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Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults

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ABSTRACT

BACKGROUND

The epidemiologic characteristics of children and young adults with acute kidney injury have been described in single-center and retrospective studies. We conducted a multinational, prospective study involving patients admitted to pediatric intensive care units to define the incremental risk of death and complications associated with severe acute kidney injury.

METHODS

We used the Kidney Disease: Improving Global Outcomes criteria to define acute kidney injury. Severe acute kidney injury was defined as stage 2 or 3 acute kidney injury (plasma creatinine level ≥2 times the baseline level or urine output <0.5 ml per kilogram of body weight per hour for ≥12 hours) and was assessed for the first 7 days of intensive care. All patients 3 months to 25 years of age who were admitted to 1 of 32 participating units were screened during 3 consecutive months. The primary outcome was 28-day mortality.

RESULTS

A total of 4683 patients were evaluated; acute kidney injury developed in 1261 patients (26.9%; 95% confidence interval [CI], 25.6 to 28.2), and severe acute kidney injury developed in 543 patients (11.6%; 95% CI, 10.7 to 12.5). Severe acute kidney injury conferred an increased risk of death by day 28 after adjustment for 16 covariates (adjusted odds ratio, 1.77; 95% CI, 1.17 to 2.68); death occurred in 60 of the 543 patients (11.0%) with severe acute kidney injury versus 105 of the 4140 patients (2.5%) without severe acute kidney injury (P<0.001). Severe acute kidney injury was associated with increased use of mechanical ventilation and renal-replacement therapy. A stepwise increase in 28-day mortality was associated with worsening severity of acute kidney injury (P<0.001 by log-rank test). Assessment of acute kidney injury according to the plasma creatinine level alone failed to identify acute kidney injury in 67.2% of the patients with low urine output.

CONCLUSIONS

Acute kidney injury is common and is associated with poor outcomes, including increased mortality, among critically ill children and young adults. (Funded by the Pediatric Nephrology Center of Excellence at Cincinnati Children's Hospital Medical Center and others; AWARE ClinicalTrials.gov number, NCT01987921.)

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Epidemiologic studies involving adults have shown that acute kidney injury is associated with increased mortality, prolonged mechanical ventilation, and prolonged length of stay in intensive care units (ICUs).[1-3] A multinational, prospective study involving 1802 adults[3] initiated the use of Kidney Disease: Improving Global Outcomes (KDIGO) guidelines to describe the epidemiology of acute kidney injury; the guidelines[4] define and stage acute kidney injury according to the plasma creatinine level and urine output (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). That study showed graded associations between the severity of acute kidney injury and outcomes. A single-center study involving adults revealed that mortality and morbidity were higher when both the plasma creatinine level and urine output were used to diagnose acute kidney injury than when either was used alone.[5] In comparison, the study of acute kidney injury in children has been limited.[6-9] Four single-center, retrospective studies involving children have used the KDIGO criteria,[10-13] but none of those assessed urine output in the diagnosis of acute kidney injury.

In studies involving adults, chronic coexisting conditions (e.g., diabetes and cirrhosis) commonly confound the interpretation of the risk that acute kidney injury confers with respect to mortality. Children generally do not have chronic coexisting conditions, so pediatric studies provide a unique opportunity to show a direct role of acute kidney injury in mediating an increased risk of death.

We conducted the Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology (AWARE) study[14] to define the epidemiology of acute kidney injury and to characterize risk factors for acute kidney injury and associated morbidity in a multinational cohort of critically ill children and young adults. We hypothesized that severe acute kidney injury was common and would increase the risk of death.

Methods

Study Design and Cohort

This was a prospective, observational study that recruited patients in 32 pediatric ICUs across Asia, Australia, Europe, and North America for 3 consecutive months in 2014; the design has been published previously.[14] In brief, all patients between 3 months and 25 years of age with a predicted ICU stay of at least 48 hours were eligible. Exclusion criteria were an estimated glomerular filtration rate (GFR) below 15 ml per minute per 1.73 m^2 of body-surface area, maintenance dialysis, or receipt of a kidney transplant in the preceding 90 days. We reviewed the medical records of eligible patients to collect data for the following time periods: up to 3 months before admission (plasma creatinine level only), daily during the first 7 days after ICU admission, and on day 28 after admission. Data on 28-day outcomes were recorded regardless of whether the patient was still in the ICU or had been discharged or had died. All centers obtained approval from health research ethics boards before commencement of the study.

