. While the timing of AKI onset did not seem to hold a large significance, we found that

Table 5. Cumulative incidence of 28-day discharge while accounting for death as a competing risk by AKI group

Study group	n	Mortality events	Discharge events	28-Day discharge incidence (95% CI)	Gray's P-value	Pairwise (1)	Pairwise (2)	Pairwise (3)	Pairwise (4)
Recurrent	58	6	50	86.2% (73.8%, 93.0%)	**<0.001**	—			
Late-persistent	31	4	27	87.1% (65.1%, 95.7%)		1.000	—		
Late-transient	120	4	115	95.8% (89.8%, 98.3%)		**0.001**	**0.038**	—	
Early-persistent	301	58	239	79.4% (74.4%, 83.5%)		1.000	1.000	**0.001**	—
Early-transient	668	2	662	99.1% (97.9%, 99.6%)		**0.001**	**0.002**	**0.001**	**0.001**

Values in bold denote statistical significance.

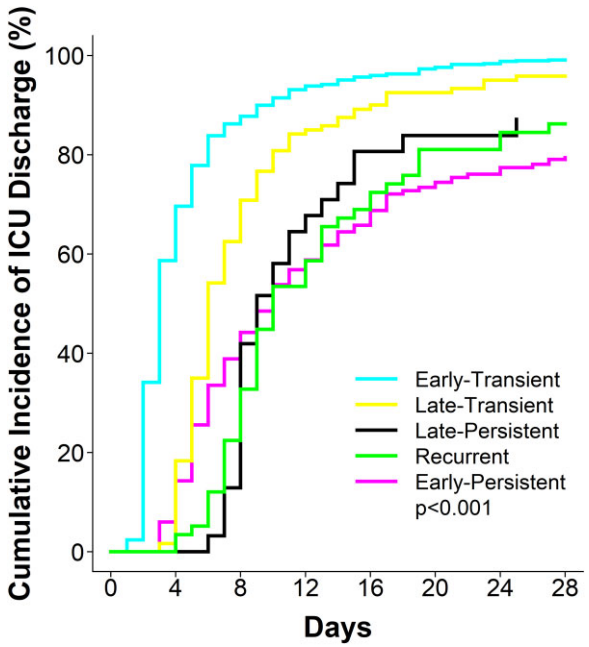

FIGURE 2: Cumulative incidence of 28-day discharge while accounting for death as a competing risk by AKI group.

AKI trajectory and renal recovery are valuable information for prognostication, with AKI resolution potentially playing an important part. Our findings with regard to the recurrent and early-persistent subgroups are intriguing and raise questions regarding identifying underlying causes. These subgroups may also represent rich targets for further investigation and clinical interventions.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by A.R., S.G. and A.A.A. The first draft of the manuscript was written by A.R., with major revisions from A.A.A., S.G. and R.K.B. As first author, A.R. is responsible for the integrity of the work as a whole, from inception to published article. All authors reviewed and commented on previous versions of this manuscript. All authors read and approved of the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, AR. The data belong to the AWARE investigators group and are not publicly available due to containing information that could compromise the privacy of research participants.

ETHICAL APPROVAL

Previously published with the AWARE study of all participating AWARE institutions.

CONFLICT OF INTEREST STATEMENT

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