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Sepsis-Associated Acute Kidney Disease

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Introduction: About one-third of critically ill patients with acute kidney injury (AKI) develop persistently decreased kidney function, known as acute kidney disease (AKD), which may progress to chronic kidney disease (CKD). Although sepsis is the most common cause of AKI, little is known about sepsis-associated AKD.

Methods: Using data from a large randomized trial including 1341 patients with septic shock, we studied patients with stage 2 or 3 AKI on day 1 of hospitalization. We defined AKD as a persistently reduced glomerular filtration rate for >7 days. In addition to clinical data, we measured several urinary biomarkers (tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 [TIMP-2*IGFBP7], neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule-1 [KIM-1], liver-type fatty acid binding protein, and type 4 collagen) at 0, 6, and 24 hours, to predict AKD.

Results: Of 598 patients, 119 (19.9%) died within 7 days, 318 (53.2%) had early reversal of AKI within the first 7 days, whereas 161 (26.9%) developed AKD. In patients with early reversal, 45 (14.2%) had relapsed AKI after early reversal, and only about one-third of these recovered. Among patients developing AKD, only 15 (9.3%) recovered renal function prior to discharge. Male sex, African American race, and underlying CKD were more predominant in patients developing AKD. None of the biomarkers tested performed well for prediction of AKD, although NGAL modestly increased the performance of a clinical model.

Conclusions: AKD is common in patients with septic shock, especially among African American males and those with underlying CKD. Existing AKI biomarkers have limited utility for predicting AKD but might be useful together with clinical variables. Novel predictive biomarkers for renal recovery are needed.

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Globally, more than half of all patients in the intensive care unit (ICU) suffer from AKI, and sepsis is the most common etiology.[1,2] Evidence from epidemiologic studies has shown that AKI is associated not only with short-term adverse effects but also important long-term consequences.[3–5] Despite apparent recovery from AKI, patients are still at risk for recurrent kidney injury, which can worsen clinical outcomes.[6,7]

Both AKI severity and duration are associated with progression to CKD and other adverse clinical outcomes.[8] Persistent reduction in glomerular filtration rate beyond 7 days but for less than 90 days is considered AKD.[9,10] Data on the epidemiology and course of AKD are still limited, and few studies have

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[13]A complete list of ProCESS and ProGReSS-AKI Investigators is available in the Appendix and at https://crisma.upmc.com/progressakistudy.

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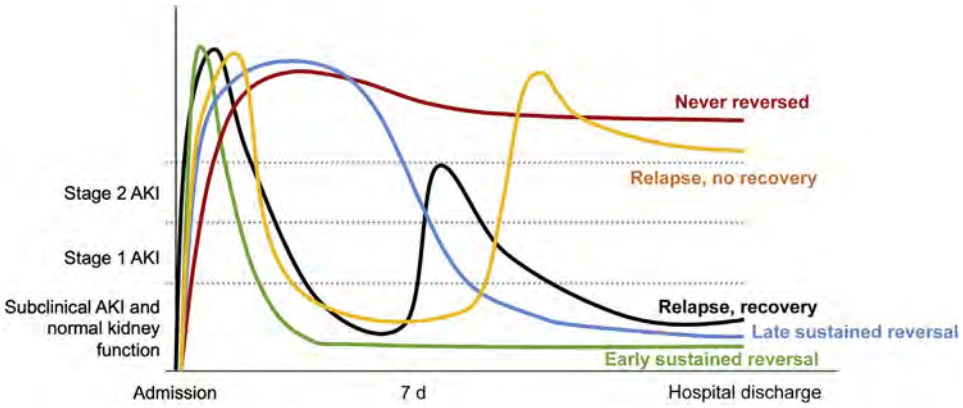

Figure 1. Trajectories after acute kidney injury (AKI).

focused on sepsis-associated AKD. However, several observational studies have shown that the shorter the duration of AKI, the better the outcome. About 70% to 90% of hospitalized patients with AKI experience recovery of kidney function within 3 to 4 days of AKI onset.[11,12] In several studies, complete and sustained reversal of AKI within 48 to 72 hours was associated with better outcomes than was AKI of longer duration.[11,13–17] However, when compared to those with no AKI, patients with AKI with early reversal still experienced a higher risk of in-hospital mortality and developing *de novo* CKD.[11,12] We recently reported distinct recovery phenotypes following AKI among nearly 17,000 critically ill patients.[7] About 64% of patients with stage 2 or 3 AKI had normal kidney function within 7 days after AKI onset, which was associated with the most-favorable long-term outcomes. Interestingly, the remaining 36% had persistent AKI beyond 7 days, compatible with AKD, and this was associated with poorer outcomes. In the setting of sepsis, early reversible AKI within 24 hours was associated with improved survival.[18] Another study in patients with sepsis-associated AKI found that persistent AKI for more than 7 days was associated with increased ICU length of stay, ventilator use, and cardiovascular failure, but not in-hospital mortality by 30 days.[19] A recent meta-analysis showed that duration of AKI was independently associated with long-term mortality, cardiovascular events, and development of incident CKD of stage 3 or greater.[20] This accumulating evidence emphasizes the clinical impact of persistently reduced kidney function following AKI. This group of patients may need more-intensive monitoring and follow-up care.[9] Thus, we sought to examine AKD and associated outcomes in patients with sepsis. Given that early recognition of patients at risk of developing AKD would provide clinicians with a better chance of early implementation of interventions to facilitate recovery, we also examined whether clinical variables either alone or together with existing AKI biomarkers could predict AKD in these patients.

METHODS

Study Design

We performed secondary analyses using data from the ProCESS (Protocolized Care for Early Septic Shock) trial. Full details of the ProCESS trial have been published elsewhere,[21] and additional details related to AKI in this cohort have also been published.[22] In brief, ProCESS was a multicenter randomized controlled trial comparing alternative resuscitation strategies for patients with septic shock in the US. Patients who had either confirmed or suspected infection with hypotension were enrolled and randomized to be resuscitated by early goal-directed therapy,[23] protocol-based standard care, or usual care during the initial 6 hours of hospital admission. In this analysis, we focused on patients with stage 2 or 3 AKI and stratified them by different AKI trajectories using the definitions developed in our previous study[7] (see below). We analyzed the performance of urinary biomarkers collected at 0, 6, and 24 hours after hospital admission in order to differentiate patients with AKD and early reversal of AKI. The in-hospital and long-term survival, up to 1 year, associated with different trajectories of AKI were also determined.