Definitions and Measurements

The baseline plasma creatinine level was defined as the lowest level in the 3 months before admission. The estimated GFR was calculated with the use of the original Schwartz formula.[15] When the baseline plasma creatinine level was unavailable, the estimated GFR was assumed to be 120 ml per minute per 1.73 m^2, as validated previously.[16] We applied KDIGO criteria for the plasma creatinine level and urine output to define and classify acute kidney injury; however, use of renal-replacement therapy was a secondary outcome and was omitted from the definition of stage 3 kidney injury.[4] We required at least one plasma creatinine measurement or at least 12 hours of recorded urine output in the first 7 days after admission to assess for acute kidney injury. When the two criteria resulted in different stages, we chose the higher stage. We defined severe acute kidney injury as stage 2 or 3 acute kidney injury (plasma creatinine level ≥2 times the baseline level or urine output <0.5 ml per kilogram of body weight per hour for ≥12 hours), because these stages have been associated with increased mortality in studies involving children.[7,11,17] To evaluate the effect of the severity of acute kidney injury on secondary outcomes, we defined the maximum stage of acute kidney injury as the highest stage observed during the first 7 days after ICU admission.

OUTCOMES

The primary outcome was 28-day mortality. Secondary outcomes were length of stay in the ICU, receipt and duration of mechanical ventilation, receipt of extracorporeal membrane oxygenation, and receipt of renal-replacement therapy.

STATISTICAL ANALYSIS

Categorical data are presented as counts and percentages and were analyzed with the chi-square test and Fisher's exact test, as appropriate. Normality was tested with the Kolmogorov–Smirnov test. Skewed distributions are described with medians and interquartile ranges and were compared with the use of the Wilcoxon rank-sum test and Kruskal–Wallis test. Normal distributions are described with means and standard deviations and were compared with the use of Student's t-test. The two-sided alpha level was set at 0.05. With respect to missing data, we performed sensitivity analyses to assess for differences in demographic and clinical characteristics, the rate of acute kidney injury, and secondary outcomes when data on the 28-day outcome (alive vs. dead) were unavailable and to assess for differences in 28-day mortality and secondary outcomes when data on the baseline plasma creatinine level were unavailable (Tables S2 and S3 in the Supplementary Appendix).

We used multivariable logistic-regression models for the primary analysis to determine the association between the maximum stage of acute kidney injury and risk of death, with adjustment for risk factors that differed between survivors and nonsurvivors. Variables were entered into models when the alpha level of the risk factor was less than 0.15 in bivariate analysis. Kaplan–Meier survival curves and log-rank tests were used to describe the effect of the maximum stage of acute kidney injury on 28-day mortality. The preferred illness-severity scoring system at each center (the Pediatric Risk of Mortality III [PRISM-III] score, Pediatric Logistic Organ Dysfunction [PELOD] score, or Pediatric Index of Mortality 2 [PIM-2] score)[18] was incorporated in the model for the patients at that center. The risk of death associated with acute kidney injury was evaluated as a categorical variable. In this multivariate analysis, a maximum stage of 2 or 3 was considered to be severe acute kidney injury, and no acute kidney injury or stage 1 was the reference. Linear regression models were created to determine the predictors of length of stay in the ICU. Analyses were conducted with the use of JMP software, version 11.0.0 (SAS Institute), and Microsoft Excel 2010. The protocol and statistical analysis plan are available at NEJM.org.

RESULTS

PATIENT CHARACTERISTICS

We screened 6821 patients, of whom 5237 (76.8%) met the eligibility criteria. Data on 28-day outcomes were available for 4984 patients (95.2%). Figure 1 shows the process from screening to assessment of the primary outcome. Patient demographic and clinical characteristics are shown in Table 1.

A total of 4683 patients had known status with respect to both acute kidney injury and 28-day outcome; among these patients, acute kidney injury developed in 1261 patients (26.9%; 95% confidence interval [CI], 25.6 to 28.2) and severe acute kidney injury developed in 543 (11.6%; 95% CI, 10.7 to 12.5) during the first 7 days after ICU admission. The maximum stage of acute kidney injury was stage 1 in 718 patients (15.3%), stage 2 in 294 patients (6.3%), and stage 3 in 249 patients (5.3%).

