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Utilization of Small Changes in Serum Creatinine with Clinical Risk Factors to Assess the Risk of AKI in Critically Ill Adults

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Abstract

Background and objectives Disease biomarkers require appropriate clinical context to be used effectively. Combining clinical risk factors, in addition to small changes in serum creatinine, has been proposed to improve the assessment of AKI. This notion was developed in order to identify the risk of AKI early in a patient's clinical course. We set out to assess the performance of this combination approach.

Design, setting, participants, & measurements A secondary analysis of data from a prospective multicenter intensive care unit cohort study (September 2009 to April 2010) was performed. Patients at high risk using this combination approach were defined as an early increase in serum creatinine of 0.1–0.4 mg/dl, depending on number of clinical factors predisposing to AKI. AKI was defined and staged using the Acute Kidney Injury Network criteria. The primary outcome was evolution to severe AKI (Acute Kidney Injury Network stages 2 and 3) within 7 days in the intensive care unit.

Results Of 506 patients, 214 (42.2%) patients had early creatinine elevation and were deemed at high risk for AKI. This group was more likely to subsequently develop the primary endpoint (16.4% versus 1.0% [not at high risk], $P<0.001$). The sensitivity of this grouping for severe AKI was 92%, the specificity was 62%, the positive predictive value was 16%, and the negative predictive value was 99%. After adjustment for Sequential Organ Failure Assessment score, serum creatinine, and hazard tier for AKI, early creatinine elevation remained an independent predictor for severe AKI (adjusted relative risk, 12.86; 95% confidence interval, 3.52 to 46.97). Addition of early creatinine elevation to the best clinical model improved prediction of the primary outcome (area under the receiver operating characteristic curve increased from 0.75 to 0.83, $P<0.001$).

Conclusion Critically ill patients at high AKI risk, based on the combination of clinical factors and early creatinine elevation, are significantly more likely to develop severe AKI. As initially hypothesized, the high-risk combination group methodology can be used to identify patients at low risk for severe AKI in whom AKI biomarker testing may be expected to have low yield. The high risk combination group methodology could potentially allow clinicians to optimize biomarker use.

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Introduction

AKI is common in critically ill patients; it occurs in 5.5%–36.1% of intensive care unit (ICU) patients (1–5). The poor outcomes associated with AKI (5–7) remain unacceptable, and one of the reasons for the lack of progress is that current functional kidney diagnostic tests (*e.g.*, serum creatinine [sCr] and urine output) fail to diagnose AKI in a timely fashion (8,9). A substantial amount of research has been conducted to discover and validate new AKI biomarkers (10–12) that could be used to direct therapeutic and supportive interventions before functional decline. These biomarkers have been referred to as the "search for the renal troponin" (8,9,13). However, when any biomarker is used in the wrong clinical context, the biomarker has diminished discriminative capacity. As an example, when troponin is used among critically ill patients outside of the clinical syndrome of cardiac angina, it does not identify acute myocardial infarction well and performs poorly as a biomarker (14,15). Similarly, if we perform daily blood or urine samples for AKI biomarkers in every patient admitted to the ICU without appropriate risk assessment, testing is neither efficient nor cost effective (13). The question at hand is in which at-risk patient should we test AKI biomarkers?

The term "renal angina" (RA) has been recently proposed as an empirical clinical concept to better determine which patients are at highest risk for AKI (13).

The rationale of the concept comes from the analogy taken from the cardiology field for cardiac angina, which is used to increase suspicion of acute myocardial infarction. Chest pain and dyspnea are key symptoms that increase the clinical suspicion for acute coronary syndrome (ACS). In patients who have classic angina, biomarkers like troponin are used to rule in or help rule out the diagnosis. However, AKI does not hurt; thus, there are no classic physical signs and symptoms early in the course of AKI to alert the clinician of ongoing injury. RA is a concept that uses known risk factors for AKI and early signs of injury to develop a methodology akin to cardiac angina to identify patients at higher risk. The initial RA proposal has a pediatric and adult definition (pRA and aRA, respectively) (13). The pRA uses criteria congruent with pediatric Risk, Injury, Failure, Loss, and End-Stage Kidney classification (pRIFLE), while the aRA uses RIFLE. The key components of RIFLE in aRA are short durations of oliguria and small changes in serum creatinine in combination with clinical risk factors to achieve aRA. The authors proposed thresholds that were based on available epidemiologic literature and clinical practice, which represented testable hypotheses (13). Since the publication of the original proposal, Basu *et al.* have operationalized and validated a definition for pRA by deriving a renal angina index (16). Although the concept of aRA is an intriguing and logical proposal, it has not yet been validated in adults.

