

Kidney Biomarkers and Major Adverse Kidney Events in Critically Ill Patients

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Abstract

Background Several biomarkers of AKI have been examined for their ability to predict AKI before serum creatinine. Few studies have focused on using kidney biomarkers to better predict major adverse kidney events (MAKE), an increasingly used composite outcome in critical care nephrology research.

Methods Single-center prospective study collecting blood and urine samples from critically ill patients with AKI Kidney Disease Improving Global Outcomes stage 2 or above, and matched controls from a single, tertiary care intensive care unit (ICU). Samples were collected at 24–48 hours after AKI diagnosis (patients) or ICU admission (controls), 5–7 days later, and 4–6 weeks after discharge for patients with AKI. The primary outcome of interest was MAKE at hospital discharge (MAKE-DC), consisting of the composite end point of death, RRT dependence, or a decrease in estimated glomerular filtration to <75% of baseline.

Results Serum/urinary neutrophil gelatinase-associated lipocalin (NGAL), serum/urinary cystatin C, and urinary kidney injury molecule-1 early in the AKI or ICU course were all significantly higher in patients with MAKE-DC compared with those not experiencing MAKE-DC. Additionally, serum/urinary NGAL and serum cystatin C measurements at the first time point remained significantly associated with MAKE events at 3, 6, and 12 months. Serum cystatin C, and to a lesser extent serum NGAL, significantly improved upon a logistic regression clinical prediction model of MAKE-DC (AUROC 0.94 and 0.87 versus 0.83; $P=0.001$ and $P=0.02$, respectively). Patients without MAKE-DC experienced a greater decline in serum NGAL from first to second measurement than those patients experiencing MAKE-DC.

Conclusions Early measures of kidney biomarkers in patients who are critically ill are associated with MAKE-DC. This relationship appears to be greatest with serum NGAL and cystatin C, which display additive utility to a clinical prediction model. Trending serum NGAL may also have utility in predicting MAKE-DC.

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Introduction

The last decade has seen an explosion of research on biomarkers of AKI. Over 15 different biomarkers have been investigated, with a combination of markers receiving US Food and Drug Administration approval in 2014 for detecting AKI within the ensuing 12 hours: the product of tissue inhibitor of metalloproteinase 2 and IGF binding protein 7 (1,2). The primary focus of these studies was the search for a biomarker that would detect AKI sooner than serum creatinine, allowing earlier recognition to improve care (3,4). A secondary aim of this line of research has been to improve risk stratification and longer-term prognostication with kidney biomarkers. This is particularly relevant for patients in the intensive care unit (ICU), where the incidence of AKI is high and conversations with family

and decisions regarding supportive therapies such as RRT can be facilitated by improved prognostication of AKI that extends beyond the period of the acute illness.

Major adverse kidney events (MAKE)—the composite of death, need of RRT, or worsened kidney function—is increasingly recognized as an important, patient-centered outcome for studies of AKI, particularly in patients who are critically ill (5). Previous studies of kidney biomarkers have primarily limited evaluation of MAKE to 30 days (MAKE-30), thus we sought to assess the relationship between early kidney biomarker measurements with MAKE at further time intervals from AKI onset. Further, limited literature has been published to predict MAKE (in the short- or long-term), specifically from clinical models of ICU patients. Preliminary data suggest that simple models

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considering severity of illness provide good performance predicting MAKE out to 30 days (6). Accordingly, we sought to assess kidney biomarker relationships with MAKE at various time points, from discharge out to 1 year of follow-up, and test the utility of adding biomarker data to a clinical prediction model for MAKE by hospital discharge (MAKE-DC).