Of the 4984 patients with data on 28-day outcomes, 73 (1.5%; 95% CI, 1.2 to 1.8) received renal-replacement therapy. A total of 169 patients (3.4%; 95% CI, 2.9 to 3.9) died within 28 days (148 in the ICU and 21 after discharge from the ICU). Nearly all clinical factors were similar in patients with available data on mortality and the 253 patients with missing data on mortality, and mortality was identical when we included these 253 patients after estimating their mortality on the basis of their identified risk factors for death (Table S2 in the Supplementary Appendix). The 2533 patients without an available measured baseline plasma creatinine level had shorter stays in the ICU and lower use of renal-replacement therapy and mechanical ventilation than the 2451 patients for whom a baseline plasma creatinine level was available. No such associations were seen in the subgroup of 102 patients with a known renal or urologic coexisting condition; within that subgroup, there were no significant differences in these variables between those who did not have an available measured baseline

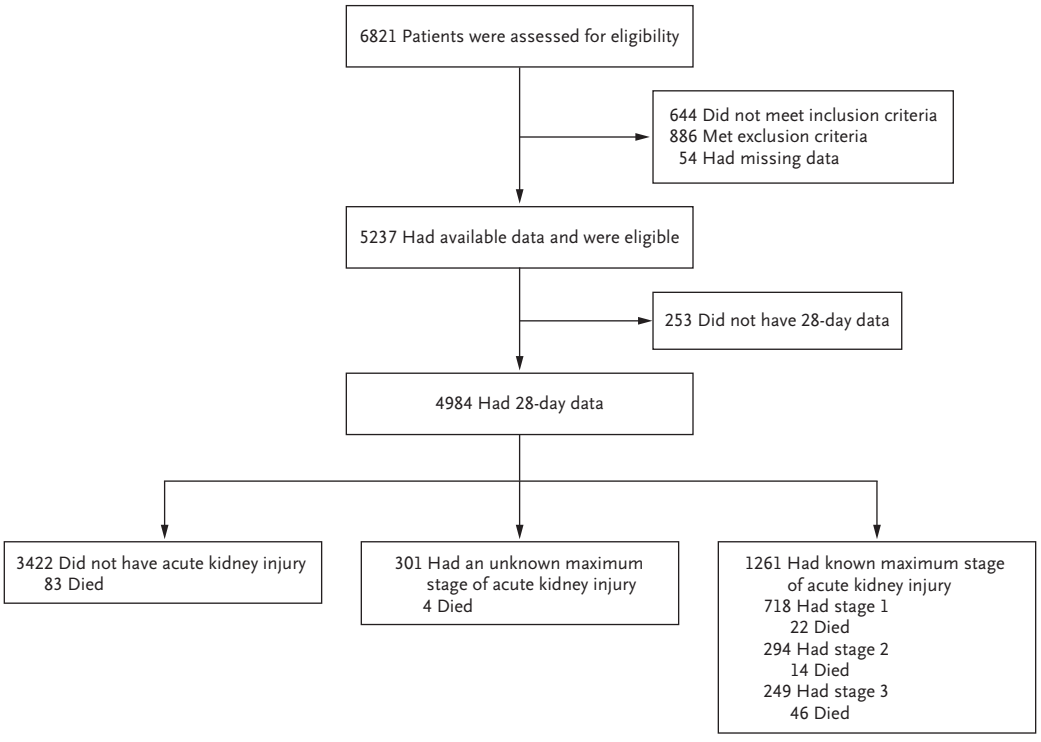


Figure 1. Screening, Eligibility, and 28-Day Primary Outcome.

The primary outcome was death by day 28 after admission to the pediatric intensive care unit (ICU). The 253 patients who did not have 28-day data were excluded from outcome analyses. The maximum stage of acute kidney injury was defined as the highest stage observed during the first 7 days after ICU admission. The stages of acute kidney injury were defined according to the Kidney Disease: Improving Global Outcomes plasma creatinine criteria (stage 1: an increase in the creatinine level to 1.5 to 1.9 times the baseline level that is known or presumed to have occurred within the past 7 days or an increase by ≥0.3 mg per deciliter [26.5 μmol per liter] within the past 48 hours; stage 2: a level 2.0 to 2.9 times the baseline level; stage 3: a level 3.0 times the baseline level, an increase to ≥4.0 mg per deciliter [354 μmol per liter], or, in patients <18 years of age, a decrease in the estimated glomerular filtration rate to <35 ml per minute per 1.73 m^2) and urine-output criteria (stage 1: <0.5 ml per kilogram of body weight per hour for 6 to <12 hours; stage 2: <0.5 ml per kilogram per hour for ≥12 hours; stage 3: <0.3 ml per kilogram per hour for ≥24 hours or anuria for ≥12 hours).

plasma creatinine level and those who did (Table S3A and S3B in the Supplementary Appendix).

