Acute Kidney Injury Predicts Outcomes of Non–Critically Ill Patients

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OBJECTIVE: To evaluate whether acute kidney injury (AKI), defined as an increase in the serum creatinine level of 0.3 mg/dL or more within 48 hours, predicts outcomes of non–critically ill patients.

PATIENTS AND METHODS: Among the adults admitted from June 1, 2005, to June 30, 2007, to the medical wards of a community teaching hospital, 735 patients with AKI and 5089 controls were identified. Demographic and health information, serum creatinine values, and outcomes were abstracted from patients' computerized medical records. Outcomes of patients with AKI were compared with those of controls. In an additional case-control analysis, more detailed clinical information was abstracted from the medical records of 282 pairs of randomly selected, age-matched AKI cases and controls. Conditional multivariate logistic regression analyses were used to adjust for potential confounders of AKI effect on outcomes.

RESULTS: Overall, patients with AKI had higher in-hospital mortality (14.8% vs 1.5%; $P < .001$), longer lengths of stay (median 7.9 vs 3.7 days; $P < .001$), and higher rates of transfer to critical care areas (28.6% vs 4.3%; $P < .001$); survivors were more likely to be discharged to an extended care facility (43.1% vs 20.3%; $P < .001$). Conditional multivariate logistic regression analyses of the 282 pairs of cases and controls showed that patients with AKI were 8 times more likely to die in hospital (odds ratio [OR], 7.9; 95% CI [confidence interval], 2.9–15.3) and were 5 times more likely to have prolonged (≥ 7 days) hospital stays (OR, 5.2; 95% CI, 3.5–7.9) and require intensive care (OR, 4.7; 95% CI, 2.7–8.1), after adjustment for age, comorbidities, and other potential confounders.

CONCLUSION: In this study, AKI was associated with adverse outcomes in non–critically ill patients.

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AKI = acute kidney injury; CI = confidence interval; CKD = chronic kidney disease; ECF = extended-care facility; GFR = glomerular filtration rate; ICU = intensive care unit; LOS = length of stay; NGAL = neutrophil gelatinase-associated lipocalin; OR = odds ratio; RR = risk ratio; RRT = renal replacement therapy

Renal dysfunction is a common cause or complication of acute illness and is associated with excess morbidity and mortality.^{1–11} No universally accepted definition for acute kidney dysfunction has been established. To the extent that nonuniform definitions hinder scientific inquiry, formulation of robust, scientifically valid definitions may expedite future studies of the epidemiology, pathophysiology, and treatment of renal failure. In 2005, Chertow et al² published seminal findings suggesting that increases in the serum creatinine level as small as 0.3 mg/dL (to convert to $\mu\text{mol/L}$, multiply by 88.4) are highly associated with patients' outcomes. Later that year, heavily influenced by

Chertow's observation, the Acute Kidney Injury Network ratified the following interim diagnostic criteria for acute kidney injury (AKI): "An abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL ($\geq 26.4 \mu\text{mol/L}$), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg per hour for more than six hours)."⁸ We found this definition—simplified to any increase in serum creatinine level of 0.3 mg/dL or more within 48 hours—to be strongly associated with outcomes of critically ill patients.¹ The hypothesis for our study was that AKI similarly predicts in-hospital mortality, need for renal replacement therapy (RRT), and prolonged hospital stays of non–critically ill patients.

PATIENTS AND METHODS

This combined retrospective cohort and case-control study was conducted after approval by the institutional review board of Bridgeport Hospital, a 350-bed community teaching hospital affiliated with the Yale New Haven Health System. All adults admitted to the hospital medical wards from June 1, 2005, to June 30, 2007, were potentially eligible for inclusion. Patients were excluded if they had less than 2 creatinine measurements during their hospital stay, had undergone RRT in the 12 weeks before hospitalization, required RRT in the first 48 hours of hospitalization, or were directly admitted to critical care units. For patients with more than 1 hospitalization during the study period, only data from the first admission were analyzed.