Materials and Methods

Study Design and Participants

This was a secondary analysis of the AKI biobank from the Klotho and AKI Study Group (7). In brief, this single center, prospective study enrolled adult patients ≥ 18 years old over a 1-year period admitted to the ICU with stage ≥ 2 AKI per Kidney Disease Improving Global Outcomes criteria and matched controls on the basis of age (10-year intervals), sex, and baseline eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation (60–89 and ≥ 90 ml/min per 1.73 m²) (8,9). Patients must have had a baseline eGFR ≥ 60 ml/min per 1.73 m², which was determined using the most recent serum creatinine within the 6-month period before ICU admission. Patients were excluded if they had ESKD, a kidney or any other solid organ transplant, evidence of AKI before ICU admission, or uroepithelial tumors (7). This study was approved by the Institutional Review Board at University of Texas Southwestern Medical Center and all participants or their legally authorized representatives provided written, informed consent.

Data Collection and Laboratory Analysis

Blood and urine samples were taken from all patients at an initial time point (T1), 24–48 hours after AKI diagnosis (patients) or ICU admission (controls). A second set of samples (T2) was obtained 5–7 days after this initial collection. For patients with AKI, a third set (T3) was collected 4–6 weeks after discharge if patients survived and followed up with a clinic visit. These time points were chosen for the original study for their relevance to prognostication and detection of subclinical AKI. Blood and urine samples were centrifuged at 1000 \times g at 4°C for 10 minutes, supernatant aliquoted into cryovials, and stored at –80°C until biomarker measurement. Serum neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C, and urinary NGAL, cystatin C, and kidney injury molecule-1 (KIM-1) were measured using ELISA (BioPorto Diagnostics, Needham, MA; R&D Systems, Minneapolis, MN). Capillary electrophoresis was used to measure urinary creatinine (Ucr) and serum creatinine was obtained from routine clinical care (10). Baseline demographics, comorbidities, and clinical data associated with ICU admission were collected from electronic medical records using medical history and admission/discharge diagnoses, including the Acute Physiology and Chronic Health Evaluation (APACHE) II as a measure of illness severity within the first 24–48 hours of ICU admission and the Charlson Comorbidity Index (CCI) as a measure of comorbidity burden (11,12).

Outcomes

The primary study objective was to compare biomarker measurements between patients with and without the

outcome of MAKE at the following time points: DC, 90 days (90), 6 months (6 months), and 1 year (1 year). At the specified time point, MAKE was defined as any of the following: death, RRT dependence, or decrease in eGFR to $<75\%$ of baseline (5). Secondarily, we sought to assess whether biomarker measurements at time T1 improved upon a clinical prediction model for MAKE-DC. In an exploratory analysis, we examined the trajectory of the biomarkers between times T1 and T2 (the Δ change in biomarker = value at time T2 – value at time T1) in those patients with and without MAKE-DC.

Statistical Analyses

Urinary biomarkers were normalized to Ucr in reporting. Categorical data are presented as proportions and continuous data as medians with interquartile ranges or means \pm SD depending on the distribution. Categorical variables were compared using a chi-squared or Fisher's exact test, as appropriate. Continuous variables were compared using an independent samples *t* test or Mann–Whitney *U* test. A logistic regression model for MAKE-DC was generated using a simple clinical prediction model with two variables, APACHE II and CCI, on the basis of the number of MAKE-DC events in the dataset. APACHE II was calculated within the first 24–48 hours of ICU admission, which corresponds to the first biomarker time point (median time from ICU admission to sample collection of 2 days), includes up to eight numeric points for kidney function, and also allowed for adjustment of other variables associated with mortality in the ICU (12). Collinearity was assessed with the use of variance inflation factors. The added value of individual biomarkers from T1 was assessed with their addition to the model with the use of the area under the receiver operating characteristic curve (AUROC). Statistical significance was considered a two-sided *P* value <0.05 . Patients with missing data (e.g., anuric for urinary biomarkers or lost to follow-up) were excluded from the respective analysis. Analyses were performed in Stata (Version 16.1; Stata Corp, College Station, TX) and R (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study included a total of 106 patients: 54 with AKI and 52 matched controls. Patient characteristics are shown in Table 1. Per the study design, AKI and controls were not different in age, sex, or baseline eGFR. A greater proportion of patients with AKI were in the medical ICU compared with a greater proportion of control patients that were admitted to the surgical ICU. Patients with AKI tended to be more acutely ill overall, as evidenced by higher APACHE II and a greater need for vasopressors and mechanical ventilation. Patients with AKI also had more liver disease and higher CCIs compared with controls.