SEVERE ACUTE KIDNEY INJURY AS AN INDEPENDENT RISK FACTOR FOR DEATH

Comparative analyses between survivors and nonsurvivors are shown in Table 2. On average, the maximum stage of acute kidney injury was higher in nonsurvivors than in survivors. Severe acute kidney injury was associated with an increased risk of death (odds ratio, 1.77; 95% CI, 1.17 to 2.68) after adjustment for 16 covariates. Death occurred in 60 of the 543 patients (11.0%) with severe acute kidney injury as compared with 105 of the 4140 patients (2.5%) without severe acute kidney injury (P<0.001). The use of renal-replacement therapy was the second strongest predictor (after the use of vasoactive support) of death by day 28 after admission (odds ratio, 3.38; 95% CI, 1.74 to 6.54). Severe acute kidney injury conferred an increased risk of death after adjustment for center-preferred illness-severity scores (P<0.001 for each score: PRISM-III [1263 patients], PIM-2 [1363 patients] and PELOD [859 patients]), with odds ratios ranging from 2.41 to 5.12 (P<0.05 across scores) (Table S4A in the Supplementary Appendix).

MAXIMUM STAGE OF ACUTE KIDNEY INJURY AND OUTCOMES

A stepwise increase in the maximum stage of acute kidney injury conferred an incremental risk of death (P<0.001) (Fig. 2). The risk of death associated with a maximum stage of 3 exceeded

Table 1. Baseline Characteristics of the Study Cohort.*

Variable	Value
Patients — no.	5237
Male sex — no. (%)	2878 (55.0)
Race or ethnic group — no. (%)†	
White	3120 (59.6)
Black	883 (16.9)
Native American	61 (1.2)
Asian	480 (9.2)
Hawaiian or Pacific Islander	27 (0.5)
Other or unknown	666 (12.7)
Age — mo	
Median	66.0
IQR	18.8–151.1
Height at ICU admission — cm	114.8±37.7
Body-surface area — m^2	
Median	0.77
IQR	0.49–1.30
Patients with a measured baseline plasma creatinine level — no. (%)	2539 (48.5)
Estimated GFR — ml/min/1.73 m^2‡	
All patients	
Median	120.0
IQR	120.0–165.6
Patients with a measured baseline plasma creatinine level	
Median	168.7
IQR	120.5–224.6
Primary diagnosis group at ICU admission — no. (%)§	
Shock	1244 (23.8)
Cardiovascular	210 (4.0)
Respiratory	1986 (37.9)
Surgical or trauma	1597 (30.5)
Central nervous system	958 (18.3)
Pain management or sedation	182 (3.5)
Coexisting condition — no. (%)§	
Cardiovascular	658 (12.6)
Pulmonary	1922 (36.7)
Neurologic	1846 (35.2)
Gastrointestinal	925 (17.7)
Renal or urologic	329 (6.3)
Hematologic	356 (6.8)
Oncologic	399 (7.6)
Immunologic	124 (2.4)
Infectious disease	376 (7.2)
Rheumatologic	62 (1.2)
Neuromuscular	702 (13.4)
Metabolic	575 (11.0)
History of transplantation	
Any — no. (%)	219 (4.2)
Type of transplantation — no./total no. (%)	
Hematopoietic stem cell	93/219 (42.5)
Liver	82/219 (37.4)
Kidney	13/219 (5.9)
Small bowel	5/219 (2.3)
Pancreas	1/219 (0.5)
Multivisceral	2/219 (0.9)
Heart	20/219 (9.1)
Lung	12/219 (5.5)

* Plus–minus values are means ±SD. ICU denotes intensive care unit, and IQR interquartile range.

† Race and ethnic group were reported by patients 18 years of age or older who were physically able to provide the information or by parents or guardians if the patient was younger than 18 years of age or too critically ill to provide the information.

‡ The estimated glomerular filtration rate (GFR) was calculated with the original Schwartz formula, in which estimated GFR = k × patient height (in centimeters) ÷ plasma creatinine (in milligrams per deciliter); k is a constant defined as 0.45 (infant younger than 1 year of age), 0.55 (child or female adolescent), or 0.70 (male adolescent).[19]

§ Patients could be part of more than one diagnosis group or have more than one coexisting condition.

the corresponding risk associated with no acute kidney injury or a maximum stage of 1 or 2 ($P<0.001$ for all comparisons). A maximum stage of 2 carried increased risk when compared with no acute kidney injury but not when compared with a maximum stage of 1. Patients with a maximum stage of 1 had longer ICU stays and greater provision and duration of mechanical ventilation than patients without acute kidney injury. Increases in the maximum stage of acute kidney injury were associated with increased length of stay after adjustment for illness-severity scores (Table S4B in the Supplementary Appendix). An increase in the maximum stage of acute kidney injury was associated with increased use of renal-replacement therapy, increased use of

Table 2. Bivariate and Multivariable Logistic-Regression Analysis of Predictors of Death by Day 28 after Admission.