Patients

The ProCESS trial was approved by the University of Pittsburgh Institutional Review Board. Our cohort included those patients with stage 2 or 3 AKI according to Kidney Disease: Improving Global Outcomes criteria[10] that either were present at the time of enrollment or developed within the first 24 hours of hospitalization. Patients with end-stage kidney disease or prior kidney transplant, with known baseline creatinine >4 mg/dl, or with missing enrollment serum creatinine values, and those who withdrew from the

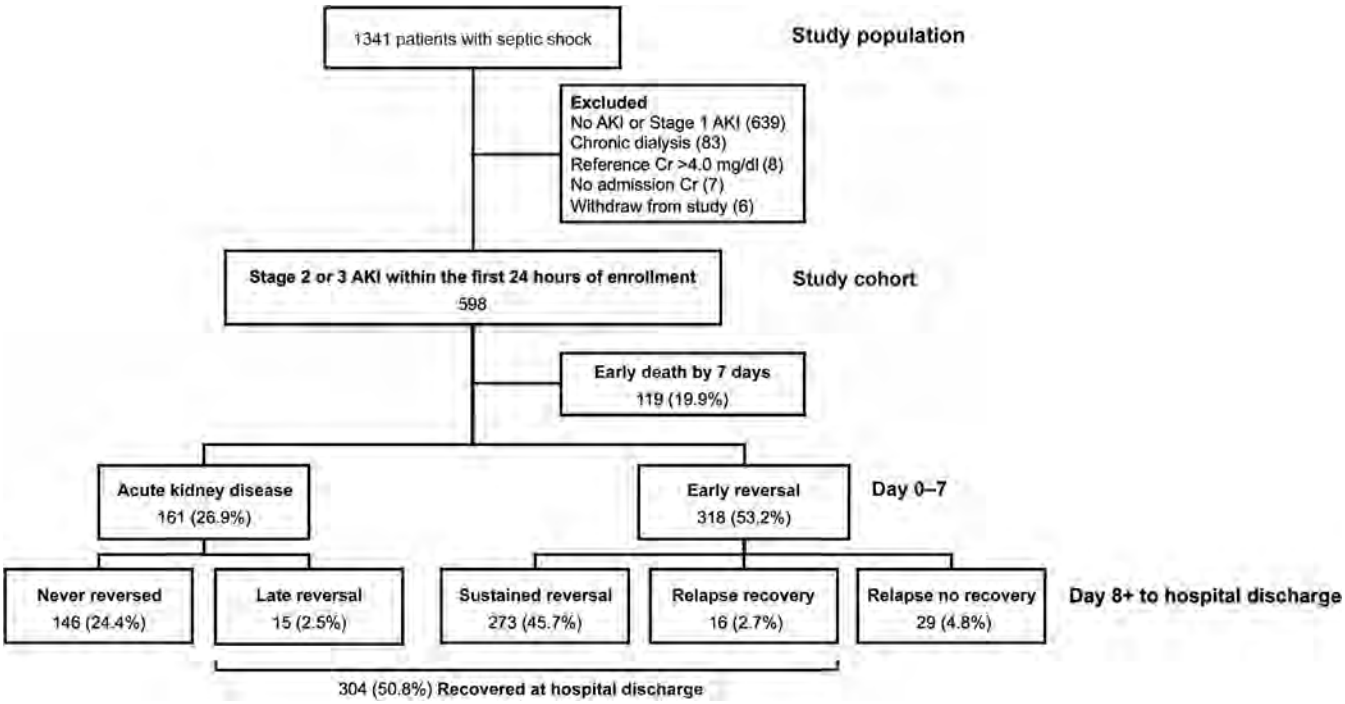

Figure 2. Study flow. AKI, acute kidney injury; Cr, creatinine.

trial, were excluded. From a total of 1341 patients in the ProCESS trial, our analysis cohort was 598 patients.

Definitions of Recovery Status

We classified patients by AKI definition and staging according to the Kidney Disease: Improving Global Outcomes criteria, using both serum creatinine and urine output. AKI stages were determined each day until ICU discharge or at least 72 hours, based on maximum severity by either creatinine or urine output criteria. We determined baseline serum creatinine level within 12 months prior to hospital admission, taking a median value if multiple measurements were available. Reference serum creatinine level was determined by the lower of baseline and admission serum creatinine level as previously described.[15,24,25] For patients with missing baseline or admission serum creatinine level (without history of CKD), we calculated[26] a serum creatinine level by solving the Modification of Diet in Renal Disease equation as recommended in the Kidney Disease: Improving Global Outcomes AKI guideline, assuming a glomerular filtration rate of 75 ml/min per 1.73 m^2. Missing urine output was not imputed and did not contribute to staging for patients.

Figure 1 illustrates the definition of trajectories after AKI onset used in our study. *Early reversal* was defined as the absence of any stage of AKI (even stage 1) by either serum creatinine or urine output criteria for at least a 24-hour period on any day within 7 days of the first documented onset of AKI. Patients with stable kidney function through hospital discharge after early reversal were considered to have *sustained reversal* of AKI. Those who had persistent AKI of stage 1 or greater for more than 7 days up to 90 days after AKI onset were classified as having AKD, according to consensus criteria for AKD following AKI.[9] Those who appeared to have normalized their kidney function after day 7 were classified as having *late reversal*. Subsequent AKI of any stage after initial early reversal was considered a *relapse*. In cases with multiple subsequent AKI episodes, we considered only the first relapse episode for further analyses. After 7 days, we determined recovery status again only at hospital discharge. We defined *recovery* to mean alive, free of renal replacement therapy, and with an absence of AKI by both criteria. Death before hospital discharge was considered to be nonrecovery. AKI trajectories were adjudicated by computer and verified by a nephrologist.

Clinical Data Collection and Biomarker Measurement

In the ProCESS trial, clinical data for participants were collected from the time of enrollment until hospital discharge, including demographics, prior health history, hourly urine output during ICU stay, severity of illness, and reference serum creatinine level. Blood and urine samples were obtained at 0, 6, and 24 hours for chemistry and biomarker testing. Serum creatinine level was determined daily for at least the first 7 days and according to clinical need thereafter. We determined the stage of AKI each day, based on maximum severity by either creatinine or urine output criteria.

