



# Major Adverse Kidney Events in Pediatric Sepsis

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## Abstract

**Background and objectives** Major adverse kidney events, a composite of death, new kidney replacement therapy, or persistent kidney dysfunction, is a potential patient-centered outcome for clinical trials in sepsis-associated kidney injury. We sought to determine the incidence of major adverse kidney events within 30 days and validate this end point in pediatric sepsis.

**Design, setting, participants, & measurements** We conducted a retrospective observational study using the Pediatric Health Information Systems Plus database of patients >6 months to <18 years old with a diagnosis of severe sepsis/septic shock; orders for bacterial blood culture, antibiotics, and at least one fluid bolus on hospital day 0/1; and known hospital disposition between January 2007 and December 2011. The primary outcome was incidence of major adverse kidney events within 30 days. Major adverse kidney events within 30 days were validated against all-cause mortality at hospital discharge, hospital length of stay, total hospital costs, hospital readmission within 30 days and 1 year, and lowest eGFR between 3 months and 1 year after discharge. We reported incidence of major adverse kidney events within 30 days with 95% confidence intervals using robust SEM and used multivariable logistic regression to test the association of major adverse kidney events within 30 days with hospital costs and mortality.

**Results** Of 1685 admissions, incidence of major adverse kidney events within 30 days was 9.6% (95% confidence interval, 8.1% to 11.0%), including 4.5% (95% confidence interval, 3.5% to 5.4%) death, 1.7% (95% confidence interval, 1.1% to 2.3%) kidney replacement therapy, and 5.8% (95% confidence interval, 4.7% to 6.9%) persistent kidney dysfunction. Patients with versus without major adverse kidney events within 30 days had higher all-cause mortality at hospital discharge (28% versus 1%;  $P < 0.001$ ), higher total hospital costs (\$61,188; interquartile range, \$21,272–140,356 versus \$28,107; interquartile range, \$13,056–72,697;  $P < 0.001$ ), and higher proportion with eGFR < 60 ml/min per 1.73 m<sup>2</sup> between 3 months and 1 year after discharge (19% versus 4%;  $P = 0.001$ ). Major adverse kidney events within 30 days was not associated with length of stay or readmissions.

**Conclusions** In children with sepsis, major adverse kidney events within 30 days are common, feasible to measure, and a promising end point for future clinical trials.

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## Introduction

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection, and it is a common cause of critical illness for children (1–3). AKI occurs in up to one third of children with severe sepsis or septic shock, and it is a risk factor for adverse outcomes (4–6). In the Sepsis Prevalence Outcomes and Therapies study, stage 2/3 AKI was evident in 21% of patients with sepsis, with an increased odds for death or new moderate disability (4). In the Assessment of Worldwide AKI, Renal Angina, and Epidemiology study, a stepwise increase in stage of AKI also conferred an incremental risk of death (7). Consequently, the potential to prevent, ameliorate, or reverse AKI has become an important therapeutic goal for children with sepsis.

Clinical trials require end points that are sufficiently common, feasible to measure with minimal risk of bias, and valued by patients and families. A recent

systematic review concluded that pediatric sepsis trials should use composite outcomes capturing both mortality and long-term morbidity (8). For trials in which the intervention of interest is biologically mediated through the kidney, an outcome that reflects long-term morbidity due to the effect of AKI on patients is warranted. The composite outcome of major adverse kidney events (MAKE) has been proposed as a clinically meaningful, patient-centered end point (9). MAKE includes death, new kidney replacement therapy (KRT), and persistent kidney dysfunction, which are all measurable distinct events with little opportunity for misclassification bias that relate to long-term health and wellbeing (9). Although even transient AKI can progress to CKD and affect health-related quality of life (10–15), failure to recover from AKI before hospital discharge has been shown to identify the highest-risk subgroup (16). Moreover, new requirement for KRT during hospitalization increases risk of

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CKD and death beyond hospitalization (17,18). Finally, major adverse kidney events within 30 days (MAKE30) were recommended as a patient-centered outcome for phase 3 trials by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (19), and a reduction in MAKE30 with the use of balanced fluids compared with 0.9% saline recently confirmed the utility of this outcome in adult trials (20,21).

There are no data on the incidence of MAKE in pediatric sepsis or its validity as an end point in pediatric sepsis trials. We, therefore, sought to determine the incidence of MAKE30 and validate this end point in children with sepsis. We focused on MAKE30, because clinical outcomes are more likely attributable to sepsis the closer they occur to sepsis onset; also, shorter time intervals are more feasible and affordable, and they expose to less loss to follow-up.

## Materials and Methods

### Study Design

We conducted a retrospective observational study of patients with severe sepsis or septic shock included in the Pediatric Health Information Systems Plus (PHIS+) database between January 2007 and December 2011. The PHIS+ is an administrative database of inpatient hospitalizations from six children's hospitals in the United States (22). Data quality is monitored through a joint effort between the Children's Hospital Association (Overland Park, KS) and participating hospitals. The use of this deidentified dataset was not considered human subjects research in accordance with 45 CFR 46.102(f) and the policies of the Children's Hospital of Philadelphia Institutional Review Board.

### Study Population

Inclusion criteria were age >6 months and <18 years old; a principal or secondary diagnosis of severe sepsis or septic shock; orders for bacterial blood culture, broad-spectrum parenteral antibiotics, and at least one 0.9% saline or lactated Ringer fluid bolus on hospital day 0 or 1; and known disposition from the hospital. Age was limited to >6 months old to balance availability of baseline creatinine with inclusion of the infant age group at high risk for adverse sepsis outcomes. Day 0/1 culture, antibiotics, and fluid bolus were required to optimize the likelihood that sepsis was present at or near hospital admission. To identify severe sepsis and septic shock, we used previously published combinations of either (1) International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes for an invasive infection (Supplemental Table 1) plus acute organ dysfunction (Supplemental Table 2) or (2) ICD-9-CM codes for severe sepsis (785.52) or septic shock (995.92) (2,23,24). Patients transferred into or out of a PHIS+ site were excluded to ensure knowledge of acute therapies and outcomes.

### Data Collection

Demographics, comorbid conditions, payer, and sepsis-related therapies were obtained from the PHIS+ database. Comorbid conditions were categorized using pediatric complex chronic conditions (CCCs) (25). Exposure to nephrotoxic injury negated by just-in-time action drugs (Supplemental Table 3) was also determined (26). AKI

within the first 7 days of hospitalization was determined using the Kidney Disease Improving Global Outcomes classification (27).