Acute kidney injury cases were defined as patients with an absolute increase in serum creatinine of 0.3 mg/dL or more within any 48-hour period. Non-AKI control patients were defined as patients without an increase in serum

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creatinine of 0.3 mg/dL or more during their hospital stay. Patients in whom creatinine levels increased by 0.3 mg/dL or more after more than 48 hours were not included in the final analysis because most lacked creatinine measurements in the 48 hours before the noted increase, preventing accurate classification.

A sample of the AKI cases and controls was selected for the case-control portion of the study; for this sample, more detailed data abstraction and comprehensive analyses to adjust for potential confounders were conducted. From the total cohort of eligible AKI cases, 282 were randomly sampled using a computer-generated random-sampling process. The cases were then grouped into decades of age (eg, 20-29 years, 30-39 years). Both cases and controls were stratified into 8 age groups. A 1:1 frequency matching approach was used, whereby an equal number of cases and controls were randomly sampled in each decade group. No individual pairing (or individual matching) of cases and controls was done. In all, 282 cases and 282 controls were sampled. The sample size of 564 assured a study power of 80% to 90%, assuming a mortality rate of 1.5% in the control group and an expected odds ratio (OR) of mortality of at least 5.

DATA COLLECTION

Patients' demographic and laboratory data were downloaded from the hospital's electronic database. The following information was also ascertained: age, sex, race, RRT, transfer to critical care areas, hospital lengths of stay (LOSs), and mortality and disposition destinations (home vs extended-care facilities [ECFs]).

Potential confounders, such as the discharge diagnoses, comorbidities, and nephrotoxic medications, were not available in the electronic database. Information on these variables was manually extracted from the patients' complete medical records for the sampled cases and controls. Discharge diagnoses were categorized on the basis of the *International Classification of Diseases, Ninth Revision, Clinical Modification*⁹ groups as cardiovascular, pulmonary, gastrointestinal, related to infectious disease, and related to metabolism and nutrition, among others. Comorbidities included coronary artery disease; chronic heart failure; hypertension; diabetes mellitus; chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (GFR) of less than 60 mL/min at baseline as determined by the Modification of Diet in Renal Disease formula; cirrhosis; chronic obstructive pulmonary disease; and cancer. Risk factors for acute kidney dysfunction included clinically documented volume depletion (eg, vomiting, diarrhea, hemorrhage) and use of nonsteroidal anti-inflammatory medications, angiotensin-converting enzyme inhibitors, angiotensin II receptor

blockers, radiologic contrast agents, thiazides, loop diuretics, trimethoprim-sulfamethoxazole, aminoglycosides, acyclovir, or cyclosporine.

STATISTICAL ANALYSES

In the cohort study, median values and interquartile ranges are reported for age and hospital LOS. Wilcoxon rank sum tests were used to compare medians between patients with and without AKI. Categorical variables are reported as percentages and compared with χ^2 tests. Risk ratios (RRs) and 95% confidence intervals (CIs) were used to examine the effects of AKI, old age (>65 years), and race (white vs nonwhite) on outcomes. Outcomes of interest included in-hospital mortality, prolonged LOS (≥ 7 days), and ECF discharge.

For the case-control component of the study, conditional logistic regression analyses were used to assess the association of AKI with outcomes, including in-hospital mortality, discharge to an ECF, transfer to an intensive care unit (ICU), hospital LOS of 3 days or more, and hospital LOS of 7 days or more, and to adjust simultaneously for age, sex, race, 2 or more comorbidities, and presence of CKD. Nephrotoxic medication and volume depletion were considered causative of AKI and were not adjusted in the model. Stratified analyses (Mantel-Haenszel approach) were used to adjust for matching age groups and to examine the association between AKI and race (white vs nonwhite), sex, use of nephrotoxic medications, volume depletion, 2 or more comorbidities, and CKD. The magnitude of association was documented with the adjusted Mantel-Haenszel OR. Two-tailed *P* values based on the corrected Mantel-Haenszel χ^2 test statistic are reported.^{12,13}

All analyses were performed using SAS version 8.2 software (SAS Institute, Cary, NC) and Epi Info version 3.4.1 software (Centers for Disease Control and Prevention, Atlanta, GA). A 2-tailed *P* value of <.05 was considered statistically significant.