Table 1. Baseline characteristics

Characteristic	Early death (n = 119)	AKD (n = 161)	Early reversal (n = 318)	*P* value 3 groups	*P* value 2 groups[a]
Age, yr	67 (52–76)	60 (51–73)	62 (51–75)	0.14	0.37
Male sex	60 (50.84)	115 (71.4)	165 (51.9)	<0.001	<0.001
Race					
White	82 (68.9)	93 (57.8)	223 (70.1)	0.02	0.02
African American	27 (22.7)	60 (37.3)	79 (24.8)	0.01	0.01
Others	10 (8.4)	8 (5.0)	16 (5.0)	0.36	0.98
Body weight, kg	74.9 (63.9–94.0)	86.1 (70.0–103.4)	79.3 (67.1–96.6)	0.02	0.03
Comorbidities					
Hypertension	80 (67.2)	90 (55.9)	205 (64.5)	0.10	0.07
Diabetes mellitus	50 (42.0)	59 (36.6)	116 (36.5)	0.54	1.00
Chronic lung disease	20 (16.8)	27 (16.8)	82 (25.8)	0.03	0.03
Chronic kidney disease	24 (20.2)	33 (20.5)	41 (12.9)	0.04	0.03
Cancer	32 (26.9)	23 (14.4)	47 (14.8)	0.01	1.00
Cerebral vascular disease	13 (10.9)	16 (9.9)	43 (13.5)	0.51	0.30
Congestive heart failure	16 (13.4)	14 (8.7)	38 (11.9)	0.42	0.35
History of myocardial infarction	11 (9.2)	19 (11.8)	30 (9.4)	0.68	0.43
Cirrhosis	15 (12.6)	14 (8.7)	21 (6.6)	0.13	0.46
Peripheral vascular disease	18 (15.1)	9 (5.6)	20 (6.3)	0.01	0.84
Dementia	9 (7.6)	12 (7.5)	28 (8.8)	0.90	0.73
AIDS	4 (3.4)	4 (2.5)	9 (2.8)	0.89	1.00
Charlson comorbidity score	3 (1–6)	2 (1–4)	2 (1–3)	<0.001	0.66
APACHE III score	73 (59–94)	62 (49–81)	60 (48–74)	<0.001	0.24
Total SOFA score	10 (7–13)	9 (6–11)	7 (5–10)	<0.001	<0.001
Source of Infection					
Pneumonia	33 (27.7)	38 (23.6)	101 (31.8)	0.17	0.06
Urosepsis	27 (22.7)	50 (31.1)	70 (22.0)	0.08	0.03
Intra-abdominal	25 (21.0)	18 (11.2)	42 (13.2)	0.05	0.53
Skin and soft tissue	6 (5.0)	11 (6.8)	21 (6.6)	0.80	0.93
Catheter-related	0 (0)	4 (2.5)	6 (1.9)	0.25	0.74
Central nervous system	1 (0.8)	2 (1.2)	2 (0.6)	0.79	0.61
Endocarditis	0 (0)	2 (1.2)	2 (0.6)	0.45	0.61
Unknown	17 (14.3)	19 (11.8)	45 (14.2)	0.75	0.57
Other	8 (6.7)	14 (8.7)	20 (6.3)	0.62	0.33
Positive blood culture	47 (39.5)	67 (41.6)	106 (33.3)	0.16	0.08
Initial lactate, mg/dl	5.9 (4.4–9.0)	4.8 (3.0–7.0)	4.6 (2.8–6.2)	<0.001	0.15
Creatinine, mg/dl					
Hospital admission	2.31 (1.59–3.20)	3.20 (2.21–4.48)	2.20 (1.58–2.98)	<0.001	<0.001
Reference value	1.01 (0.80–1.36)	0.94 (0.80–1.07)	1.03 (0.81–1.30)	0.01	0.004
Max AKI stage in first 24 h of admission					
Stage 2	74 (62.2)	71 (44.1)	227 (71.4)	<0.001	<0.001
Stage 3	45 (37.8)	90 (55.9)	91 (28.6)	<0.001	<0.001
Resuscitation strategies in the first 6 h					
EGDT	42 (35.3)	47 (29.2)	109 (34.3)	0.46	0.26
PSC	32 (26.9)	58 (36.0)	100 (31.4)	0.26	0.31
UC	45 (37.8)	56 (34.8)	109 (34.3)	0.78	0.91

(Continued on next column)

Table 1. (Continued) Baseline characteristics

Characteristic	Early death (n = 119)	AKD (n = 161)	Early reversal (n = 318)	*P* value 3 groups	*P* value 2 groups[a]
Refractory hypotension	59 (49.6)	78 (48.4)	180 (56.6)	0.17	0.09
Pre-randomization fluid volume, L	2.00 (1.00–3.00)	2.00 (1.00–3.00)	2.00 (1.01–3.00)	0.60	0.56
6-h fluid volume, L	3.00 (1.69–4.50)	2.60 (1.53–4.15)	2.84 (1.74–4.15)	0.80	0.92
Received antibiotics by intervention	86 (72.9)	121 (75.2)	258 (81.1)	0.11	0.13

AKD, acute kidney disease; AKI, acute kidney injury; APACHE III, Acute Physiology and Chronic Health Evaluation III; EGDT, early goal-directed therapy; PSC, protocol-based standard care; SOFA, Sequential Organ Failure Assessment; UC, usual care.
[a]*P* value for AKD compared with early-reversal groups.
Data shown as n (%) or median (interquartile range).

Urine samples for biomarker testing were collected at the time of enrollment (0 hour), at the end of 6-hour resuscitation, and at 24 hours, by standard methods. The centrifuged samples were stored at −80 °C and thawed immediately prior to analysis. We analyzed biomarker levels at each time point in relation to clinical AKI trajectories. We investigated several urinary biomarkers, including markers of kidney stress—TIMP-2 and IGFBP7, measured using a clinical immunoassay (Astute Medical, San Diego, CA); markers of tubular injury—NGAL using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN); KIM-1 (Bioassay Works, Ijamsville, Maryland); liver-type fatty acid binding protein (CMIC Holdings Co., Ltd., Tokyo, Japan); and a marker of glomerular injury—type IV collagen (Stanbio Laboratory, Boerne, Texas).

Outcomes

Our primary outcome was AKD at 7 days following AKI stage 2 to 3 (first day). Secondary outcomes included ICU and hospital length of stay, in-hospital mortality, and mortality at 90 days and 1 year. Vital status was determined from the National Center for Health Statistics National Death Index database.