### Outcomes

The primary outcome was MAKE30, a composite of all-cause death, new KRT, or persistent kidney dysfunction at 30 days or hospital discharge, whichever occurred first. New KRT was defined as having (1) a procedure charge for dialysis catheter (38.95) with a charge for dialysis (39.95) or (2) PHIS+ charge codes for dialysis supplies (PHIS+ supply codes 143,000, 256,011, 241,361, 244,521, 255,119, 525,201, 525,205, 525,211, and 525,221) (28). Persistent kidney dysfunction was defined as a final inpatient serum creatinine value  $\geq 200\%$  of the baseline value (*i.e.*, at least a doubling of baseline creatinine) and a minimum absolute increase of  $\geq 0.3$  mg/dl (9,20,21). We determined baseline serum creatinine for each patient by using the lowest recorded creatinine available between 12 months and 24 hours before the index admission. For patients without such data available, we imputed an estimated baseline creatinine using previously established median values for age and sex (Supplemental Table 4) (29). Although PHIS+ data collection began in 2007, only admissions available starting January 1, 2008 were included in this study to ensure that all patients had the potential to determine a measured baseline creatinine in the year before admission. Several sensitivity analyses were performed for baseline creatinine, including imputing baseline creatinine using upper limits of normal for age and sex (Supplemental Table 4) and using a multiple imputation strategy on the basis of age, sex, race, CCC, and minimum serum creatinine measured within the first 7 days of hospitalization (30). Patients with an ICD-9-CM code for ESKD undergoing dialysis (ICD-9-CM 585.6) present on admission or recorded during the most recent prior hospitalization were ineligible to meet the criteria for new KRT or persistent kidney dysfunction but could qualify for MAKE30 if they died in the hospital within 30 days.

Outcomes used to validate MAKE30 as an important end point included all-cause mortality through hospital discharge, hospital length of stay (LOS), total hospital costs, hospital readmission within 30 days and 1 year of discharge, and lowest eGFR in the period between 3 months and 1 year after discharge. Because height was not recorded in PHIS+, we used a validated height-independent eGFR equation (31). For hospital mortality, only KRT and persistent kidney dysfunction were considered to determine their association with death; thus, patients who would have met criteria for MAKE30 due to death within 30 days were excluded from this portion of the analysis. Total hospital costs were calculated as the overall Center for Medicare and Medicaid wage/price index-adjusted abstract-based charges multiplied by the overall hospital- and year-specific ratio-to-cost charge. For outcomes beyond hospital discharge (*i.e.*, readmission and lowest eGFR), only hospital survivors within the first 4 years of data were included to ensure at least 1 year of follow-up. Lowest eGFR between 3 months and 1 year after discharge was determined from subsequent hospital admissions (if available), because PHIS+ does not contain data outside of the inpatient setting.

### Statistical Analyses

All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). Data are presented as medians (interquartile ranges [IQRs]) or proportions and compared using Wilcoxon rank sum and or chi-squared tests, respectively. The incidence of MAKE30 was calculated for the primary and sensitivity analyses with the 95% confidence interval (95% CI) using robust SEM to account for repeat patient visits. To assess normative values for imputing baseline creatinine, we used linear regression to compare the measured creatinine with what would otherwise have been an imputed baseline in the subset of patients who had a measured baseline creatinine. Because measured creatinine would be expected to be higher than an imputed normal baseline value for patients with CKD, this correlation analysis excluded patients with kidney and urologic CCC. The creatinine values used for imputing baseline by age and sex were compared with the mean and 95% CI of measured values. Validation outcomes were compared between patients with MAKE30 and patients without MAKE30 using Wilcoxon rank sums for continuous outcomes and chi-squared tests for categorical outcomes. Lowest eGFR between 3 months and 1 year after discharge was analyzed as the proportion with eGFR <90 and <60 ml/min per 1.73 m<sup>2</sup> to approximate CKD. We used multivariable logistic regression to differentiate the effect of AKI versus persistent kidney dysfunction on mortality at hospital discharge and test the independent association of the nonmortal components of MAKE30 with hospital mortality after adjusting for baseline differences. We also modeled the natural log of costs and adjusted for the same independent variables as with mortality. Costs were transformed back to the original scale for presentation. Statistical significance was defined as  $P < 0.05$ .

### Results

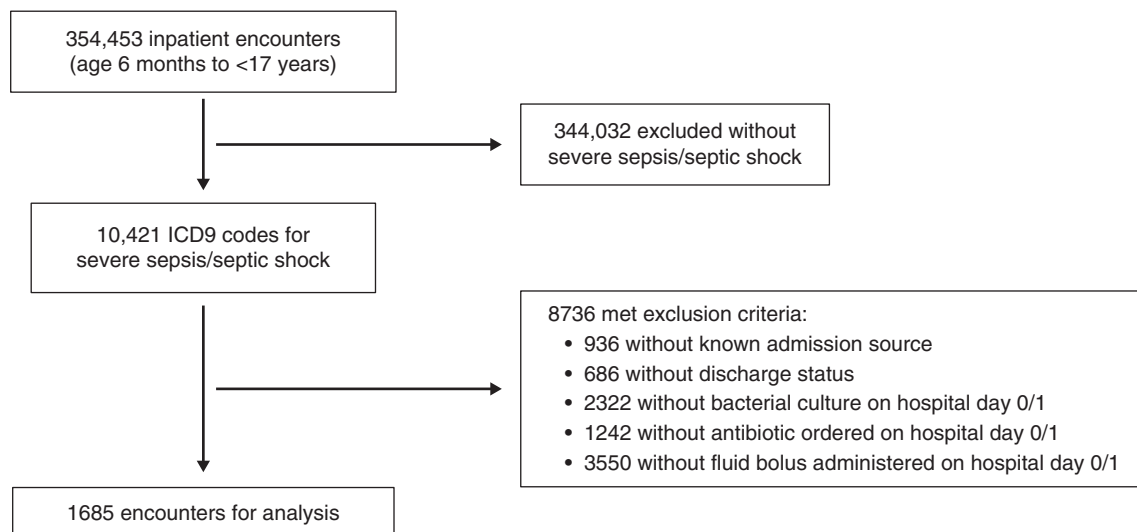
Of the 354,453 hospitalizations in the PHIS+ database, 1685 (0.5%) patient encounters were identified with

severe sepsis or septic shock and met all eligibility criteria (representing 1460 unique patients) (Figure 1). Overall, stage 2/3 AKI occurred in 527 (31%) within 7 days of admission. Measured baseline creatinine was available for 988 (59%) encounters. The imputed median baseline creatinine was correlated with the measured baseline creatinine after excluding those with kidney and urologic CCC ( $r^2=0.17$ ;  $P < 0.001$ ) (Supplemental Figure 1), and imputed baseline creatinine was either within or above the 95% CI of measured values for all age and sex strata (Supplemental Table 5). The creatinine value used to determine persistent kidney dysfunction was measured at a median of hospital day 7 (IQR, 3–15) (Supplemental Figure 2).