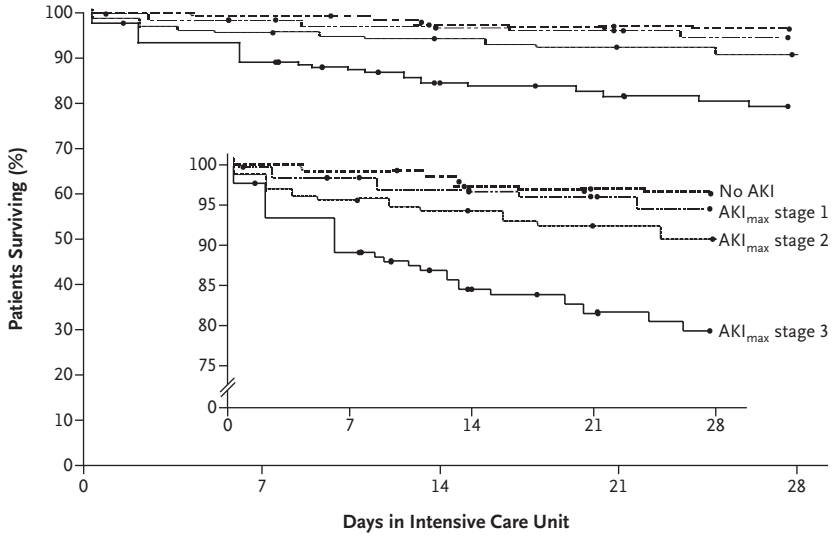
Variable	Bivariate Analysis			Multivariable Logistic-Regression Analysis
	Survivors (N=4815)	Nonsurvivors (N=169)	P Value	Odds Ratio (95% CI)*
Primary diagnosis group at ICU admission — no. (%)†				
Shock	1101 (22.9)	92 (54.4)	<0.001	1.93 (1.31–2.84)
Cardiovascular	178 (3.7)	28 (16.6)	<0.001	2.71 (1.50–4.89)
Respiratory	1814 (37.7)	87 (51.5)	0.003	1.27 (0.86–1.86)
Surgical or trauma	1481 (30.8)	12 (7.1)	<0.001	0.42 (0.22–0.80)
Central nervous system	873 (18.1)	46 (27.2)	0.003	2.42 (1.60–3.68)
Pain management or sedation	164 (3.4)	2 (1.2)	0.06	0.33 (0.07–1.54)
Coexisting condition at baseline — no. (%)†				
Cardiovascular	607 (12.6)	40 (23.7)	<0.001	1.20 (0.75–1.91)
Pulmonary	1785 (37.1)	60 (35.5)	0.68	—
Neurologic	1699 (35.3)	57 (33.7)	0.68	—
Gastrointestinal	875 (18.2)	32 (18.9)	0.80	—
Renal or urologic	307 (6.4)	14 (8.3)	0.34	—
Hematologic	307 (6.4)	35 (20.7)	<0.001	2.99 (1.86–4.82)
Oncologic	353 (7.3)	23 (13.6)	0.01	1.70 (0.97–2.90)
Immunologic	101 (2.1)	8 (4.7)	0.04	1.31 (0.54–3.18)
Infectious disease	351 (7.3)	25 (14.8)	0.006	1.06 (0.60–1.80)
Rheumatologic	61 (1.3)	1 (0.6)	0.38	—
Neuromuscular	601 (12.5)	21 (12.4)	0.98	—
Metabolic	539 (11.2)	22 (13.0)	0.16	—
History of transplantation — no. (%)	195 (4.0)	15 (8.9)	0.007	0.86 (0.43–1.70)
Estimated GFR — ml/min/1.73 m^2				
Median	120	120	0.95	—
IQR	120–166	120–181		
Maximum stage of acute kidney injury — no./total no. (%)‡			<0.001	
No acute kidney injury	3339/4518 (73.9)	83/165 (50.3)		—
Stage 1	696/4518 (15.4)	22/165 (13.3)		—
Stage 2	280/4518 (6.2)	14/165 (8.5)		—
Stage 3	203/4518 (4.5)	46/165 (27.9)		—
Stage 2 or 3: severe acute kidney injury	483/4518 (10.7)	60/165 (36.4)	<0.001	1.77 (1.17–2.68)
Ventricular assist device — no. (%)	7 (0.1)	0	0.49	—
Extracorporeal membrane oxygenation — no. (%)	20 (0.4)	6 (3.6)	0.002	1.12 (0.37–3.39)
Renal-replacement therapy — no. (%)	49 (1.0)	24 (14.2)	<0.001	3.38 (1.74–6.54)
Mechanical ventilation — no. (%)	1456 (30.2)	125 (74.0)	<0.001	3.02 (2.16–4.76)
Vasoactive support — no. (%)	618 (12.8)	108 (63.9)	<0.001	4.67 (3.18–6.87)