Biomarker values at time points T1, T2, and T3 are compared between patients with AKI and controls in Table 2. Seven patients with AKI were anuric and thus unable to contribute urine specimens. Death, discharge, or loss to follow-up were other reasons for absences of repeated measurements at the later time points of T2 and T3. Serum and urine biomarkers at all time points were higher, often by several orders of magnitude, in patients with AKI compared

Table 1. Patient characteristics

Characteristics	AKI (n=54)	No AKI (n=52)	P Value
Age (yr)	55.8±16.7	58.0±14.5	0.47
Sex (% men)	31 (57.4)	29 (55.8)	0.87
Race (%)			
White	34 (63.0)	40 (76.9)	0.18
Black	12 (22.2)	5 (9.6)	
Over	8 (14.8)	7 (13.5)	
ICU type, n (%)			
SICU	9 (16.7)	18 (34.6)	0.001
MICU	26 (48.2)	6 (11.5)	
CCU	10 (18.5)	15 (28.9)	
Other ICU	9 (16.7)	13 (25)	
Diabetes (%)	17 (31.5)	10 (19.2)	0.15
Hypertension (%)	27 (50.0)	29 (55.8)	0.55
Heart failure (%)	15 (27.8)	17 (32.7)	0.59
Liver disease (%)	18 (33.3)	6 (11.5)	0.007
Cancer (%)	23 (42.6)	23 (45.1)	0.80
Baseline serum creatinine (mg/dl)	0.86±0.26	0.82±0.20	0.32
Baseline eGFR (ml/min)	88 (69.5–104)	92 (78.3–103)	0.40
APACHE II	20 (16–26)	12 (9–19)	<0.001
Number pressors/inotropes	1.5 (0–3)	0 (0–1)	0.001
Mechanical ventilation (%)	34 (63.0)	20 (38.5)	0.01
Charlson Comorbidity Index	4 (2.8–7)	2 (2–4)	<0.001

ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SICU, Surgical ICU; MICU, Medical ICU; CCU, Coronary Care Unit.

with controls, with the exception of urinary KIM-1/Ucr at time point T2. Of note, patients with AKI with measurements at time point T3, several weeks after AKI, demonstrated sustained elevations in biomarkers, particularly serum NGAL and cystatin C, that were as high as or higher than values in the control group at time T1.

Of 106 patients enrolled in the study, 49 (46.2%) experienced MAKE at discharge. Patients experiencing MAKE-DC had longer ICU [10 (3–18) versus 2 (2–5) days] and hospital

lengths of stay [17 (9–31) versus 8 (4–15) days] compared with patients without MAKE-DC, respectively ($P<0.001$ for both). Of the 49 patients experiencing MAKE at discharge, 24 (49.0%) were categorized by death, 5 (10.2%) by RRT dependence at discharge, and 20 (40.8%) by decrease in eGFR to <75% of baseline.

All biomarkers assessed at time T1 were significantly more elevated in patients experiencing MAKE-DC than those that did not (Table 3). Serum NGAL and cystatin C