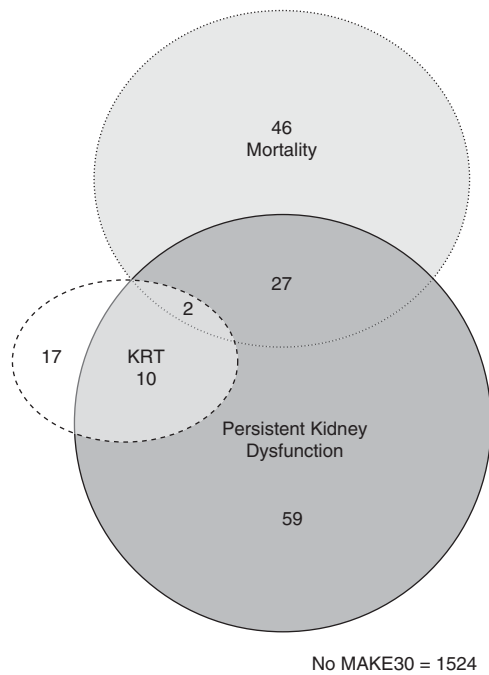
The incidence of MAKE30 was 9.6% (95% CI, 8.1% to 11.0%), including 4.5% (95% CI, 3.5% to 5.4%) with death, 1.7% (95% CI, 1.1% to 2.3%) with new KRT, and 5.8% (95% CI, 4.7% to 6.9%) with persistent kidney dysfunction. Characteristics for patient encounters with and without MAKE30 are shown in Table 1 (Supplemental Table 6 shows patient characteristics across components of MAKE30). Patient encounters with MAKE30 were more likely to have stage 2/3 AKI than patient encounters without MAKE30 (73% versus 27%;  $P < 0.001$ ), whereas encounters with stage 2/3 AKI were more likely than those without any AKI or with stage 1 AKI to have persistent kidney dysfunction (17% versus 0.8%;  $P < 0.001$ ) and develop MAKE30 (22% versus 4%;  $P < 0.001$ ). Of the 75 MAKE30 nonsurvivors, 48% had stage 2/3 AKI in the first 7 days, and 39% had either persistent kidney dysfunction or KRT (Figure 2, Supplemental Table 7 shows mutually exclusive combinations of MAKE30 components).

Sensitivity analyses for incidence of MAKE30 and its components are shown in Table 2. Point estimates varied little, and the 95% CIs overlapped for all permutations.

Patients who met the KRT or persistent kidney dysfunction criteria for MAKE30 compared with patients who did not had significantly higher mortality when followed out to



**Figure 1. | Patient identification and inclusion.** ICD9, International Classification of Diseases, Ninth Edition.



**Figure 2.** | Venn diagram of major adverse kidney events within 30 days (MAKE30) components. KRT, kidney replacement therapy.

hospital discharge (28% versus 1%;  $P < 0.001$ ). Moreover, although stage 2/3 AKI itself was associated with mortality at hospital discharge (odds ratio, 2.9; 95% CI, 1.9 to 4.4;  $P < 0.001$ ), this relationship was largely mediated through persistent kidney dysfunction, because AKI was no longer associated with mortality after controlling for persistent kidney dysfunction (adjusted odds ratio, 1.5; 95% CI, 0.9 to 2.5;  $P = 0.12$ ) (Supplemental Figure 3). Patient encounters with MAKE30 by any of the three components compared with those without MAKE30 also had no difference in hospital LOS (10; IQR, 5–20 versus 9; IQR, 5–18 days;  $P = 0.53$ ), but they did have higher total hospital costs (\$61,188; IQR, \$21,272–140,356 versus \$28,107; IQR, \$13,056–72,697;  $P < 0.001$ ).

Twenty-nine percent of encounters had follow-up data available beyond hospital discharge, including 21 of 83 survivors with MAKE30 and 431 of 1502 survivors without MAKE30 (median durations from discharge to follow-up were 121; IQR, 117–138 and 134; IQR, 106–194 days, respectively). Of the 452 hospital survivors with follow-up data available, there were no differences between readmission within 30 days (37% versus 31%;  $P = 0.32$ ) or 1 year of discharge (55% versus 58%;  $P = 0.68$ ), but patients with MAKE30 were more likely to have eGFR  $< 90$  ml/min per  $1.73 \text{ m}^2$  (33% versus 11%;  $P = 0.003$ ) and  $< 60$  ml/min per  $1.73 \text{ m}^2$  (19% versus 4%;  $P = 0.001$ ) between 3 months and 1 year after discharge.

In multivariable analyses, KRT or persistent kidney dysfunction was independently associated with mortality at hospital discharge (Table 3). Total hospital costs also remained higher in patients with versus without MAKE30 after adjusting for age, sex, race, number of CCCs, and payer (\$68,914; IQR, \$45,386–75,663 versus \$41,166; IQR, \$21,837–43,512;  $P < 0.001$ ).

## Discussion

Nearly one in ten children presenting with severe sepsis or septic shock developed an MAKE, defined as death, new KRT, or persistent kidney dysfunction, within 30 days of admission. MAKE30 was associated with higher hospital resource utilization (estimated by costs) and low eGFR after hospital discharge. In addition, the nonmortal components of MAKE30 were strongly associated with mortality at hospital discharge. These data support MAKE30 as common, feasible to measure, and a promising end point for future clinical trials in pediatric sepsis testing therapies biologically mediated through the kidney.

Mortality as an end point in pediatric sepsis trials is limited by low incidence and fails to account for the potential effect of therapies on organ-specific morbidity (8). Composite outcomes that include both mortality and measures of morbidity more fully capture the health effect of sepsis on children and have the advantage of being more common with increased statistical efficiency (32). To be most useful, composite outcomes should be coherent without complete coincidence (*i.e.*, each component should reflect related but different aspects of pathobiology), and each component must be of high importance to patients (33).

A workgroup convened by the NIDDK recommended a composite of death, KRT, and “a sustained loss of kidney function at a discrete time point (e.g., 30 days)” as a clinically meaningful end point for trials (19,34). This guidance was later expanded to include persistent kidney dysfunction “at hospital discharge truncated at 30 days” (35). Subsequently, clinical trials in adults have adopted this revised definition of MAKE30 to minimize costs and loss to follow-up after hospital discharge (20,21). The incidence of MAKE30 is 5%–16% in hospitalized adults and up to 35% in adult sepsis (20,21,36,37). Although MAKE30 was less frequent in pediatric sepsis, an incidence near 10% among children with community-acquired sepsis renders MAKE30 more common than mortality and as common as new or progressive multiple organ dysfunction syndrome (38). Although new or progressive multiple organ dysfunction syndrome has also been suggested as a composite end point for pediatric sepsis trials, it requires complex data abstraction, lacks sensitivity for improvement in any particular organ system, and has not been validated as a composite outcome (39).

The components of MAKE largely reflect the severity of kidney injury sustained during sepsis (*i.e.*, coherence). Numerous studies show an association of AKI and KRT with hospital death in pediatric sepsis (4–6,40), and 10%–17% of children with moderate to severe AKI who survive hospitalization develop CKD within 3 years (11,12). Moreover, those with enduring kidney dysfunction have worse outcomes than patients who recover from AKI (41). Yet, we acknowledge that the operational definition of MAKE that we and others reported is truncated at hospital discharge. Although this feature has practical advantages for a trial, it is distinguished from the concept of “acute kidney disease” or nonrecovery of AKI (42), and it is likely that some who fulfill MAKE30 will recover kidney function after discharge. However, in adult sepsis, failure to recover serum creatinine to within 150% of baseline by hospital discharge (median LOS of 7 days) was associated with increased ESKD and long-term mortality (16).