Multiple risk factors for the development of AKI have been described in critically ill patients and include, but are not limited to, CKD, cardiovascular disease (CVD), elevated bilirubin, cancer, high-risk surgery, hypotension, increased body mass index, and hypertension (1,17–20). However, because many of the aforementioned risk factors are common in critically ill patients, developing a risk factor profile to identify patients at risk has proven challenging. The aim of this study was to determine the incidence of slight increases in serum creatinine in a large multicenter ICU cohort study and compare the characteristics and clinical outcomes among patients with and without this increase.

Materials and Methods

Study Design and Data Collection

We performed a secondary analysis of data from 601 patients enrolled in a prospective multicenter ICU cohort study of adult patients (age≥18 years) admitted to 10 ICUs from September 2009 to April 2010 (NEFROlogia e Cura INTensiva [NEFROINT]) that was designed to describe epidemiology of AKI in Italian ICUs (4). Detailed methods of data collection have been previously described (21). Collected data included demographics, anthropometrics, admission diagnosis, comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE II) (22), Simplified Acute Physiology Score II (SAPS II) (23), and Sequential Organ Failure Assessment (SOFA) (24) scores on admission, daily vital signs, and laboratory data. A single sCr was recorded per day; if a patient had multiple sCr determinations, the worst value was recorded. Renal replacement therapy (RRT) details and mortality were also reported. This study was approved by the ethics committee of St. Bortolo Hospital, Vicenza, Italy. Because of the anonymous and noninterventional nature of the study, the ethics committees of the participating study centers (listed in Acknowledgments) waived the need for informed consent.

For the current study, exclusion criteria were ESRD, kidney transplantation, severe AKI present on ICU admission (see below), and ICU stay less than 48 hours.

Definitions

The proposed definition for aRA included serum creatinine and urine output. Because we did not have information on urine output, this analysis only includes serum creatinine. We followed the approach to identify individuals at higher risk. Further details are provided in Supplemental Table 1. First, we gathered information on risk factors for developing AKI according to the existing literature (17–20,25) and classified them into three categories as previously described (26): chronic major, chronic minor, and acute risk factors for AKI (Table 1). Definitions of risk factors are listed in Supplemental Table 1.

Patients were then grouped into three hazard tiers (13) (summarized in Table 1). Very high risk (VHR) for AKI describes patients with septic shock or patients receiving vasopressors and mechanical ventilation. High risk (HR) describes patients with one acute plus one major risk factor, one acute plus two minor risk factors, or two acute risk factors. Patients with these characteristics had a reported AKI incidence of 10.2% (26). Moderate risk (MR) describes patients with one chronic major or one acute risk factor (but not both), multiple major risk factors without acute risk factors, or multiple major and minor risk factors without acute risk factors (26). Approximately 4% of patients with these features developed AKI (26). Patients who did not fulfill any of these criteria were classified as low risk.

The change in sCr was calculated daily for each patient. Within each hazard tier or tranche, the higher risk group was defined by an acute increase in sCr from the previous day (Table 1): VHR group if sCr increased by ≥0.1 mg/dl; HR group if sCr increased by ≥0.3 mg/dl; MR group if sCr increased by ≥0.4 mg/dl (13).

AKI was defined using the sCr criteria of the Acute Kidney Injury Network (AKIN) definition (27). Patients who received RRT were considered AKIN stage 3. Severe AKI was defined as AKIN stages 2 and 3.

Study End Points

The primary outcome of interest was development of severe AKI within the first 7 days in the ICU. Secondary outcomes included severe AKI and need for RRT at any time in the ICU, ICU mortality, and ICU length of stay.