Statistical Analyses

Statistical comparisons for categorical and continuous data were performed using χ^2/Fisher exact test and Mann-Whitney U test/Kruskal-Wallis test, respectively. Data are reported as counts (percentages) for categorical data, and median with interquartile range for continuous data. No imputation was performed for missing data. The predictive value for biomarkers was analyzed using receiver operating curve (ROC) analysis, and the area under the ROC curve (AUC) was calculated. Previously, validated risk factors for each outcome (such as AKD, early reversal) were analyzed and transformed as appropriate, followed by

Table 2. Validation of multivariable clinical model for predicting AKD

Variable	aOR	95% CI	*P* value
Age, by unit of 5 yr	1.00	1.00–1.00	0.83
Male	2.56	1.79–3.67	<0.001
Race			
African American vs. White	1.89	1.12–3.19	0.02
Others vs. White	1.32	0.49–3.60	0.59
Hypertension	0.68	0.43–1.09	0.11
Cardiac disease	0.76	0.39–1.48	0.42
APS-III score,[a] by units of 10	1.18	1.09–1.29	<0.001
Weight-adjusted urine output,[a,b] by 100 ml	0.98	0.97–0.99	<0.001
Vasopressor[c]	1.01	0.54–1.88	0.98
Mechanical ventilation[c]	0.44	0.25–0.75	0.003

AKD, acute kidney disease; aOR, adjusted odds ratio; APS-III, Acute Physiology Score III; CI, confidence interval.
[a]Square-root transformation was used for selected variables in the model.
[b]The available urine volume in the 24 hours after intensive-care unit admission was summed and divided by the weight.
[c]Captured in 6 hours after randomization.
N = 476; area under the receiver operating characteristic curve = 0.71 (95% CI, 0.66–0.76); goodness-of-fit *P* value = 0.49.

multivariable logistic regression. Odds ratios with 95% confidence intervals (CIs) of estimated odds ratios were reported. For AKD prediction, in order to provide more statistical accuracy, bootstrapping was performed with 50 bootstrap samples.

Survival analyses were performed using Cox proportional hazard models adjusted by age, and adjusted hazard ratios were reported. The log rank test was used to compare survival curves. All statistical analyses were performed using Stata, version 15.1 (StataCorp, College Station, TX), R version 3.5.2 (The R Foundation for Statistical Computing) and EZR version 1.38 (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan), which is a graphical user interface for R.[27] A *P* value of less than 0.05 was considered to indicate statistical significance, for all tests performed.

RESULTS

AKI Trajectories and Baseline Characteristics

From the study population of 1341 patients, 598 (44.6%) patients had moderate to severe AKI (stage 2 or 3) within the first 24 hours of hospital admission (372 [63.2%] had stage 2 AKI, and 226 [36.8%] had stage 3 AKI). Of these, 119 (19.9%) patients died within 7 days after enrollment and were not included in our primary analysis (Figure 2). At 7 days, 318 (53.2%) patients had early recovery of kidney function, whereas 161 (26.9%) patients had persistent AKI compatible with AKD. The majority of patients (273 [45.7%]) who had early recovery had sustained normal kidney function throughout the remaining hospital course and were thus categorized as early sustained reversal, whereas the remaining patients (45 [7.5%]) had one or more relapse episodes of AKI, and about two-thirds of these did not ultimately recover by hospital discharge. On the other hand, 90% of patients with AKD never reversed AKI. Only 15 (2.5%) patients experienced reversal later after 7 days. Overall, 304 patients (50.8%) achieved complete recovery of kidney function at hospital discharge.

Table 1 summarizes the main baseline patient characteristics by clinical status at 7 days. The median age was comparable between the 2 groups. Male sex and African American race were more predominant in the AKD group. Patients with AKD also had significantly higher median body weight (86.1 kg vs. 79.3 kg; $P = 0.03$). As expected, the AKD group had a significantly higher rate of preexisting CKD than the early reversal group (20.5% vs. 12.9%; $P = 0.03$). The AKD group also had a higher baseline sequential organ failure assessment score (9 vs. 7; $P < 0.001$). Pneumonia and urinary tract infection were the 2 most common sources of sepsis. However, urosepsis was more common in the AKD group (31.1% vs. 22.0%; $P = 0.03$) and was the only site of infection that was significantly associated with developing AKD (odds ratio, 1.60; 95% CI, 1.04–2.44; $P = 0.031$; Supplementary Table S1). Serum creatinine level at hospital admission in the AKD group was significantly higher than that in the early reversal group (3.20 mg/dl vs. 2.20 mg/dl; $P < 0.001$), despite a slightly lower reference serum creatinine value for patients who developed AKD (0.94 mg/dl vs. 1.03 mg/dl; $P = 0.004$).

Clinical Model for Prediction of AKD

We validated a clinical model that had already been developed for predicting nonrecovery AKI from our previous study in 15,266 critically ill patients with an AUC-ROC of 0.65.[7] Male sex, African American race, and high acute physiology score III significantly increased the odds of developing AKD (Table 2). By contrast, high urine output and the use of mechanical ventilation significantly favored early reversal of AKI. In the current study, this clinical model provided an AUC-ROC of 0.71 (95% CI, 0.66–0.76).

Biomarkers for Prediction of AKD

The median levels of urinary biomarkers at 0, 6, and 24 hours were compared between the AKD and the early-reversal groups (Table 3). The baseline biomarker levels at enrollment did not differ between these 2 groups. Baseline urinary TIMP-2*IGFBP7 levels in both groups were higher than the diagnostic cutoff level of 0.3 $(ng/ml)^2/1000$, but they were not statistically different. However, patients developing AKD had significantly higher urinary TIMP-2*IGFBP7 levels at both 6 hours (1.31 vs. 0.49 $(ng/ml)^2/1000$; $P < 0.001$) and 24 hours (0.59 vs. 0.36 $(ng/ml)^2/1000$; $P = 0.003$) compared to patients with early reversal (Figure 3). The median changes of TIMP-2*IGFBP7 level from baseline to 6 and