**Table 1. Patient encounter characteristics**

Variable <sup>a</sup>	No MAKE30	MAKE30
N	1524	161
Age, yr	8 (3–13)	10 (3–14)
<b>Age categories</b>		
6 mo to <1 yr	89 (6)	14 (9)
1 to <6 yr	530 (35)	41 (25)
6 to <13 yr	479 (31)	53 (33)
13 to <18 yr	426 (28)	53 (33)
Sex, girls	758 (50)	71 (44)
<b>Race</b>		
Non-Hispanic white	1042 (68)	115 (71)
Non-Hispanic black	209 (14)	16 (10)
Hispanic	121 (8)	11 (7)
Asian	47 (3)	4 (3)
Other	105 (7)	15 (9)
<b>Payer</b>		
Private	693 (45)	76 (47)
Government	696 (46)	65 (41)
Other payer	135 (9)	20 (12)
Admission through ED <sup>b</sup>	1284 (84)	125 (78)
Pediatric ICU admission <sup>b</sup>	974 (64)	126 (78)
<b>Number of complex chronic conditions<sup>b</sup></b>		
None	272 (18)	10 (6)
One	259 (17)	30 (19)
Two	231 (15)	22 (14)
Three or more	762 (50)	99 (61)
<b>Type of complex chronic condition</b>		
Cardiovascular	325 (21)	45 (28)
Respiratory	255 (17)	14 (9)
Neurologic/neuromuscular	483 (32)	51 (32)
Hematologic/immunodeficiency <sup>b</sup>	201 (13)	34 (21)
Malignancy	307 (20)	42 (26)
Kidney/urologic <sup>b</sup>	164 (11)	57 (35)
Gastrointestinal <sup>b</sup>	660 (43)	51 (32)
Metabolic <sup>b</sup>	231 (15)	47 (30)
Other congenital/genetic	194 (13)	19 (12)
Neonatal	50 (3)	5 (3)
Technology dependency	737 (48)	88 (55)
Transplantation <sup>b</sup>	214 (14)	35 (22)
Creatinine, mg/dl, baseline <sup>c</sup>	0.3 (0.3–0.5)	0.4 (0.3–0.6)
eGFR, ml/min per 1.73 m <sup>2</sup> , baseline <sup>d</sup>	107 (107–177)	115 (107–190)
<b>AKI<sup>b,e</sup></b>		
Stage 1	145 (10)	10 (6)
Stage 2	289 (19)	31 (19)
Stage 3	120 (8)	87 (54)
<b>Therapies</b>		
Noninvasive mechanical ventilation	209 (14)	26 (16)
Invasive mechanical ventilation, ETT <sup>b</sup>	698 (46)	111 (69)
Invasive mechanical ventilation, tracheostomy	164 (11)	10 (6)
Lactated Ringer fluid	30 (2)	3 (2)
Blood transfusion <sup>b</sup>	49 (3)	13 (8)
Vasoactive medication <sup>b</sup>	574 (38)	107 (67)
Corticosteroids <sup>b</sup>	559 (37)	88 (55)
Diuretics <sup>b</sup>	537 (35)	95 (59)
Extracorporeal membrane oxygenation <sup>b</sup>	19 (1)	12 (8)
<b>NINJA drug exposure</b>		
Aminoglycosides	491 (32)	64 (40)
Two or more nonaminoglycoside NINJA drugs	713 (47)	71 (44)
Fewer than two NINJA drugs and no aminoglycoside	320 (21)	26 (16)

MAKE30, major adverse kidney events within 30 days; ED, emergency department; ICU, intensive care unit; ETT, endotracheal tube; NINJA, nephrotoxic injury negated by just-in-time action (25).

<sup>a</sup>Data are presented as *n* (percentage) or median (interquartile range).

<sup>b</sup>Variable differed between patients with MAKE30 versus patients without MAKE30 at the  $P < 0.05$  level.

<sup>c</sup>Baseline creatinine was measured for 988 (59%) patients and imputed for 697 (41%) patients.

<sup>d</sup>Baseline eGFR was calculated using the height-independent equation: eGFR (milliliters per kilogram per 1.73 m<sup>2</sup>) = 107.3 / (measured or estimated baseline creatinine / Q), whereas Q is equal to the median serum creatinine concentration for children on the basis of age and sex (Supplemental Table 4) (30).

<sup>e</sup>Stage 2 and 3 AKI within the first 7 days of admission was determined using the Kidney Disease Improving Global Outcomes classification system (26).

**Table 2. Incidence of major adverse kidney events within 30 days by primary and sensitivity analyses**

Permutation	N	MAKE30 (95% CI)	Mortality, n (%)	KRT, n (%)	PKD, n (%)
<b>Baseline creatinine measured or imputed using median normal value for age and sex</b>					
Primary analysis	1685	9.6% (8.1 to 11.0)	75 (4.5)	29 (1.7)	98 (5.8)
Measured baseline creatinine only	988	9.8% (7.9 to 11.7)	44 (4.5)	12 (1.2)	68 (6.9)
Imputed baseline creatinine for all patients	1685	8.7% (7.3 to 10.0)	75 (4.5)	29 (1.7)	83 (4.9)
First hospitalization only	1460	9.8% (8.4 to 11.4)	67 (4.6)	28 (1.9)	85 (5.8)
Admitted through ED only	1409	8.9% (7.4 to 10.4)	55 (3.9)	24 (1.7)	73 (5.2)
Excluding patients with existing ESKD	1665	9.5% (8.1 to 11.0)	73 (4.4)	29 (1.7)	98 (5.9)
Baseline creatinine measured or imputed using upper limit of normal value for age and sex	1685	9.1% (7.7 to 10.5)	75 (4.5)	29 (1.7)	89 (5.3)
Baseline creatinine measured or imputed using multiple imputations	1685	9.6% (8.2 to 11.0)	75 (4.5)	29 (1.7)	95 (5.6)

Multiple imputation strategy included the following variables: age, sex, race, chronic comorbid conditions, and minimum serum creatinine measured within the first 7 days of hospitalization. MAKE30, major adverse kidney events within 30 days; 95% CI, 95% confidence interval; KRT, kidney replacement therapy; PKD, persistent kidney dysfunction (defined as at least doubling of the baseline serum creatinine at hospital discharge or hospital day 30, whichever came first); ED, emergency department.

Another potential concern with MAKE30 is that some deaths may not be attributable to or involve kidney injury. In our study, only 48% of MAKE30 deaths had stage 2/3 AKI, and only 39% also had at least one of the kidney-specific MAKE components. Nonetheless, because patients with MAKE30 incurred higher hospital costs and were more likely to have low eGFR after discharge, the components of this end point are associated with meaningful effects on

patients' lives. Moreover, because 78% of patients with stage 2/3 AKI did not develop persistent kidney dysfunction, require new KRT, or die and because the effect of AKI on hospital mortality was largely mediated through persistent kidney dysfunction, MAKE30 more specifically captured meaningful events in children with sepsis than AKI itself.