* The reference for the odds ratio is the absence of the corresponding risk factor. Variables were entered into the multivariable logistic-regression model (and, therefore, odds ratios were calculated) when the alpha level of the risk factor was less than 0.15 in bivariate analysis.

† Patients could be part of more than one diagnosis group or have more than one coexisting condition.

‡ The analysis was limited to patients with known status with respect to both acute kidney injury and 28-day outcome (alive vs. dead). The stages of acute kidney injury were defined according to the Kidney Disease: Improving Global Outcomes plasma creatinine criteria (stage 1: an increase in the creatinine level to 1.5 to 1.9 times the baseline level that is known or presumed to have occurred within the past 7 days or an increase by ≥0.3 mg per deciliter [26.5 μmol per liter] within the past 48 hours; stage 2: a level 2.0 to 2.9 times the baseline level; stage 3: a level 3.0 times the baseline level, an increase to ≥4.0 mg per deciliter [354 μmol per liter], or, in patients <18 years of age, a decrease in the estimated GFR to <35 ml per minute per 1.73 m^2) and urine-output criteria (stage 1: <0.5 ml per kilogram of body weight per hour for 6 to <12 hours; stage 2: <0.5 ml per kilogram per hour for ≥12 hours; stage 3: <0.3 ml per kilogram per hour for ≥24 hours or anuria for ≥12 hours). The 16 covariates assessed for the multivariable logistic-regression model were a diagnosis at ICU admission of shock, cardiovascular disease, respiratory disease, surgical or trauma, central nervous system disorder, or pain or sedation; the presence of cardiovascular, hematologic, oncologic, immunologic, or infectious conditions at baseline; a history of transplantation; and the use of extracorporeal membrane oxygenation, renal-replacement therapy, mechanical ventilation, or vasoactive support.

	P Value		
	vs. No AKI	vs. AKI_{max} Stage 1	vs. AKI_{max} Stage 2
No AKI	—	—	—
AKI_{max} Stage 1	0.32	—	—
AKI_{max} Stage 2	0.02	0.18	—
AKI_{max} Stage 3	<0.001	<0.001	<0.001



No. of Patients					
No AKI	3422	3369	3356	3348	3339
AKI_{max} stage 1	718	705	701	698	696
AKI_{max} stage 2	294	286	284	282	280
AKI_{max} stage 3	249	223	212	205	203

Figure 2. Kaplan–Meier Survival Curves According to Maximum Stage of Acute Kidney Injury (AKI_{max}).
Death occurred in four patients in whom AKI_{max} was unknown; these patients were excluded from the analysis. The inset shows the same data on an expanded y axis.

extracorporeal membrane oxygenation, and increased use and duration of mechanical ventilation (Table S5 in the Supplementary Appendix).

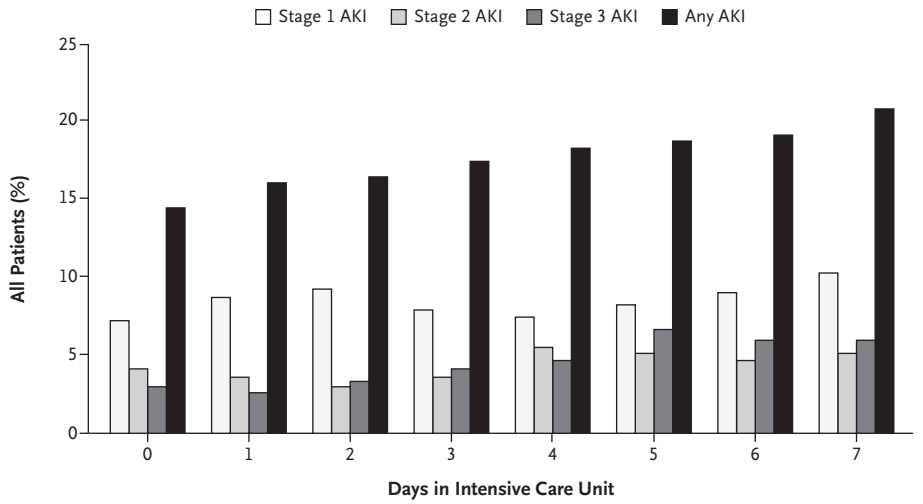
COMPARISON OF PLASMA CREATININE LEVEL AND URINE OUTPUT IN DEFINING ACUTE KIDNEY INJURY