Table 3. Biomarker levels at 0, 6, and 24 hours

Urinary biomarker	Time measured (h)	Early death	AKD	Early reversal	*P* value 3 groups	*P* value 2 groups[a]
TIMP-2*IGFBP7, (ng/ml)^2/1000	0	1.32 (0.30–3.91) n = 78	1.48 (0.39–5.28) n = 108	1.12 (0.29–2.93) n = 239	0.23	0.11
	6	1.69 (0.30–4.33) n = 79	1.31 (0.34–3.38) n = 126	0.49 (0.17–1.60) n = 263	<0.001	<0.001
	24	1.63 (0.48–5.01) n = 62	0.59 (0.17–1.92) n = 129	0.36 (0.13–1.08) n = 264	<0.001	0.003
NGAL, ng/ml	0	331.7 (117.3–577.6) n = 12	465.2 (14.7–629.5) n = 11	332.9 (38.4–629.5) n = 42	0.95	0.93
	6	897.9 (130.6–2098.4) n = 21	1907.4 (391.6–2098.4) n = 47	714.4 (161.6–2098.4) n = 82	0.04	0.01
	24	1168.0 (414.9–2098.4) n = 21	1244.3 (365.8–2098.4) n = 47	613.6 (117.7–2098.4) n = 82	0.11	0.09
KIM-1, pg/ml	0	1.50 (0.76–4.84) n = 36	1.30 (0.70–3.70) n = 47	1.30 (0.40–2.80) n = 123	0.21	0.16
	6	1.60 (0.90–4.77) n = 34	1.30 (0.58–3.54) n = 59	1.00 (0.50–3.61) n = 130	0.08	0.63
	24	1.82 (0.78–5.36) n = 30	1.33 (0.40–3.46) n = 59	1.20 (0.50–3.09) n = 125	0.30	0.99
L-FABP, pg/ml	0	73.6 (44.2–1779.0) n = 16	49.8 (16.9–155.4) n = 27	89.4 (15.9–247.8) n = 61	0.39	0.65
	6	187.3 (92.90–2121.6) n = 11	54.1 (16.9–145.3) n = 29	77.3 (19.8–165.8) n = 66	0.04	0.64
	24	52.5 (25.6–4552.8) n = 10	45.4 (20.5–138.9) n = 29	56.8 (13.8–117.6) n = 66	0.72	0.84
Type IV collagen, mcg/L	0	13.02 (7.31–36.85) n = 33	23.94 (5.11–69.68) n = 44	13.93 (5.30–27.05) n = 116	0.34	0.14
	6	22.27 (12.65–58.90) n = 32	22.55 (9.23–82.59) n = 56	14.10 (6.10–41.6) n = 122	0.048	0.13
	24	26.93 (15.87–71.84) n = 28	23.89 (8.09–71.58) n = 56	21.72 (9.17–40.94) n = 117	0.49	0.45

AKD, acute kidney disease; IGFBP7, insulin-like growth factor-binding protein 7; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid binding protein; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinases-2.
[a]*P* value for AKD compared with early-reversal groups.
Data shown as median (interquartile range).

24 hours were not different between the 2 groups (Supplementary Table S2). The remaining biomarkers did not differ between the 2 groups at any time point.

Urinary biomarkers measured at each time point were used for predicting AKD (Table 4). None of the 5 biomarkers at baseline were predictive for AKD at 7 days (AUC-ROC < 0.6). TIMP-2*IGFBP7 at 6 hours had an AUC-ROC of 0.63 (95% CI, 0.57–0.69; $P < 0.001$) for predicting AKD. NGAL at 6 hours also performed similarly, with an AUC-ROC of 0.63 (95% CI, 0.53–0.73; $P = 0.02$). The remaining biomarkers (KIM-1, liver-type fatty acid binding protein, and type IV collagen) were not predictive for AKD (AUC-ROCs < 0.60). The changes between two timepoints of TIMP-2*IGFBP7 levels during the first 24 hours also demonstrated an AUC-ROC of <0.60 for predicting AKD (Supplementary Table S2).

We further explored the prediction performance for AKD by adding urinary TIMP-2*IGFBP7 and NGAL into the clinical model (Table 5 and Supplementary Table S3). When we added TIMP-2*IGFBP7 at 6 hours into the clinical model, the AUC-ROC was slightly increased to 0.72 but was not statistically significantly different when compared to that for the clinical model alone ($P = 0.18$; Figure 4a). However, NGAL at 6 hours significantly increased the AUC-ROC to 0.74 (95% CI, 0.65–0.83) when the marker was added to the clinical model ($P = 0.02$; Figure 4b). The clinical model plus both TIMP-2*IGFBP7 and NGAL at 6 hours provided a similar AUC-ROC of 0.74 (95% CI, 0.65–0.83; $P = 0.02$; Figure 4c).

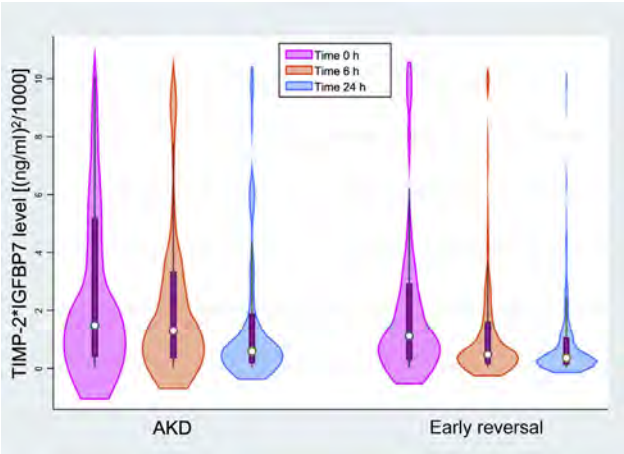

Figure 3. Distribution of tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 (TIMP-2*IGFBP7) level at baseline, and 6 and 24 hours by clinical status at 7 days. AKD, acute kidney disease.

Clinical Outcomes Related to AKI Trajectories

More patients in the AKD group received renal replacement therapy by the first week (11.7% vs. 1.3%; $P < 0.001$). The crude mortality up to 1 year was not different between patients with AKD and those with early reversal (Table 6). The observed unadjusted median hospital length of stay in our cohort was significantly different between these 2 groups (11 vs. 10 days; $P = 0.045$), but the ICU length of stay was not. Survival analyses using Cox proportional hazard model adjusted by age (Figure 5) showed no significant difference in mortality (between patients developing AKD and those with early reversal) by 90 days (adjusted hazard ratio, 1.17; 95% CI, 0.81–1.71; $P = 0.40$) and 1 year (adjusted hazard ratio, 1.20; 95% CI, 0.87–1.65; $P = 0.27$).