The validity and value of MAKE30 to children with sepsis and their families are of critical importance. There

**Table 3. Multivariable analysis of the association of nonfatal components of major adverse kidney events within 30 days with all-cause hospital mortality**

Variable	aOR	95% CI	P Value
<b>Nonmortal components of MAKE30</b>			
No RRT or persistent kidney dysfunction	Reference		
KRT or persistent kidney dysfunction	7.7	4.7 to 12.6	<0.001
<b>Age categories</b>			
6 mo to <1 yr	1.5	0.6 to 3.4	0.38
1 to <6 yr	1.2	0.7 to 2.1	0.49
6 to <13 yr	0.99	0.6 to 1.7	0.96
13 to <18 yr	Reference		
<b>Sex</b>			
Girls	Reference		
Boys	1.3	0.8 to 1.9	0.30
<b>Race</b>			
Non-Hispanic white	Reference		
Non-Hispanic black	0.5	0.2 to 1.1	0.08
Hispanic	1.1	0.5 to 2.4	0.85
Asian	0.8	0.2 to 3.3	0.71
Other	1.5	0.8 to 3.0	0.28
<b>Number of complex chronic conditions</b>			
None	Reference		
One	21.1	2.8 to 160	0.003
Two	15.0	1.9 to 115	0.01
Three or more	20.3	2.8 to 148	0.003
<b>Payer</b>			
Private	Reference		
Government	0.8	0.5 to 1.3	0.39
Other payer	1.4	0.7 to 3.0	0.31

aOR, adjusted odds ratio; 95% CI, 95% confidence interval; MAKE30, major adverse kidney events within 30 days; KRT, kidney replacement therapy.

is clear face validity, with death a traditional end point for pediatric sepsis trials and kidney dysfunction linked to increased mortality. For construct validity, need for KRT and persistence of kidney dysfunction are both associated with the more patient-centered outcome of CKD. Concurrent validity is supported by the strong association of KRT and persistent kidney dysfunction with hospital costs and hospital mortality, and predictive validity is suggested by the association of MAKE30 with low eGFR after discharge. Numerous studies also suggest that adults value kidney function and independence from dialysis higher than survival. Although data are limited in pediatrics, severe AKI has been associated with lower health-related quality of life in children, especially a decline in physical function (15). Although it is reasonable to extrapolate that MAKE30 would, therefore, be meaningful to children and their families, definitive evidence that reducing the nonmortal components of MAKE will translate into improved long-term kidney outcomes requires confirmation (43).

There are several limitations. First, only patients who were retrospectively coded as severe sepsis/septic shock were analyzed. In a clinical trial, enrollment will occur prospectively, perhaps before an infection or sepsis can be confirmed. If MAKE30 occurs at a higher rate in sepsis compared with “sepsis mimickers,” then the incidence of MAKE30 could be lower than we observed here. Second, baseline creatinine was imputed in 41% of patients, and even measured creatinine before admission may fail to accurately capture kidney dysfunction present before sepsis. However, our data show that median creatinine for age and sex often slightly exceeded the upper confidence limit of measured baseline creatinine (and thus, provides a conservative estimate of MAKE30), with no difference in MAKE30 incidence when using higher imputed levels or multiple imputation. Still, we acknowledge that imputed baselines were on the basis of normative values in patients of white race (29). Third, only 29% of patients had data available to determine follow-up eGFR, and only inpatient laboratory data were available; although we evaluated lowest creatinine, we could not distinguish between CKD and a repeat episode of AKI as the cause of low eGFR after hospital discharge. Additional investigation into a potential causal link between MAKE30 and CKD, long-term morbidity and mortality, and post-discharge health services utilization are needed. Fourth, deaths incorporated within MAKE30 without AKI or concurrence of persistent kidney dysfunction or KRT likely include “nonkidney events.” Fifth, although data in PHIS+ were contributed by six centers over several years, all were large academic children’s hospitals, and the data were collected 7–11 years ago, which may limit generalizability across settings and time.

In summary, MAKE30 is common, feasible to measure, and a promising end point that could be used in future clinical trials for pediatric sepsis in which the intervention of interest may be biologically mediated through the kidney. The ease of collection and additional prognostic value compared with AKI suggest MAKE30 as a useful study end point. Additional efforts to validate the effect of MAKE30 in larger studies of pediatric sepsis with more complete postdischarge data are warranted.

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## Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.12201018/-/DCSupplemental>.

Supplemental Figure 1. Imputed versus measured baseline creatinine values.

Supplemental Figure 2. Hospital day on which serum creatinine to define persistent kidney dysfunction was measured.

Supplemental Figure 3. Mediation analysis of the association of stage 2/3 AKI with mortality at hospital discharge.

Supplemental Table 1. International Classification of Diseases, Ninth Edition, Clinical Modification codes for invasive infection.

Supplemental Table 2. International Classification of Diseases, Ninth Edition, Clinical Modification codes for organ dysfunction.

Supplemental Table 3. Nephrotoxic injury negated by just-in-time action (NINJA) drugs.

Supplemental Table 4. Creatinine values to determine baseline kidney function for patients without measured baseline creatinine.

Supplemental Table 5. Imputed versus measured baseline creatinine values for patients with known measured baseline creatinine after excluding those with kidney and urologic chronic comorbid conditions.

Supplemental Table 6. Patient encounter characteristics by components of major adverse kidney events within 30 days.

Supplemental Table 7. Distribution across components of major adverse kidney events within 30 days.

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**Supplemental Table 1: *International Classification of Diseases, Ninth Edition, Clinical Modification* Codes for Invasive Infection**

<b>ICD-9-CM Code<sup>a</sup></b>	<b>Description</b>
001	Cholera
002	Typhoid/paratyphoid fever
003	Other salmonella infection
004	Shigellosis
005	Other food poisoning
008	Intestinal infection not otherwise classified
009	Ill-defined intestinal infection
010	Primary tuberculosis infection
011	Pulmonary tuberculosis
012	Other respiratory tuberculosis
013	Central nervous system tuberculosis
014	Intestinal tuberculosis
015	Tuberculosis of bone and joint
016	Genitourinary tuberculosis
017	Tuberculosis not otherwise classified
018	Miliary tuberculosis
020	Plague
021	Tularemia
022	Anthrax
023	Brucellosis
024	Glanders
025	Melioidosis
026	Rat-bite fever
027	Other bacterial zoonoses
030	Leprosy
031	Other mycobacterial disease
032	Diphtheria
033	Whooping cough
034	Streptococcal throat/scarlet fever
035	Erysipelas
036	Meningococcal infection
037	Tetanus