RESULTS

CHARACTERISTICS AND OUTCOMES OF THE OVERALL COHORT

Of the 16,039 patients admitted to medical wards during the study period, the following were excluded: 5406 patients for whom this was not a first admission, 128 patients who received RRT before admission or within the first 48 hours of hospitalization, 1968 patients who were initially admitted to the ICU, and 2504 patients who had no or only 1 creatinine measurement. Of the 6033 remaining eligible patients, 209 (3.5%) were excluded who had increases in serum creatinine level of 0.3 mg/dL or more but at unspecified time intervals (eg, when creatinine values were not measured daily). The final cohort consisted of 5824 pa-

FIGURE. Flow of patients through the study. AKI = acute kidney injury; ICU = intensive care unit; RRT = renal replacement therapy.

^a For patients with multiple admissions, only the first admission was included.

^b Patients with no or only one creatinine value during their hospital stay.

^c Patients with creatinine increase of ≥ 0.3 mg/dL (to convert to $\mu\text{mol/mL}$, multiply by 88.4) in >48 h, including those with missing creatinine data within 48 h.

^d Cases were defined as patients with an absolute increase in serum creatinine of ≥ 0.3 mg/dL within 48 h.

^e Controls were defined as patients with no absolute increase in serum creatinine ≥ 0.3 mg/dL during their hospital stay.

tients, of whom 735 (12.6%) were AKI cases and 5089 (87.4%) were controls (Figure).

The mean $\pm$ SD age of the total cohort was 66.3 ± 18.8 years. Of the 5824 patients in the cohort, 2723 (46.8%) were males, 3962 (68.0%) were white, 993 (17.1%) were African American, and 786 (13.5%) were Hispanic. Overall, 73 (1.3%) required new RRT and 429 (7.4%) required transfer to critical care areas during their hospital stay. In-hospital mortality was 3.2% and the mean $\pm$ SD LOS was 5.7 ± 6.5 days. Of the survivors, 4354 (77.2%) were discharged home and 1286 (22.8%) required posthospital care in an ECF.

Patients with AKI were older (mean $\pm$ SD age, 72.9 ± 15.0 vs 65.4 ± 19.2 years; $P < .001$), and were more likely to be older than 65 years (72.4% vs 54.0%) when compared with non-AKI controls (Table 1). In univariate analysis, patients with AKI had significantly higher in-hospital mortality than

controls (RR, 10.1; 95% CI, 7.6-13.4). Other factors associated with in-hospital mortality were age greater than 65 years (RR, 4.3; 95% CI, 2.9-6.4) and nonwhite race (RR, 0.4; 95% CI, 0.3-0.7), but sex was not associated with mortality. Acute kidney injury was also a significant risk factor for a hospital stay of 7 or more days (RR, 3.2; 95% CI, 3.0-3.5), ICU transfer (RR, 6.6; 95% CI, 5.6-7.9), and discharge to an ECF (RR, 2.1; 95% CI, 1.9-2.4).

Characteristics of the 209 excluded patients who had an increase in serum creatinine level of 0.3 mg/dL or more after more than 48 hours or an unknown time horizon were also compared with AKI cases and controls (Table 2). Although in-hospital mortality rates (4.8%) and ICU transfer rates (18.2%) for these patients were midway between those of AKI cases and controls, their age distribution, LOS, and ECF placement rates were similar to those of patients with AKI.

TABLE 1. Demographic Characteristics and Outcomes of Patients in the Cohort^a

	AKI controls (n=5089)	AKI cases (n=735)	P value ^b
Age (y)			<.001
≤65	2340 (46.0)	203 (27.6)	
>65	2749 (54.0)	532 (72.4)	
Median (IQR)	67.7 (50.9-81.8)	76.2 (63.9-84.4)	
Sex			.83
Female	2707 (53.2)	394 (53.6)	
Male	2382 (46.8)	341 (46.4)	
Race			.005
White	3435 (67.5)	527 (71.7)	
Black	871 (17.1)	122 (16.6)	
Hispanic	711 (14.0)	75 (10.2)	
Other	72 (1.4)	11 (1.5)	
In-hospital mortality	75 (1.5)	109 (14.8)	<.001
Hospital length of stay (d), median (IQR)	3.7 (2.2-5.9)	7.9 (4.7-14.2)	<.001
New renal replacement therapy	0	73/564 (12.9)	<.001
Transfer to ICU	219 (4.3)	210 (28.6)	<.001
Discharge disposition of survivors			<.001
Home	3998/5014 (79.7)	356/626 (56.9)	
Extended-care facilities	1016/5014 (20.3)	270/626 (43.1)	