Table 4. Urinary biomarkers for predicting AKD

Urinary biomarker	Time measured (h)	N	AUC-ROC for prediction of AKD	95% CI	*P* value
TIMP-2*IGFBP7	0	347	0.55	0.49–0.62	0.11
	6	389	0.63	0.57–0.69	<0.001
	24	393	0.59	0.53–0.65	0.003
NGAL	0	53	0.51	0.31–0.71	0.93
	6	129	0.63	0.53–0.73	0.02
	24	129	0.59	0.49–0.69	0.09
KIM-1	0	170	0.57	0.48–0.67	0.16
	6	189	0.52	0.43–0.61	0.63
	24	184	0.50	0.41–0.60	0.99
L-FABP	0	88	0.47	0.35–0.59	0.65
	6	95	0.47	0.35–0.59	0.64
	24	95	0.49	0.36–0.61	0.84
Type IV collagen	0	160	0.58	0.47–0.69	0.14
	6	178	0.57	0.48–0.66	0.13
	24	173	0.54	0.44–0.63	0.45

AKD, acute kidney disease; AUC-ROC, area under the receiver operating characteristic curve; CI, confidence interval; IGFBP7, insulin-like growth factor-binding protein 7; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid binding protein; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinases-2.

Sensitivity Analyses

Because death and AKD are competing risks, we included 119 patients who died early by 7 days in sensitivity analyses (Figure 2). These patients were incorporated into the never-reversed group. Thus, a total of 294 (49.2%) patients were considered to be nonrecovery at hospital discharge, including those who had never-reversed AKI and those with relapsed AKI and no recovery, whereas 304 (50.8%) patients had recovered (early reversal, late sustained reversal, and relapse with recovery).

Long-term survival was related to recovery patterns at hospital discharge (Figure 6), not AKD status at day 7. Nearly 10% of patients developing AKD (15 of 161) eventually recovered, and nearly 10% of those with early reversal (29 of 318) had an AKI relapse from which they did not recover.

We validated the same clinical model to discriminate between recovery and nonrecovery AKI (Supplementary Table S4). The clinical model performed less well to predict nonrecovery AKI (AUC-ROC of 0.68; 95% CI, 0.64–0.73). None of the candidate biomarkers were predictive for nonrecovery AKI at hospital discharge (Supplementary Tables S5 and S6).

Table 5. Comparison of prediction models for AKD

Model	N	AUC-ROC	95% CI	*P* value
A: clinical model (reference)	476	0.71	0.66–0.76	—
B: clinical model + TIMP-2*IGFBP7[a] at 6 h	386	0.72	0.66–0.77	0.18
D: clinical model + NGAL[b] at 6 h	125	0.74	0.65–0.83	0.02
F: clinical model + TIMP-2*IGFBP7[a] + NGAL[b] at 6 h	124	0.74	0.65–0.83	0.02

AKD, acute kidney disease; AUC-ROC, area under the receiver operating characteristic curve; CI, confidence interval; IGFBP7, insulin-like growth factor-binding protein 7; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinases-2.
[a]Variable was transformed on log scale (natural logarithm).
[b]Variable was transformed on square-root scale.
See Supplementary Table S2 for full models.

DISCUSSION

This study is the first to examine clinical risk for AKD in patients with sepsis, and one of the first studies to demonstrate various patterns of renal recovery after sepsis-associated AKI. When we compared the clinical outcomes between patients with AKD and those who had early reversal of AKI, we found no significant difference in mortality rates up to 1 year. This finding appeared to be due to 3 factors. First, about 20% of patients died before day 7 and thus were never classified as having AKD. Second, about 10% of patients with AKD experienced late recovery, and their outcomes mirrored those of patients with early sustained reversal. Third, about 10% of patients with early sustained reversal experienced an AKI relapse from which they did not recover, and these patients had outcomes similar to patients with AKD. Said differently, kidney function at hospital discharge was more predictive of long-term survival than AKD status at 7 days. Federspiel *et al*. also showed no difference in 30-day mortality between persistent AKI beyond 7 days and AKI with shorter duration.[19]

Overall, our results suggest that the recovery trajectories after AKI in patients with septic shock are similar to those of other critically ill patients, as previously reported (Figures 2 and 5).[7] Either early or late reversal of AKI was associated with high likelihood of survival by 1 year. However, relapsed AKI with or without recovery and never-reversed AKI were associated with a significantly worse prognosis compared to the reversal groups. The rate of AKD at 7 days in this study was similar to that in 2 previous reports. We recently reported a rate of 36.2% for nonreversal AKI by 7 days in critically ill patients.[7] A *post hoc* analysis of a randomized controlled trial in patients with sepsis and acute respiratory distress syndrome found that the rate of persistent AKI beyond 7 days was 32.4%.[19] In our primary analyses, which excluded patients with early death, 90.7% of patients with AKD at 7 days ultimately experienced nonrecovery at hospital discharge. These findings highlight the importance of early recognition of patients at risk for AKD. On the other hand, for patients experiencing early reversal, 85.8% experience no further AKI episodes and had recovery at hospital discharge. However, the remaining 14.2% of this group experienced one or more relapse episodes of AKI during hospitalization, which was related to an adverse outcome as well. The rate of relapse of AKI in patients with severe sepsis was also