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038	Septicemia
039	Actinomycotic infections
040	Other bacterial diseases
041	Bacterial infection in other diseases not otherwise specified
090	Congenital syphilis
091	Early symptomatic syphilis
092	Early syphilis latent
093	Cardiovascular syphilis
094	neurosyphilis
095	Other late symptomatic syphilis
096	Late syphilis latent
097	Other and unspecified syphilis
098	Gonococcal infections
100	Leptosprosis
101	Vincent's angina
102	Yaws
103	Pinta
104	Other spirochetal infection
110	Dermatophytosis
111	Dermatomycosis not otherwise classified or specified
112	Candidiasis
114	Coccidioidomycosis
115	Histoplasmosis
116	Blastomycotic infection
117	Other mycoses
118	Opportunistic mycoses
320	Bacterial meningitis
322	Meningitis, unspecified
324	Central nervous system abscess
325	Phlebitis of intracranial sinus
420	Acute pericarditis
421	Acute or subacute endocarditis
451	Thrombophlebitis
461	Acute sinusitis
462	Acute pharyngitis

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463	Acute tonsillitis
464	Acute laryngitis/tracheitis
465	Acute upper respiratory infection of multiple sites/not otherwise specified
481	Pneumococcal pneumonia
482	Other bacterial pneumonia
485	Bronchopneumonia with organism not otherwise specified
486	Pneumonia, organism not otherwise specified
491.21	Acute exacerbation of obstructive chronic bronchitis
494	Bronchiectasis
510	Empyema
513	Lung/mediastinum abscess
540	Acute appendicitis
541	Appendicitis not otherwise specified
542	Other appendicitis
562.01	Diverticulitis of small intestine without hemorrhage
562.03	Diverticulitis of small intestine with hemorrhage
562.11	Diverticulitis of colon without hemorrhage
562.13	Diverticulitis of colon with hemorrhage
556	Anal and rectal abscess
567	Peritonitis
569.5	Intestinal abscess
569.83	Perforation of intestine
572	Abscess of liver
572.1	Portal pyemia
575.0	Acute cholecystitis
590	Kidney infection
597	Urethritis/urethral syndrome
599.0	Urinary tract infection not otherwise specified
601	Prostatic inflammation
614	Female pelvic inflammation disease
615	Uterine inflammatory disease
616	Other female genital inflammation
681	Cellulitis, finger/toe
682	Other cellulitis or abscess
683	Acute lymphadenitis



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686	Other local skin infection
711.0	Pyogenic arthritis
730	Osteomyelitis
790.7	Bacteremia
996.6	Infection or inflammation of device/graft
998.5	Postoperative infection
999.3	Infectious complication of medical care not otherwise classified

ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification

<sup>a</sup>Where 3 or 4 digit codes are listed, all associated subcodes were included

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**Supplemental Table 2: *International Classification of Diseases, Ninth Edition, Clinical Modification* Codes for Organ Dysfunction**

<b>ICD-9-CM Code<sup>a</sup></b>	<b>Description</b>
785.5	Shock without trauma
458	Hypotension
96.7	Mechanical ventilation
348.3	Encephalopathy
293	Transient organic psychosis
348.1	Anoxic brain damage
287.4	Secondary thrombocytopenia
287.5	Thrombocytopenia, unspecified
286.9	Other/unspecified coagulation defect
286.6	Defibrination syndrome
570	Acute and subacute necrosis of liver
573.4	Hepatic infarction
584	Acute kidney failure

ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification

<sup>a</sup>Where 3 or 4 digit codes are listed, all associated subcodes were included

**Supplemental Table 3: Nephrotoxic Injury Negated by Just-in-time Action (NINJA) Drugs**

<b>PHIS+ code and drug name</b>
127101 Acyclovir
125201 Amphotericin B
121101 Amikacin sulfate,
112205 Aspirin
135105 Captopril
171917 Carboplatin
112351 Celecoxib
127103 Cidofovir
171920 Cisplatin
124147 Colistimethate sodium
167115 Cyclosporine
119113 Deferasirox
174143 Diatrizoate meglumine
174145 Diatrizoate sodium
135111 Enalapril maleate (includes enalaprilat)
127107 Foscarnet sodium
127113 Ganciclovir
121105 Gentamicin
112260 Ibuprofen
171105 Ifosfamide
112264 Indomethacin
174123 Iodixanol
174107 Iohexol
174109 Iopamidol
174119 Iopromide
174115 Ioversol
174111 Ioxaglate meglumine and ioxaglate sodium
174121 Ioxilan
112270 Ketorolac tromethamine
135121 Lisinopril
113451 Lithium
135215 Losartan potassium
147450 Mesalamine

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171201 Methotrexate
171417 Mitomycin
121247 Nafcillin sodium
112288 Naproxen
151255 Pamidronate disodium
129121 Pentamidine isethionate
121261 Piperacillin sodium
121265 Piperacillin sodium and tazobactam sodium
124151 Polymyxin B sulfate
167137 Sirolimus
124431 Sulfasalazine
167135 Tacrolimus
127173 Tenofovir
121271 Ticarcillin disodium and clavulanate potassium
121135 Tobramycin sulfate
116061 Topiramate
127133 Valacyclovir HCl
127135 Valganciclovir HCl
135225 Valsartan
124133 Vancomycin (HCl)
151263 Zoledronic acid
116007 Zonisamide

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**Supplemental Table 4: Creatinine Values to Determine Baseline Kidney Function for Patients Without Measured Baseline Creatinine**

Age	Creatinine, Median (mg/dL)		Creatinine, Upper Limit Normal (mg/dL)	
	Male	Female	Male	Female
6 mos to <1 year		0.25		0.36
1 to < 2 years		0.27		0.39
2 to <3 years		0.30		0.42
3 to <4 years		0.33		0.46
4 to <5 years		0.36		0.50
5 to <6 years		0.38		0.53
6 to < 7 years		0.43		0.58
7 to < 8 years		0.45		0.60
8 to <9 years		0.47		0.62
9 to <10 years		0.50		0.69
10 to <11 years		0.52		0.71
11 to <12 years		0.54		0.71
12 to <13 years		0.57		0.74
13 to <14 years		0.61		0.83
	<b>Male</b>	<b>Female</b>	<b>Male</b>	<b>Female</b>
14 to <15 years	0.68	0.62	0.91	1.24
15 to < 16 years	0.78	0.68	1.01	1.36
16 to <17 years	0.82	0.70	1.07	1.40
17 to <18 years	0.85	0.71	1.10	1.42



**Supplemental Table 5: Imputed Versus Measured Baseline Creatinine Values in the Primary Analysis for Patients with Known Measured Baseline Creatinine after Excluding Those with Kidney and Urologic Complex Chronic Conditions**