Table 2. Kidney biomarker measurements stratified by presence or absence of AKI

Biomarker	n	AKI (n=54)	n	No AKI (n=52)	P Value
Serum NGAL (ng/ml)					
Time 1	54	487 (342–1317)	52	163 (115–213)	<0.001
Time 2	29	441 (290–705)	7	153 (118–185)	0.001
Time 3	22	233 (178–360)			
Urinary NGAL/Ucr (ng/mg Cr)					
Time 1	47	1305 (304–6068)	52	32 (9–85)	<0.001
Time 2	26	791 (301–2436)	7	62 (29–82)	0.001
Time 3	20	72 (30–498)			
Serum cystatin C (ng/ml)					
Time 1	54	2122 (1189–2978)	52	712 (576–842)	<0.001
Time 2	29	1506 (1111–2258)	7	833 (623–974)	0.001
Time 3	21	1299 (908–2387)			
Urinary cystatin C/Ucr (ng/mg Cr)					
Time 1	47	785 (125–1561)	52	48 (9–166)	<0.001
Time 2	26	652 (182–1462)	7	63 (17–128)	0.003
Time 3	19	68 (44–325)			
Urinary KIM-1/Ucr (ng/mg Cr)					
Time 1	47	5.7 (3.3–13.9)	52	2.3 (1.2–4.4)	<0.001
Time 2	47	5.2 (3.1–8.1)	7	4.1 (0.9–5.4)	0.31
Time 3	20	2.3 (1.7–4.3)			

Time 1: 24–48 h after AKI diagnosis (patients) or intensive care unit admission (controls). Time 2: 5–7 d after time 1 collection. Time 3: 4–6 wk after discharge if patient survived and followed up with clinic visit. NGAL, neutrophil gelatinase-associated lipocalin; Ucr, urinary creatinine; Cr, creatinine; KIM-1, kidney injury molecule-1.

Table 3. Kidney biomarkers and major adverse kidney events at discharge

Kidney Biomarker	Major Adverse Kidney Events at Discharge (n=49)	No Major Adverse Kidney Events at Discharge (n=57)	P Value
Serum NGAL (ng/ml)			
Time 1	485 (340–1190)	175 (117–235)	<0.001
Time 2	452 (277–952) (n=23)	163 (120–439) (n=13)	0.01
Urinary NGAL/Ucr (ng/mg Cr)			
Time 1	1037 (283–6085) (n=42)	38 (10–103)	<0.001
Time 2	553 (82–2488) (n=20)	109 (49–1534) (n=13)	0.32
Serum cystatin C (ng/ml)			
Time 1	2283 (1153–3038)	716 (579–923)	<0.001
Time 2	1565 (1117–2464) (n=23)	974 (679–1424) (n=13)	0.006
Urinary cystatin C/Ucr (ng/mg Cr)			
Time 1	611 (122–1601) (n=42)	56 (14–620)	<0.001
Time 2	593 (41–1616) (n=20)	200 (92–726) (n=13)	0.43
Urinary KIM-1/Ucr (ng/mg Cr)			
Time 1	5.6 (3.0–13.4) (n=42)	2.4 (1.2–6.1)	<0.001
Time 2	5.2 (3.0–7.9) (n=20)	4.1 (2.2–7.5) (n=13)	0.65

NGAL, neutrophil gelatinase-associated lipocalin; Ucr, urinary creatinine; Cr, creatinine; KIM-1, kidney injury molecule-1.

were the only biomarkers at time T2 that were significantly higher in patients experiencing MAKE-DC compared with those that did not. The biomarker values at T1 and T2 between patients experiencing MAKE-DC and those that did not can be visualized in Figure 1. Serum/urinary NGAL and serum cystatin C measurements at time T1 were significantly higher in those patients with MAKE-DC, MAKE-90 days, MAKE-6 months, and MAKE-1 year. Urinary cystatin C/Ucr and urinary KIM-1/Ucr measurements at time point T1 were significantly higher in MAKE patients than non-MAKE patients out to 6 months, but not at 1 year (Supplemental Material).

The simple clinical model for MAKE-DC including APACHE II and CCI produced an AUROC of 0.827, with

both APACHE II [odds ratio (OR) 1.13; 95% confidence interval (CI), 1.06 to 1.21] and CCI (OR 1.41; 95% CI, 1.15 to 1.74) independent predictors of MAKE-DC. Both serum NGAL (AUROC=0.873) and serum cystatin C (AUROC=0.941) when independently added to the simple clinical model improved the AUROC ($P=0.02$ and $P=0.001$, respectively) as shown in Figure 2. None of the urinary biomarkers improved upon the simple clinical model for the prediction of MAKE-DC.