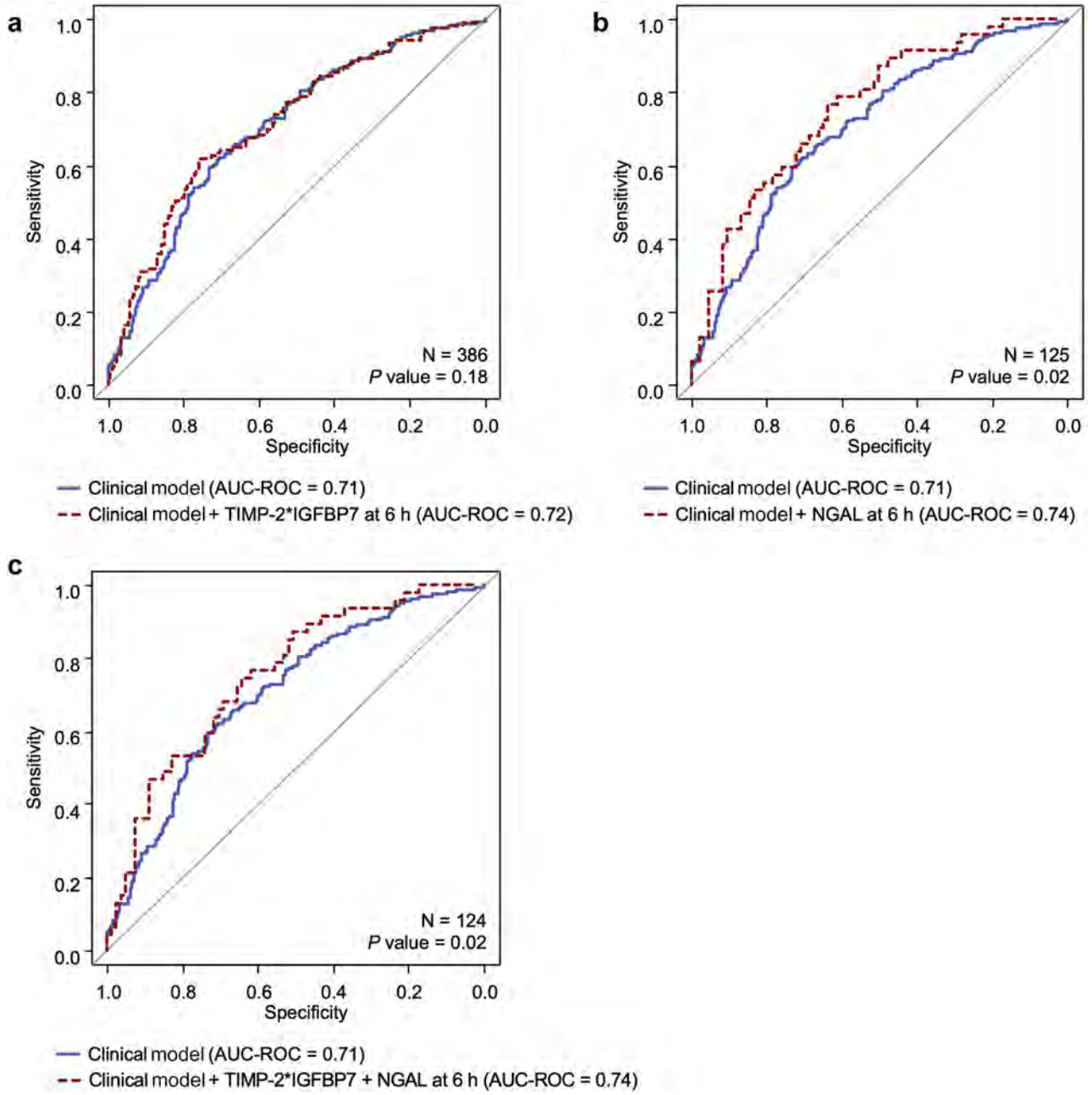

Figure 4. (a–c) Comparing areas under the receiver operating characteristic curve (AUC-ROCs) for prediction of acute kidney disease. NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2*IGFBP7, tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7.

reported by Rodrigo *et al*. at about 20%, and they also found an association with increased risk of death.[28] Interestingly, in patients with preexisting CKD, it probably does make sense that some patients have "AKI on CKD" that resolves slowly and includes a period of AKD. The term "AKD on CKD" is a little awkward, but current definitions still allow for it. With this definition, we could use the term "stable CKD" or "worsening CKD" to specify the aftermath of AKI and AKD in CKD patients.

Table 6. Clinical outcomes

Outcome	AKD (n = 161)	Early reversal (n = 318)	*P* value
Mortality			
In-hospital death by 60 d	23 (14.3)	33 (10.4)	0.21
Death by 90 d	43 (26.7)	76 (23.9)	0.50
Death by 1 yr	59 (36.6)	101 (31.8)	0.28
ICU length of stay,[a] d	4 (3–8)	4 (3–7)	0.99
Hospital length of stay, d	11 (7–20)	10 (7–15)	0.045

AKD, acute kidney disease; ICU, intensive care unit.
[a]Number of patients admitted in ICU = 453 (AKD = 151; early reversal = 302).
Data shown as n (%) or median (interquartile range).

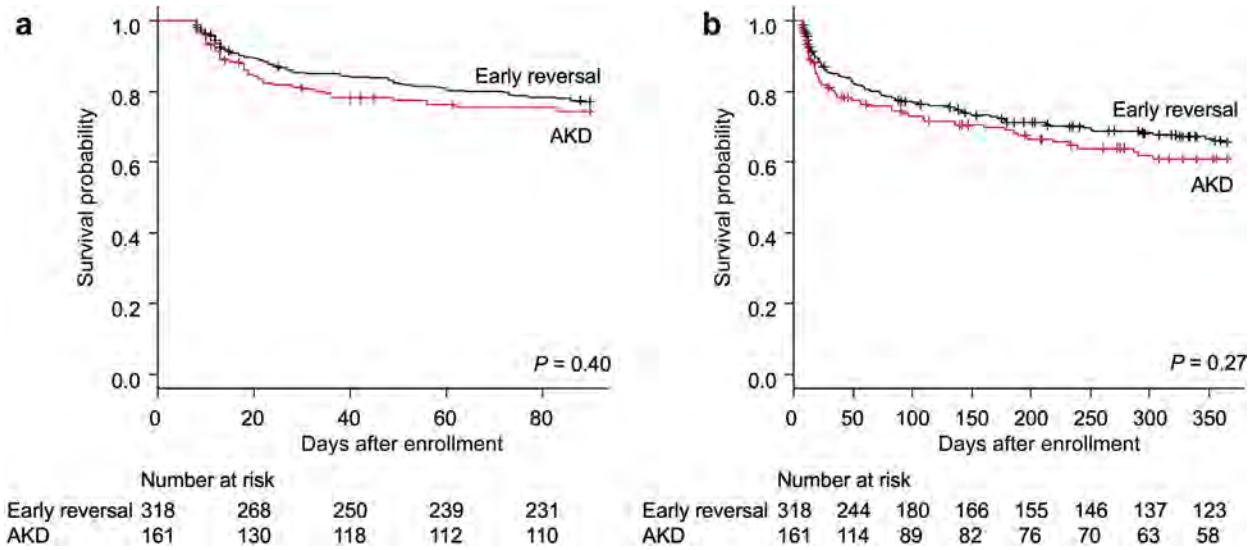

Figure 5. Patient survival comparing acute kidney disease (AKD) and early-reversal groups (a) by 90 days and (b) by 1 year.