Age	Sex	Measured Baseline Creatinine (mg/dL)			Imputed Baseline Creatinine (mg/dL)	Imputed Baseline Comparison to Actual Values
		Mean	LCL	UCL		
6 mos to <1 year	Both	0.17	0.15	0.19	0.25	Greater than UCL
1 to <2 years	Both	0.19	0.17	0.21	0.27	Greater than UCL
2 to <3 years	Both	0.19	0.18	0.21	0.3	Greater than UCL
3 to <4 years	Both	0.20	0.18	0.22	0.33	Greater than UCL
4 to <5 years	Both	0.21	0.19	0.24	0.36	Greater than UCL
5 to <6 years	Both	0.28	0.25	0.31	0.38	Greater than UCL
6 to <7 years	Both	0.24	0.21	0.27	0.43	Greater than UCL
7 to <8 years	Both	0.28	0.23	0.34	0.45	Greater than UCL
8 to <9 years	Both	0.27	0.23	0.32	0.47	Greater than UCL
9 to <10 years	Both	0.26	0.20	0.33	0.5	Greater than UCL
10 to <11 years	Both	0.32	0.28	0.36	0.52	Greater than UCL
11 to <12 years	Both	0.30	0.25	0.36	0.54	Greater than UCL
12 to <13 years	Both	0.36	0.31	0.41	0.57	Greater than UCL
13 to <14 years	Both	0.41	0.34	0.49	0.61	Greater than UCL
14 to <15 years	Male	0.38	0.28	0.51	0.68	Greater than UCL
14 to <15 years	Female	0.47	0.36	0.60	0.62	Greater than UCL
15 to <16 years	Male	0.47	0.37	0.60	0.78	Greater than UCL
15 to <16 years	Female	0.56	0.44	0.71	0.68	Between LCL and UCL
16 to <17 years	Male	0.47	0.41	0.53	0.82	Greater than UCL
16 to <17 years	Female	0.41	0.35	0.49	0.7	Greater than UCL
17 to <18 years	Male	0.45	0.38	0.52	0.85	Greater than UCL
17 to <18 years	Female	0.37	0.30	0.46	0.71	Greater than UCL

**Supplemental Table 6: Patient Encounter Characteristics by Components of MAKE30**

<b>Variable<sup>1</sup></b>	<b>No MAKE30</b>	<b>Death30<sup>2</sup></b>	<b>KRT30<sup>2</sup></b>	<b>PKD30<sup>2</sup></b>
N	1524	75	29	98
Age, years	8 (3-13)	8 (3-14)	12 (3-14)	10 (4-14)
<b>Age categories</b>				
6 months to <1 year	89 (6)	7 (9)	3 (10)	7 (7)
1 to <6 years	530 (35)	23 (31)	6 (21)	21 (21)
6 to <13 years	479 (31)	24 (32)	9 (31)	35 (36)
13 to <18 years	426 (28)	21 (28)	11 (38)	35 (36)
Sex, female	758 (50)	32 (44)	12 (41)	40 (41)
<b>Race</b>				
Non-Hispanic White	1,042 (68)	56 (75)	19 (66)	71 (72)
Non-Hispanic Black	209 (14)	5 (7)	4 (14)	10 (10)
Hispanic	121 (8)	5 (7)	1 (3)	6 (6)
Asian	47 (3)	2 (3)	1 (3)	2 (2)
Other	105 (7)	7 (9)	4 (14)	9 (9)
<b>Payer</b>				
Private	693 (45)	37 (50)	18 (62)	44 (45)
Government	696 (46)	28 (37)	10 (35)	39 (40)
Other payer	135 (9)	10 (13)	1 (3)	15 (15)
Admission through ED	1,284 (84)	55 (73)	24 (83)	73 (75)
Pediatric ICU admission	974 (64)	68 (91)	25 (86)	69 (70)
<b>Number of complex chronic conditions</b>				
None	272 (18)	1 (1)	0	10 (10)
One	259 (17)	19 (25)	0	14 (14)
Two	231 (15)	11 (15)	1 (3)	13 (13)
Three or more	762 (50)	44 (59)	28 (97)	61 (62)
<b>Type of complex chronic conditions</b>				
Cardiovascular	325 (21)	22 (29)	9 (31)	28 (29)
Respiratory	255 (17)	7 (9)	3 (10)	10 (10)
Neurologic/neuromuscular	483 (32)	36 (48)	5 (17)	25 (26)
Hematologic/immunodeficiency	201 (13)	14 (19)	10 (35)	20 (20)
Malignancy	307 (20)	20 (27)	11 (38)	24 (25)
Kidney/urologic	164 (11)	12 (16)	29 (100)	33 (34)
Gastrointestinal	660 (43)	17 (23)	10 (35)	35 (36)

Metabolic	231 (15)	23 (31)	9 (31)	26 (27)
Other congenital/genetic	194 (13)	8 (11)	2 (7)	14 (14.3)
Neonatal	50 (3)	4 (5)	0	3 (3)
Technology dependency	737 (48)	36 (48)	29 (100)	54 (55)
Transplantation	214 (14)	13 (17)	8 (28)	27 (28)
Creatinine (mg/dL), baseline <sup>3</sup>	0.3 (0.3-0.5)	0.3 (0.2-0.6)	0.5 (0.3 - 0.6)	0.4 (0.2 - 0.6)
Estimated GFR (mL/min/1.73 m <sup>2</sup> ), baseline <sup>4</sup>	107 (107-177)	107 (107- 193)	107 ( 107 - 144)	145 (107 - 204 )
Stage 2/3 AKI <sup>5</sup>	409 (27)	36 (48)	22 (76)	89 (91)
Therapies				
Non-invasive mechanical ventilation	209 (14)	11 (15)	9 (31)	17 (17)
Invasive mechanical ventilation, ETT	698 (46)	62 (83)	22 (76)	62 (63)
Invasive mechanical ventilation, tracheostomy	164 (11)	7 (9)	2 (7)	5 (5)
Lactated Ringer's fluid	30 (2)	1 (1)	0	2 (2)
Blood Transfusion	49 (3)	3 (4)	7 (24)	8 (8)
Vasoactive medication	574 (38)	61 (81)	23 (79)	57 (58)
Corticosteroids	559 (37)	44 (59)	20 (69)	56 (57)
Diuretics	537 (35)	40 (53)	25 (87)	60 (61)
Extracorporeal membrane oxygenation	19 (1)	9 (12)	3 (10)	4 (4)
NINJA drug exposure				
Aminoglycosides	491 (32)	32 (43)	10 (35)	37 (38)
≥2 non-aminoglycoside NINJA drugs	713 (47)	29 (38)	16 (55)	49 (50)
<2 NINJA drugs and no aminoglycoside	320 (21)	14 (19)	3 (10)	12 (12)

MAKE30, major adverse kidney events within 30 days; Death30, all-cause hospital mortality censored at discharge or 30 days; KRT30, new use of kidney replacement therapy censored at discharge or 30 days; PKD30, persistent kidney dysfunction censored at discharge or 30 days; ED, emergency department; ICU, intensive care unit; ETT, endotracheal tube; GFR, glomerular filtration rate; AKI, acute kidney injury; NINJA, Nephrotoxic Injury Negated by Just-in-time Action (reference 25)

<sup>1</sup>Data presented as n (%) or median (interquartile range)

<sup>2</sup>Groups are not mutually exclusive

<sup>3</sup>Baseline creatinine was measured for 988 (59%) and imputed for 697 (41%) of patients