^a Data are given as number (percentage) of patients, unless otherwise indicated. AKI = acute kidney injury; ICU = intensive care unit; IQR = interquartile range.

^b Wilcoxon rank sum tests were used for non-normally distributed variables (age and length of stay) and χ^2 tests for categorical variables.

CHARACTERISTICS AND OUTCOMES OF THE SAMPLED CASES AND CONTROLS

Demographic characteristics of the randomly sampled, frequency-matched AKI cases (n=282) and controls (n=282) are shown in Table 3. The age group-adjusted ORs for AKI of selected variables are reported in Table 4. The distribution of sex was similar to that in the total (parent) population. More cardiovascular disease (30.5% vs 25.2%) and less endocrine/metabolic disease (5.0% vs 9.6%) were noted in the AKI vs the control group. Patients with AKI had a significantly higher rate of 2 or

more comorbidities compared with controls (75.9% vs 49.6%; OR, 3.5; $P<.001$). Patients with CKD had nearly 4-fold odds of having AKI compared with those without CKD (OR, 3.9; $P<.001$). The percentage of patients who had been exposed to nephrotoxins or who had a history suggestive of intravascular volume depletion was also significantly higher in AKI cases than controls (72.3% vs 61.3%; OR, 1.7; $P=.007$ and 35.8% vs 17.4%; OR, 2.7, $P<.001$, respectively).

Results of the conditional multivariate logistic regression analyses performed in the selected case-control samples are

TABLE 2. Outcomes of AKI Cases and Controls vs Outcomes of Patients With ≥ 0.3 mg/dL Increase in Serum Creatinine Level After >48 Hours or Uncertain Creatinine Velocity^a

	AKI controls (n=5089)	AKI cases (n=735)	Patients with creatinine increase ≥ 0.3 mg/dL ^b in ≥ 48 h (n=209)
Age (y), mean $\pm$ SD	65.4 $\pm$ 19.2	72.9 $\pm$ 15.0	71.6 $\pm$ 16.0
Female	2707 (53.2)	394 (53.6)	111 (53.1)
In-hospital mortality	75 (1.5)	109 (14.8)	10 (4.8)
Hospital length of stay (d)			
Mean $\pm$ SD	4.8 $\pm$ 4.6	11.7 $\pm$ 12.3	13.7 $\pm$ 13.8
Median (IQR)	3.7 (2.2-5.9)	7.9 (4.7-14.2)	8.5 (5.7-15.0)
New renal replacement therapy	0	73/564 (12.9)	0
Transfer to ICU	219 (4.3)	210 (28.6)	38 (18.2)
Discharge disposition of survivors			
Home	3998/5014 (79.7)	356/626 (56.9)	118/199 (59.3)
Extended-care facilities	1016/5014 (20.3)	270/626 (43.1)	81/199 (40.7)

^a Data are given as number (percentage) of patients, unless otherwise indicated. AKI = acute kidney injury; ICU = intensive care unit; IQR = interquartile range.

^b SI conversion factor: To convert creatinine value to $\mu\text{mol/L}$, multiply by 88.4.