Data on the plasma creatinine level (4036 patients) or urine output (3965 patients) were available to assess for acute kidney injury in 94% of the patients with known 28-day outcomes; 3318 patients had data on both. Mortality was higher among patients with stage 3 acute kidney injury defined according to urine output than among those with stage 3 acute kidney injury defined according to the plasma creatinine level (Fig. S1 in the Supplementary Appendix).

In patients with data on both the plasma creatinine level and urine output, acute kidney injury defined according to the plasma creatinine level developed in 738 patients (22.2%) and acute kidney injury defined according to urine output developed in 528 patients (15.9%). In 355 of the 528 patients (67.2%) who met the urine-output criteria for acute kidney injury, the diagnosis of acute kidney injury would have been missed if only the plasma creatinine criteria had been used. Mortality was higher among patients with low urine output than among those with normal urine output (7.8% vs. 2.9%, $P=0.02$).

PROGRESSION OF ACUTE KIDNEY INJURY

The daily prevalence of acute kidney injury increased progressively from 14.5% to 20.4% over a period of 7 days (Fig. 3). Patients with stage 1 acute kidney injury on day 1 were more likely to have progression to stage 2 or 3 by day 7 than patients without acute kidney injury on day 1 (14.1% vs. 2.9%, $P<0.001$).



All Patients (%)								
Stage 1 AKI	7.3	9.7	9.8	9.0	8.6	9.0	9.8	10.4
Stage 2 AKI	4.1	3.9	3.5	4.2	5.4	4.4	4.3	4.7
Stage 3 AKI	3.1	2.6	3.6	4.4	4.9	5.7	5.3	5.3
Any AKI	14.5	16.2	16.8	17.5	18.9	19.1	19.4	20.4

Figure 3. Prevalence of Acute Kidney Injury, According to Stage, during the First Week of ICU Admission.
For day 0, only the serum creatinine level was used to assess for acute kidney injury because data on urine output were not available. Patients with missing data to assess for acute kidney injury were excluded from analysis.

PREDICTORS OF SEVERE ACUTE KIDNEY INJURY

Several factors were associated with severe acute kidney injury (Table S6 in the Supplementary Appendix). Transplantation was associated with the highest risk (odds ratio, 2.43; 95% CI, 1.71 to 3.40). The distribution of severe acute kidney injury was similar in patients who had undergone solid organ transplantation and those who had undergone bone marrow transplantation (Table S7 in the Supplementary Appendix).

CENTER VARIABILITY

Characteristics of the ICUs are shown in Table S8 in the Supplementary Appendix. We observed intercenter variability in the rate of severe acute kidney injury (median, 10.4%; interquartile range, 7.8 to 16.7) and in the rate of death (median, 3.2%; interquartile range, 2.0 to 6.1). The rates for each individual center and the rates pooled according to country are shown in Figures S2 and S3 in the Supplementary Appendix.

DISCUSSION

This large, prospective, multinational study of the epidemiology of acute kidney injury in children and young adults in ICUs showed that acute kidney injury occurred in one quarter of patients during the first 7 days after ICU admission. Severe acute kidney injury conferred an incremental risk of death by day 28 and was associated with increased use of renal-replacement therapy and mechanical ventilation and longer stays in the ICU. Assessment of acute kidney injury according to the plasma creatinine level alone failed to identify acute kidney injury in two thirds of the patients with low urine output, and low urine output alone conferred an increased risk of death.

The presence of chronic systemic diseases contributes to residual confounding in studies of acute kidney injury in adults. Children have a low prevalence of such chronic diseases; thus, although the incremental association between acute kidney injury and risk of death mirrors that seen in adults, our study suggests that acute kidney injury itself may be key to the associated morbidity and mortality.