AKD is thought to be part of an AKI-to-CKD transition in which maladaptive repair plays a major role. Some animal studies showed a promising role of tubular injury markers for predicting fibrosis after AKI. Albuminuria and urinary NGAL, KIM-1, and liver-type fatty acid binding protein, 1 day after ischemia-reperfusion injury, were correlated with the degree of tubulointerstitial fibrosis at 40 days.[29] Persistent expression of NGAL or KIM-1 in kidney tissue correlated with fibrosis after AKI.[30,31] However, in humans, only a few small studies have used AKI biomarkers for predicting reversal of AKI, and these have demonstrated only fair to good performance. de Geus *et al*. found that urinary NGAL measured on ICU admission had an AUC-ROC of 0.77 (95% CI, 0.64–0.90) for discrimination of sustained AKI (>24 hours; $n = 37$) and transient AKI ($n = 17$).[32] Dewitte *et al*. also reported the performance of multiple biomarkers for prediction of early renal recovery within 48 hours after AKI onset in 57 critically ill patients including urinary TIMP-2*IGFBP7 and plasma NGAL at 0 and 24 hours, which had AUC-ROCs ranging from 0.70 to 0.78.[33] Aregger *et al*. showed the predictive value of urinary IGFBP7 and NGAL measured on day 1 in 52 critically ill patients for AKI recovery within 7 days with AUC-ROCs of 0.74 and 0.70, respectively.[34] We validated a clinical model that provided only fair performance for prediction of AKD (AUC-ROC, 0.71). Furthermore, none

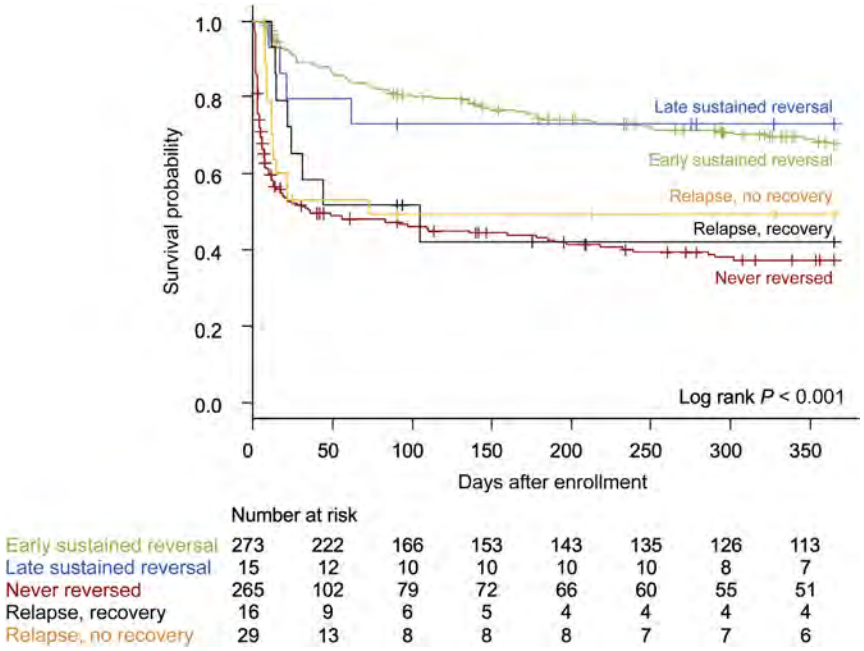

Figure 6. Patient survival by 1 year stratified by recovery trajectories of acute kidney injury at hospital discharge.

of the 5 biomarkers of AKI measured in this study were predictive for AKD at 7 days. Only urinary NGAL measured at 6 hours significantly improved the prediction of AKD when added to the clinical model (AUC-ROC = 0.74). Thus, new markers to predict AKD need to be developed.

Timing of biomarker measurement is an important factor because each marker has different kinetics, and knowing the exact onset of renal recovery is nearly impossible. Findings from our previous report indicated that the median time to reversal of AKI ranged from 30 to 47 hours after its onset.[7] For this reason, we only analyzed biomarkers within the first 24 hours of recognized AKI.

To our knowledge, this is the first study specifically examining the epidemiology and outcome of AKD and also reporting the performance of existing AKI biomarkers for prediction of AKD at 7 days. Our analyses were based on data from a multicenter randomized controlled trial, which provided access to a large set of clinical data, timely sample collection, and standardized definition of AKI and clinical outcomes. We also used the current definition of AKD.[9] Nevertheless, there are some limitations. First, although sepsis is presumed to be the insult occurring prior to admission, in some cases, the etiology of AKI may be multifactorial and not solely sepsis-associated. However, data for other insults of AKI were not collected in the original ProCESS trial. Second, some AKI trajectories used in our study have no uniform consensus definition. Our definition of relapsed AKI is pragmatic. A new rise in serum creatinine level and/or fall in urine output after early reversal of AKI could be either a new episode of AKI resulting from new insults or a stuttering course from the previous AKI episode. Third, as our data are derived from patients with sepsis shock who developed AKI within 24 hours of hospital admission, which might be considered to be community-acquired, generalizability of these results needs to be validated in other AKI phenotypes and in hospital-acquired settings. Fourth, we did not, as a rule, adjust for multiple comparisons when looking at individual biomarkers, because our goal was to identify whether any AKI markers might be used to predict AKD. Last, we have a limited number of patients in some recovery patterns (relapsed AKI and late-reversal AKI), the results related to these subgroups should be interpreted with caution.

In conclusion, AKD is common in patients with septic shock. The existing biomarkers of kidney injury are clearly not useful for prediction of AKD. Urinary NGAL might be useful when added to a clinical model. The discovery and development of novel biomarkers for AKD are still needed. Long-term survival of patients with sepsis-associated AKI is strongly related to recovery status at hospital discharge.

APPENDIX

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DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Site of infection and risk of developing AKD.

Table S2. TIMP-2*IGFBP7 level changes between 2 time points and predictive value for AKD at 7 days.

Table S3. Clinical models with urinary biomarkers for predicting AKD.

Table S4. Validation of clinical model for predicting nonrecovery AKI at hospital discharge.

Table S5. Urinary biomarkers for predicting nonrecovery AKI at hospital discharge.

Table S6. Clinical model with urinary biomarkers for predicting nonrecovery AKI at hospital discharge.

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