TABLE 3. Demographic Characteristics and Outcomes of Patients Selected for the Age-Matched, Case-Control Study^a

	Controls (n=282)	Patients with AKI (n=282)
Age group (y)		
20-29	4 (1.4)	4 (1.4)
30-39	7 (2.5)	7 (2.5)
40-49	14 (5.0)	14 (5.0)
50-59	24 (8.5)	24 (8.5)
60-69	41 (14.5)	41 (14.5)
70-79	66 (23.4)	66 (23.4)
80-89	97 (34.4)	97 (34.4)
90-99	29 (10.3)	29 (10.3)
Sex		
Female	151 (53.5)	158 (56.0)
Male	131 (46.5)	124 (44.0)
Race		
White	219 (77.7)	209 (74.1)
Black	37 (13.1)	40 (14.2)
Hispanic	25 (8.9)	27 (9.6)
Other	1 (0.4)	6 (2.1)
Comorbidities ≥ 2	140 (49.6)	214 (75.9)
Primary discharge diagnosis ^b		
Circulatory	71 (25.2)	86 (30.5)
Respiratory	20 (7.1)	1.5 (5.3)
Gastrointestinal	29 (10.3)	23 (8.2)
Infectious disease-related	44 (15.6)	51 (18.1)
Endocrine/metabolism/ nutrition-related	27 (9.6)	14 (5.0)
Injury/poisoning/or others	89 (31.6)	93 (33.0)
Baseline creatinine (mg/dL), ^c mean $\pm$ SD	1.0 $\pm$ 0.5	1.5 $\pm$ 1.4
CKD	65 (23.0)	147 (52.1)
≥ 1 Nephrotoxic medications ^d	173 (61.3)	204 (72.3)
Volume depletion ^e	49 (17.4)	101 (35.8)
In-hospital mortality	7 (2.5)	43 (15.2)
Hospital length of stay (d), median (IQR)	4.0 (2.6-6.1)	7.7 (4.7-14.0)
New renal replacement therapy	0	6.4 (18/280)
Transfer to ICU	21 (7.4)	72 (25.5)
Discharge disposition of survivors		
Home	201/275 (73.1)	121/239 (50.6)
Extended-care facilities	74/275 (26.9)	118/239 (49.4)

^a Data are given as number (percentage) of patients, unless otherwise indicated. AKI = acute kidney injury; CKD = chronic kidney disease (defined by a baseline glomerular filtration rate of <60 mL/min); ICU = intensive care unit; IQR = interquartile range.

^b Diagnosis based on the *International Classification of Diseases, Ninth Revision, Clinical Modification*. Information was missing for 7 controls.

^c SI conversion factor: To convert creatinine values to μ mol/L, multiply by 88.4.

^d These include angiotensin II receptor antagonists, aminoglycosides, nonsteroidal anti-inflammatory drugs, and intravenous contrast agents.

^e Volume depletion occurred as a result of decreased oral intake of fluids and loss of fluids via gastrointestinal mechanisms (diarrhea, vomiting), excessive sweating, or blood loss.

shown in Table 5. Acute kidney injury emerged as the most potent predictor of mortality (OR, 7.9; 95% CI, 2.9-15.3). Age, 2 or more comorbidities, sex, race, and CKD were not independently associated with mortality. After adjustment for age, sex, race, comorbidities, and CKD, AKI was also associated with increased hospital LOS, more discharges to ECFs, and more frequent transfer to critical care areas.

TABLE 4. Odds Ratios for AKI of Selected Variables^{a,b}

Variable	Mantel-Haenszel summary OR (95% CI)	P value ^c
Sex (male vs female)	0.9 (0.6-1.3)	.50
Race (nonwhite vs white)	1.2 (0.8-1.9)	.30
Comorbidities ≥ 2	3.5 (2.4-5.1)	$<.001$
CKD	3.9 (2.7-5.6)	$<.001$
≥ 1 Nephrotoxic medications ^d	1.7 (1.2-2.4)	.007
Volume depletion ^e	2.7 (1.8-3.9)	$<.001$

^a AKI = acute kidney injury; CI = confidence interval; CKD = chronic kidney disease (defined by baseline glomerular filtration rate of <60 mL/min); OR = odds ratio.

^b Comparisons are made with non-AKI, frequency-matched controls; ORs were adjusted for the matching age groups.

^c P values were derived using the Mantel-Haenszel χ^2 test.

^d These include angiotensin II receptor antagonists, aminoglycosides, nonsteroidal anti-inflammatory drugs, and intravenous contrast agents.