In the exploratory analysis of biomarker trajectory from time point T1 to T2, only the change in serum NGAL (Δ NGAL) was significantly different in those patients experiencing MAKE-DC compared with those not. Those patients experiencing greater decreases in serum NGAL from time point T1 to T2 were less likely to experience MAKE-DC

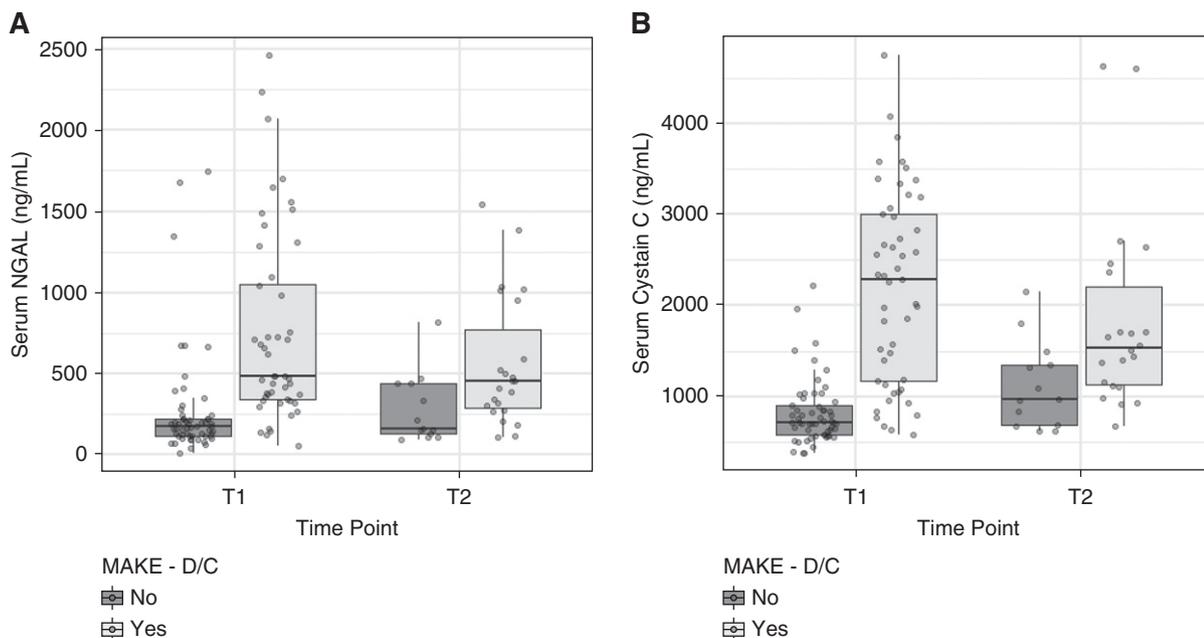


Figure 1. | Kidney biomarker trends from time 1 (24–48 hours) to time 2 (5–7 days). DC, hospital discharge; MAKE, major adverse kidney event; NGAL, neutrophil gelatinase-associated lipocalin.