The common and early occurrence of acute kidney injury reinforces the need for systematic surveillance for acute kidney injury at the time of admission to the ICU. Early identification of modifiable risk factors for acute kidney injury (e.g., nephrotoxic medications) or adverse sequelae (e.g., fluid overload) has the potential to

decrease morbidity and mortality.[19-21] Previously reported rates of acute kidney injury among children and young adults vary widely — from 5% to 82%.[6,7,11,12,22] This variation probably results from differences in case mix, illness severity, coexisting conditions, and definitions of acute kidney injury. A 5% rate of acute kidney injury was reported in a single-center study that used a 100% rise in the plasma creatinine level to define acute kidney injury,[22] whereas in another study, 82% of patients receiving at least one vasoactive medication and mechanical ventilation had acute kidney injury as defined by a 33% rise in the plasma creatinine level.[6] Since the adoption of standardized classification criteria for acute kidney injury, reported rates among critically ill children have ranged from 10 to 40%.[6,7,10-12] Although we observed intercenter variation in rates of severe acute kidney injury and death, the 95% confidence intervals overlap for the vast majority of sites and countries. The pooled 26.9% rate of acute kidney injury in the current study may therefore be regarded as a valid benchmark, given the large sample and multinational composition.

Our study results provide informative comparisons with those of a recent multicenter study in adults, the Acute Kidney Injury–Epidemiologic Prospective Investigation (AKI-EPI) study.[3] Although the rates of overall and severe acute kidney injury (57.3% and 38.9%, respectively) were higher in the adult study than the corresponding rates in our study, the associations between acute kidney injury and mortality and morbidity are similar.[3] We speculate that the relatively lower rates of acute kidney injury observed in our study represent greater renal reserve in children. Although both studies show an increased risk of death with higher KDIGO stages (odds ratios ranged from 1.18 at stage 1 to 8.21 at stage 3 in our study and from 2.19 at stage 1 to 7.18 at stage 3 in the AKI-EPI study), our study did not show an association between stage 1 acute kidney injury and mortality. The multiple coexisting conditions seen in adults may confer greater susceptibility to acute kidney injury–associated outcomes, which is, in part, supported by the higher overall mortality seen in the AKI-EPI study than in our study (18.4% vs. 3.4%). The current study reinforces the importance of using both the plasma creatinine level and urine output to define acute kidney injury.[5] This finding questions nationwide efforts to prevent urinary tract infections by not placing indwelling bladder catheters, or removing them early, in all critically ill children.[23] Our data suggest that children are more likely to survive severe acute kidney injury than adults. Because children who survive acute kidney injury are at risk for chronic kidney disease, long-term follow-up of these survivors is warranted.[24,25]

Although the daily prevalence of acute kidney injury increased from 14.5% on day 1 to 20.4% on day 7, approximately 75% of the increase occurred within 4 days after admission. This increase probably results from the earlier discharge of less severely ill patients who would be at lower risk for multiorgan failure and acute kidney injury. Such data may support the use of a 4-day time frame for future focused studies of acute kidney injury in children.

Our study has a number of strengths. It involved a large, multicenter cohort of children and young adults, which enabled a robust evaluation of relationships between exposure and outcome, and it had a prespecified protocol, operational definitions, and an analysis plan and enumerated complete standardized diagnostic criteria for acute kidney injury. The overall mortality of 3.4% is similar to the rate reported in epidemiologic studies conducted in pediatric ICUs,[26,27] which suggests that our cohort is representative.

The study also has some limitations. First, because it is an observational cohort study, we cannot make statements regarding causal relationships among acute kidney injury, exposures, and outcomes observed. Second, we cannot generalize our findings outside pediatric ICU settings. Third, we did not assess for the potential effect of the specific cause of acute kidney injury on patient outcomes. Fourth, we have no detailed information on interventions (e.g., use of diuretics) that could increase urinary output and thereby alter the observed prevalence of acute kidney injury. Fifth, we required one plasma creatinine measurement or 12 hours of recorded urine output in the ICU to constitute sufficient data for assessment of acute kidney injury. Although more data could alter the perceived rates, 94% of patients with data on 28-day outcomes met the assessment requirements for the plasma creatinine level or urine output. Sixth, assessment for acute kidney injury stopped at day 7 in our study, and it is possible that we missed events of acute kidney injury occurring later.

Seventh, secondary outcomes (e.g., provision of renal-replacement therapy or mechanical ventilation) were driven by local care practice and therefore were potentially biased by pediatric intensivists who were interested in acute kidney injury. Finally, although the current study represents a large international pediatric study, two thirds of the centers were from North America; we were unable to recruit centers from Africa and South America.

In conclusion, our study involving critically ill children and young adults showed that acute kidney injury is common and is associated with poor outcomes, including increased mortality.

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