^e Volume depletion occurred as a result of decreased oral intake of fluids and loss of fluids via gastrointestinal mechanisms (diarrhea, vomiting), excessive sweating, or blood loss.

DISCUSSION

This study confirms that AKI, defined as an increase in serum creatinine level of 0.3 mg/dL or more within 48 hours, predicts clinical outcomes of non-critically ill patients. Acute kidney injury was associated with a nearly 7-fold (adjusted OR, 7.9; 95% CI, 2.9-15.3) increased odds of death, a more than 4-fold increased odds of prolonged (≥ 7 days) LOS, and a nearly 4-fold increased odds of transfer to critical care units. These findings are consistent with our findings in a cohort of critically ill patients admitted to the same community hospital.¹

Outcomes and interventions for renal dysfunction have been explored extensively, but most studies have examined outcomes of critically ill patients.^{1,8-11,14-17} Fewer studies have reported the epidemiology of renal dysfunction in non-ICU patients.¹⁸⁻²³ Liangos et al²¹ used the 2001 National Hospital Discharge Survey to demonstrate that 1.9% of hospitalized patients were diagnosed as having acute renal failure. Acute renal failure was assumed to be present if it was mentioned in the discharge summary and independently predicted hospital mortality and prolonged LOS. In a retrospective analysis of hospitalized patients, Chertow et al² first showed that a change in serum creatinine level of more than 0.3 mg/dL during the entire course of hospitalization was associated with longer LOS and higher hospital costs. Although previous studies vary as to the incidence and prevalence of acute renal dysfunction (variably defined), most have shown adverse outcomes in patients with this condition.²²⁻²⁴

The express purpose of the Acute Kidney Injury Network was to draft an interim evidence-based definition of AKI that would then be tested for scientific validity. The proposed definition for AKI was *not* intended to be final; it was expected to be revised if or when epidemiological studies were conducted to refine its precision. We published the first

TABLE 5. Predictors of Adverse Events by Conditional Multivariate Logistic Regression in Selected Age-Matched AKI Cases and Controls^a

Adverse events	Adjusted OR	95% CI	P value
In-hospital mortality			
AKI	7.9	2.9-15.3	<.001
Age	1.0	0.9-1.1	.75
Sex	1.2	0.7-2.3	.49
Race ^b	0.8	0.3-1.8	.53
Comorbidities ≥ 2	1.0	0.8-1.3	.99
CKD	0.7	0.4-1.4	.31
Length of stay ≥ 3 d			
AKI	3.8	3.4-18.6	<.001
Age	1.0	0.9-1.1	.72
Sex	0.9	0.6-1.4	.62
Race ^b	0.9	0.5-1.5	.68
Comorbidities ≥ 2	1.1	1.0-1.4	.15
CKD	0.8	0.5-1.4	.48
Length of stay ≥ 7 d			
AKI	5.2	3.5-7.9	<.001
Age	1.0	0.9-1.0	.35
Sex	1.2	0.8-1.7	.42
Race ^b	1.0	0.6-1.7	.87
Comorbidities ≥ 2	1.0	0.9-1.2	.63
CKD	0.9	0.6-1.3	.56
Discharge to an ECF ^c			
AKI	3.0	2.0-4.6	<.001
Age	1.0	1.0-1.1	.27
Sex	0.6	0.4-0.9	.02
Race ^b	0.7	0.4-1.2	.25
Comorbidities ≥ 2	1.1	0.9-1.3	.35
CKD	0.8	0.5-1.2	.30
Transfer to ICU			
AKI	4.7	2.7-8.1	<.001
Age	1.0	0.9-1.0	.29
Sex	1.5	0.9-2.4	.11
Race ^b	1.1	0.6-2.0	.65
Comorbidities ≥ 2	1.2	1.0-1.4	.13
CKD	0.6	0.3-0.9	.03

^a AKI = acute kidney injury; CI = confidence interval; CKD = chronic kidney disease (defined as baseline glomerular filtration rate of <60 mL/min); ECF = extended-care facility; ICU = intensive care unit; OR = odds ratio.

^b For race, whites and nonwhites were compared.