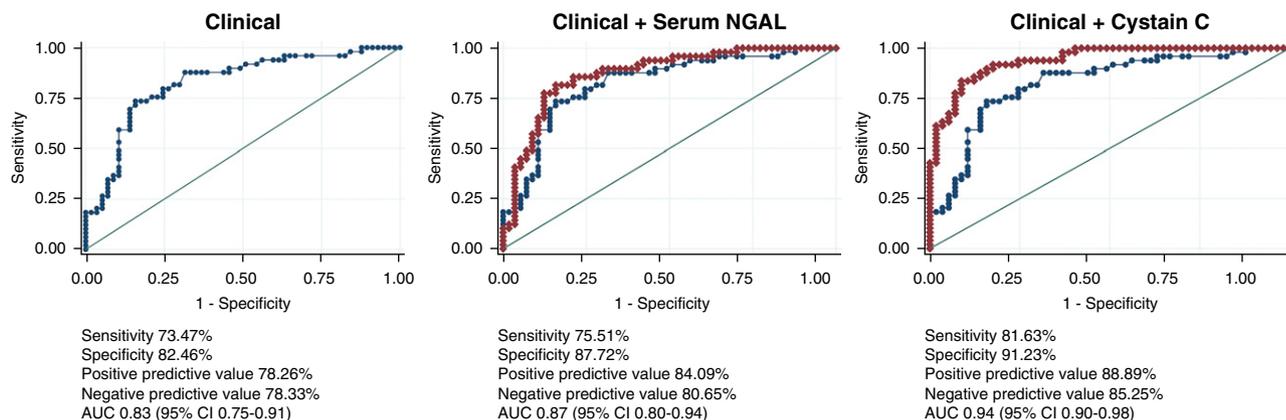


Figure 2. | Receiver operating characteristic curves for MAKE-DC. AUC, area under the curve; 95% CI, 95% confidence interval.

compared with those not ($P=0.01$) (Table 4). To account for baseline serum NGAL at time T1, both T1 and T2 serum NGAL values were assessed in a logistic regression model for MAKE-DC and the serum NGAL value at T2 remained significantly associated with MAKE-DC (OR 1.01; 95% CI, 1.00 to 1.01).

Discussion

In this study of critically ill patients, serum and urinary biomarkers of AKI early in the course of AKI, or absence of AKI in the ICU stay, were significantly higher in those patients experiencing MAKE at several time periods, including DC, 90 days, 6 months, and 1 year. Of these, serum NGAL and cystatin C appeared to have the most utility when added to a simple clinical prediction model consisting of APACHE II and CCI. We also present evidence suggesting that trending these biomarkers in AKI may carry prognostic value. Overall, for the purpose of predicting MAKE events and trending biomarkers, serum NGAL and cystatin C appeared to perform most strongly from the population in our study.

AKI biomarker panels, including multiple markers such as tubular injury and renal stress, have been theorized to have important implications for personalized medicine of patients with AKI and the potential to improve prognostic, diagnostic, and therapeutic tools (13). Although not explored in our analysis, the combination of these biomarker panels has been shown in some settings to improve the predictive capability for AKI, particularly in the postcardiac surgery setting (14–17). The value of biomarker trajectory

modeling in critical illness is gaining traction, and although AKI subphenotypes on the basis of serum creatinine have been examined, the value of repeated kidney biomarker assessments remains an area of active investigation (18). The repeated assessment of kidney biomarkers not only applies to the acute care setting, but to outpatient follow-up as well. Follow-up with a nephrologist after severe AKI has been associated with reduced all-cause mortality, and these biomarker assessments in the AKI recovery period may help to guide prognosis and therapy to reduce the development of CKD post-AKI (19). Our sample size from the post-AKI visit at 4–6 weeks after AKI was unfortunately not large enough to evaluate this utility further. We did note that serum NGAL and cystatin C values at the T3 time point in patients with AKI tended to be numerically higher than values obtained from the control group at T1 and T2, and are worthy of additional study in the post-AKI recovery setting.

This is certainly not the first study to investigate serum NGAL or cystatin C. However, the vast majority of the literature on these biomarkers is related to the prediction of AKI, for which they have generally not performed as well as anticipated (1). Given the increasing use of MAKE-DC or MAKE-30 as a primary outcome of clinical trials of AKI, particularly in the ICU setting, the ability to apply a biomarker to clinical prediction has great benefit in terms of prognostic enrichment and risk stratification in clinical trials. The association of biomarker levels with important patient-centered outcomes, including death, need of RRT, or reduced eGFR, out to 1 year is also important in the