<sup>4</sup>Baseline estimated GFR was calculated using the height-independent equation:  $eGFR \text{ mL/kg/1.73 m}^2 = 10.7.3 / (\text{measured or estimated baseline creatinine} / Q)$  with Q equal to the median serum creatinine concentration for children based on age and sex (see Supplemental Table 4 and Reference 30)

<sup>5</sup>Stage 2 and 3 AKI within the first seven days of admission was determined using the Kidney Disease Improving Global Outcomes (KDIGO) classification system (Reference 26)

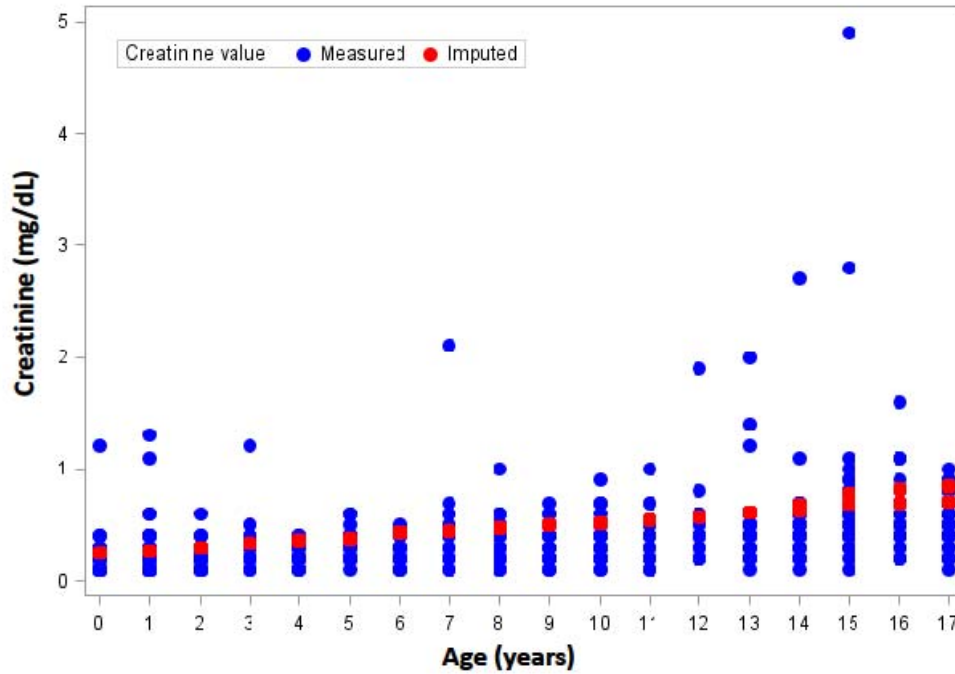
Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

**Supplemental Table 7: Distribution across Components of MAKE30**

<b>MAKE30 Component</b>	<b>Number</b>	<b>Percentage</b>
None	1524	90.4
Mortality, only	46	2.7
KRT, only	17	1.0
PKD, only	59	3.5
Mortality + KRT	0	0
Mortality + PKD	27	1.6
KRT + PKD	10	0.6
Mortality + KRT + PKD	2	0.1

MAKE30, major adverse kidney events within 30 days; KRT, kidney replacement therapy; PKD, persistent kidney dysfunction

### Supplemental Figure 1: Imputed Versus Measured Baseline Creatinine Values

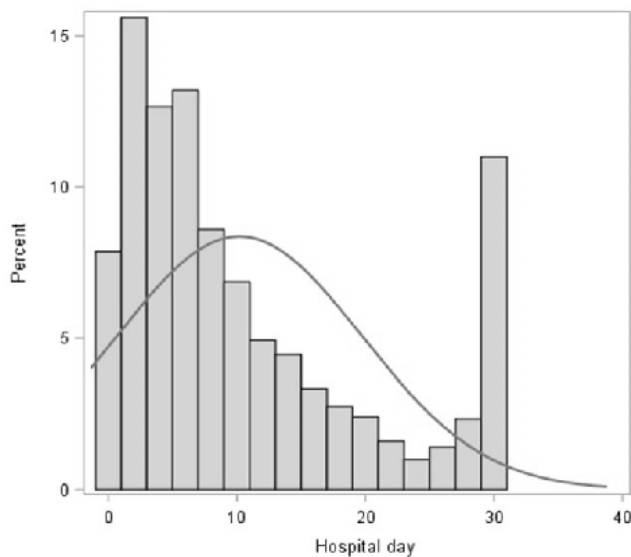


For the subset of patients with an available baseline creatinine value measured as the lowest recorded creatinine available between 12 months and 24 hours prior to the index hospital admission and who did not have kidney or urologic chronic comorbid conditions, the measured baseline creatinine value was compared to what the baseline would have been had an imputed value representing the median creatinine for age and sex been used. Imputed baseline creatinine (red values) overlap the approximate normal range indicated by the measured baseline creatinine (blue range), indicating that imputation closely approximated baseline creatinine. For patients age  $\geq 14$  years, the two imputed (red) values represent different imputed creatinine values for male and female patients.



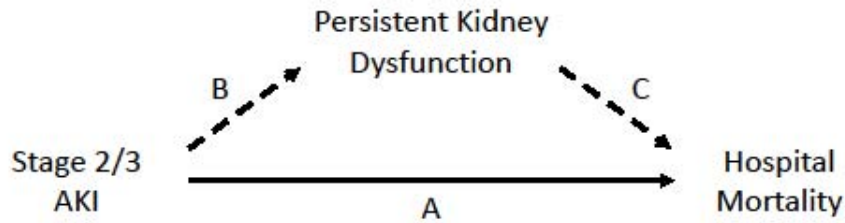
Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

## Supplemental Figure 2: Hospital Day on Which Serum Creatinine to Define Persistent Kidney Dysfunction was Measured



The serum creatinine value closest to discharge or 30 days after hospitalization, whichever came first, was used to determine persistent kidney dysfunction. The histogram depicts the hospital day on which kidney dysfunction was measured (median day 7 (IQR 3-15) of hospitalization).

**Supplemental Figure 3: Mediation Analysis of the Association of Stage 2/3 Acute Kidney Injury with Mortality at Hospital Discharge**



Model	Exposure	Outcome	OR	95% CI	P Value
A	Stage2/3 AKI	Hospital Mortality	2.9	1.9, 4.4	<0.001
B	Stage2/3 AKI	PKD	27.6	13.7, 55.8	<0.001
C	Stage2/3 AKI, adjusted for PKD	Hospital Mortality	1.5	0.9, 2.5	0.12
C	PKD, adjusted for stage 2/3 AKI	Hospital Mortality	8.0	4.4, 14.7	<0.001

Stage 2/3 acute kidney injury (AKI) within the first seven days of hospitalization was significantly associated with mortality at hospital discharge (model A) and with persistent kidney dysfunction (PKD) measured as the last available creatinine prior to hospital discharge or within 30 days of sepsis recognition, whichever came first (model B). However, stage 2/3 AKI was no longer significantly associated with mortality at hospital discharge after controlling for PKD (model C), supporting that the association of stage 2/3 AKI with hospital mortality is largely mediated through PKD.