^c These include all non-home facilities.

study to test the new definition in 496 critically ill patients. The creatinine (increase of ≥ 0.3 mg/dL in 48 hours) component of the AKI definition was associated with a nearly 4-fold odds of mortality and a LOS that was twice as long (14 vs 7 days). In light of the findings of Chertow et al² and our own findings in critically ill patients, we reasoned that the same observations might apply to patients initially admitted to our hospital wards. Interestingly, patients whose creatinine levels increased by 0.3 mg/dL or more after more than 48 hours or at unclear intervals (because of insufficient creatinine data) had outcomes midway between AKI cases and controls (Table 2). This observation confirms the results of Chertow et al² that absolute increases in creatinine level of 0.3 mg/dL or more are associated with worse outcomes irrespective of the rate of creatinine increase.

The definition of AKI provides a unique basis for future epidemiological and interventional outcomes studies and also describes a biochemical event that may be caused by a constellation of diverse pathophysiologic events. It does not distinguish between prerenal, renal, and postrenal mechanisms—the most common pathophysiologic construct for describing renal failure. For example, it is unknown whether prerenal azotemia is functional or actually involves kidney injury (vs functional, blood flow–related changes in creatinine clearance with normally functioning or even hyperfunctioning kidneys). Regarding intrinsic “renal” mechanisms of injury, AKI has been best studied with ischemic/toxic injuries (ie, acute tubular necrosis). Patient prognosis can vary dramatically with other causes of AKI, such as interstitial disease, glomerular injuries, and obstructive causes, depending on the underlying etiology. In reality, serum creatinine level is likely a relatively late and imprecise biomarker of kidney dysfunction. Other biomarkers, including IL-8, urinary cystatin C, and urinary neutrophil gelatinase-associated lipocalin (NGAL), are being investigated as potential earlier and more accurate markers of clinically important renal dysfunction.²⁴

A recent article highlights the problem of not having a unique diagnosis of renal failure. Nickolas et al²⁵ examined the sensitivity and specificity of urinary NGAL for diagnosing AKI in the emergency department. Remarkably, AKI was the outcome of interest, defined as “a new-onset 1.5-fold increase in serum creatinine level or a 25% decrease in estimated GFR from baseline values that satisfied minimal RIFLE [Risk, Injury, Failure, Loss of function, and End-stage kidney disease] criteria for serum creatinine and GFR that was sustained for at least 3 days despite volume resuscitation.” No reference was given for the origin or validity of this definition, but the authors concluded that “a single measurement of urinary NGAL helped distinguish acute injury from normal function, prerenal azotemia, and chronic kidney disease.”²⁵ The Acute Dialysis Quality Initiative found 44 studies published before 2004 using more than 20 definitions of renal failure.⁵ Until investigators can agree on a unique definition, research in this area will be impeded, and replicability, at the basis of most scientific inquiry, will be hindered if not rendered impossible.

Our study had several limitations. First, some data were missing because of the retrospective study design. Sufficient laboratory data were unavailable for about 15% of patients admitted during the study period. Second, we excluded 209 patients whose creatinine level increased by 0.3 mg/dL or more during an uncertain time interval. Some of those patients would likely have been categorized as AKI cases (if creatinine levels had been measured daily). Third, age was associated with outcomes in the

univariate analysis, prompting us to perform age-matched comparisons to adjust for the potentially confounding effect of age on outcomes. As a result, we could not ascertain the potential interacting effect of age and AKI on the selected outcomes. Finally, these data do not demarcate prognoses on the basis of underlying causative pathophysiology and so cannot be used to determine precise mortality estimates for subgroups of patients (eg, prerenal vs renal, glomerulonephritis vs acute tubular necrosis vs obstructive uropathy).

CONCLUSION

An abbreviated definition of AKI (ie, an increase in serum creatinine level of 0.3 mg/dL or more within 48 hours) is associated with adverse clinical outcomes, including in-hospital mortality, prolonged hospital LOS, need for intensive care, and discharge to an ECF. If our findings can be replicated at other centers, then the Acute Kidney Injury Network criteria for AKI provide a simple, scientifically valid definition that could foster research in this field.

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