Table 4. Change in kidney biomarkers and major adverse kidney events

Δ Biomarker	Major Adverse Kidney Events at Hospital Discharge ($n=49$)	No Major Adverse Kidney Events at Hospital Discharge ($n=57$)	P Value
Δ serum NGAL (ng/ml)	12 (–143 to 58) ($n=23$)	–84 (–363 to –41) ($n=13$)	0.01
Δ urinary NGAL (ng/mg Cr)	–41 (–2491 to 144) ($n=19$)	–20 (–869 to 80) ($n=13$)	0.92
Δ serum cystatin C (ng/ml)	–82 (–1121 to 734) ($n=23$)	–87 (–232 to 142) ($n=13$)	0.68
Δ urinary cystatin C (ng/mg Cr)	–112 (–545 to 552) ($n=19$)	18 (–547 to 105) ($n=13$)	0.89
Δ urinary KIM-1 (ng/mg Cr)	0 (–6 to 2) ($n=19$)	–1 (–8.5 to 0) ($n=13$)	0.19

Δ , value at 5–7 d (Time 2) minus value at 24–48 h (Time 1). NGAL, neutrophil gelatinase-associated lipocalin; Cr, creatinine; KIM-1, kidney injury molecule-1. Results are shown as median (interquartile range).

consideration of family discussions, discharge planning, and goals of care in the ICU setting.

A major strength of our study is the prospective design and follow-up of biomarkers and clinical outcomes at repeated time intervals, including out to 1 year. Although biomarkers are generally recognized to respond differently depending on the specific kidney insult (*i.e.*, sepsis, ischemia, *etc.*), our study encompassed medical, surgical, and cardiac ICUs, which increases its generalizability to several different areas of practice and research. Although each type of kidney insult may produce its own specific pattern of kidney biomarker expression, often the kidney injury in the ICU is multifactorial, thus biomarkers applicable to a wide variety of clinical settings are desirable. We used well-established criteria for the diagnosis of AKI and the outcome of interest (MAKE) (5,8).

Our findings are not without their noted limitations. First, the cohort was from a single center and relatively small sample size. Because of death or loss to follow-up, missing data were more prevalent than preferred for both biomarker measurement at time T2 or T3 and MAKE events after DC, which increases the chance of bias when analyzed using complete-case analysis as we have done. These factors limited the number of covariates we could include in the clinical prediction model, and the possibility exists that a more detailed clinical prediction model for MAKE events may not benefit from the addition of biomarker measurements. Although we noted the broad population of the cohort as a strength, it could potentially represent a limitation if it diluted the effect of any one biomarker in a specific patient population, such as sepsis. Because of the number of biomarkers and time points evaluated, multiple comparisons were performed that may increase the chance of type I error. Finally, we only included AKI stage 2 and greater without CKD at baseline, thus patients with AKI stage 1 or CKD may not be adequately addressed in this study. Insufficient data were available for analyses accounting for repeated measures of data, such as a mixed effects Cox model, which would be preferable for longitudinal biomarker studies. Evaluation of AKI during critical illness is affected by death as a competing event, which was present in this study as well, as death competed with a patient's chance of being RRT-dependent or with a reduced eGFR at discharge. Potential approaches in future studies include repeated measures time-to-event models with death as a competing event. Future research offers the opportunity to evaluate the predictive performance of these biomarkers, particularly serum NGAL and cystatin C, and more specifically their trajectories, in larger numbers of critically ill patients with AKI to further investigate the dose-response relationship and trajectory relationships between biomarker elevation and pertinent clinical outcomes.

Disclosures

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Author Contributions

A.H. Flannery and J.A. Neyra conceptualized and designed the study; F. Gianella, V.M. Ortiz-Soriano, V. Prado, and J.A. Neyra were responsible for sample acquisition and data capture and management; K. Bosler was responsible for biomarker measurements. A.H. Flannery and J. Lambert were responsible for statistical analysis; O.W. Moe and R.D. Toto were responsible for funding support and resources; J.A. Neyra was responsible for study supervision; A.H. Flannery and J.A. Neyra wrote the original manuscript draft; and all authors reviewed, edited and approved the manuscript.

Supplemental Material

This article contains the following supplemental material online at <http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0003552020/-/DCSupplemental>.

- Supplemental Table 1. Major adverse kidney events at 90 days.
- Supplemental Table 2. Major adverse kidney events at 6 months.
- Supplemental Table 3. Major adverse kidney events at 1 year.

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