Statistical Analyses

Categorical variables are expressed as number of cases and proportion, and they are compared with the Mantel–Haenszel chi-squared or Fisher exact test. Continuous variables were evaluated for normality of distribution by visual inspection of histograms and the Kolmogorov–Smirnov test. None were normally distributed, and, therefore, they are expressed as median (interquartile range [IQR]). Comparison between any two groups was performed using the Mann–Whitney *U* test, and comparison between three or more groups was performed using the Kruskal–Wallis test.

The sensitivity, specificity, and other diagnostic accuracy measures of the early creatinine elevation as a predictor for severe AKI were calculated for the entire cohort and within each hazard tier.

Patients with and without early creatinine elevation (in the entire cohort and by subgroups of number of AKI risk factors or hazard tier) were compared for the primary end point using the Kaplan–Meier product limit survival plot. A multivariable logistic regression analysis was performed to evaluate the association with creatinine elevation after adjustment for other clinical factors, and all variables were forced into the model. Exploratory univariate analyses for several variables were first performed to identify possible confounders associated with severe AKI for potential inclusion in the multivariable analysis. For these analyses, severity of illness scores were recalculated minus the points derived from the renal component to avoid redundancy with sCr on ICU admission when these variables were simultaneously included in multivariable regression. They are expressed as nonrenal APACHE II, nonrenal SAPS II, and nonrenal SOFA. Because all factors significant on univariate analysis were part of the definition for the hazard tiers, the final clinical models included nonrenal SOFA score, admission sCr (transformed to the natural log), and either the number of AKI risk factors or hazard tier. Among the severity of illness scores, admission nonrenal SOFA had the strongest univariate association with the primary end point, and it was used in the model. Creatinine elevation was then added to the clinical models. Goodness of fit and calibration of the models were evaluated using the Hosmer and Lemeshow test, Nagelkerke R^2, and C statistic. Comparison of the areas under the receiver operating characteristic curve of the models was tested using the nonparametric method in the work by DeLong *et al.* (28). Sensitivity analyses were performed substituting either nonrenal APACHE II or nonrenal SAPS II for nonrenal SOFA score in the model. Unadjusted and adjusted odds ratios (ORs) are reported.

All statistical analyses were performed using the SPSS 20 (SPSS, Inc., Chicago, IL) and R version 3.0 (www.r-project.org) software packages, with two-sided P value<0.05 considered statistically significant.

Table 1. Operational definitions of risk factors, hazard tiers (tranches), and early Cr elevation

Classification of risk factors for AKI (definitions in Supplemental Table 1)
- Chronic major
  - *Advanced age*
  - *Diabetes mellitus*
  - *Cardiovascular disease*
  - *CKD*
- Chronic minor
  - *Hypertension*
  - *Morbid obesity*
  - *Hyperbilirubinemia*
  - *Cerebrovascular accident*
  - *AIDS*
  - *Cancer*
- Acute
  - *Hypotension*
  - *High-risk surgery*
  - *Nephrotoxin exposure*
  - *Sepsis*

Classification of patients into hazard tranches
- Hazard tier (tranche) 1: very high risk
  - *Patients with septic shock, or*
  - *Patients receiving vasopressors and mechanical ventilation*
- Hazard tier (tranche) 2: high risk
  - *1 acute risk factor +1 major chronic risk factor, or*
  - *1 acute risk factor +2 minor chronic risk factor, or*
  - *2 acute risk factors*
- Hazard tier (tranche) 3: moderate risk
  - *1 major chronic risk factor or 1 acute risk factor (but not both), or*
  - *Multiple chronic major and minor risk factors without acute risk factors*

Within each hazard tier, early Cr elevation is present if there is an increase in serum creatinine[a]
- Hazard tier 1 (very high risk): ↑ 0.1 mg/dl
- Hazard tier 2 (high risk): ↑ 0.3 mg/dl
- Hazard tier3 (moderate risk): ↑ 0.4 mg/dl

Classification of risk factors into chronic major, chronic minor, and acute are adapted from reference 26. Cr, creatinine.
[a]Changes in serum creatinine were calculated daily throughout the intensive care unit stay.

Results

Study Population

Of 601 patients enrolled in the NEFROINT study (4), we excluded patients with ESRD (n=20), kidney transplantation (n=5), AKIN stages 2 and 3 on admission (n=49), and ICU stay of less than 48 hours (n=21). Therefore, 506 patients were included in the analysis (Figure 1).

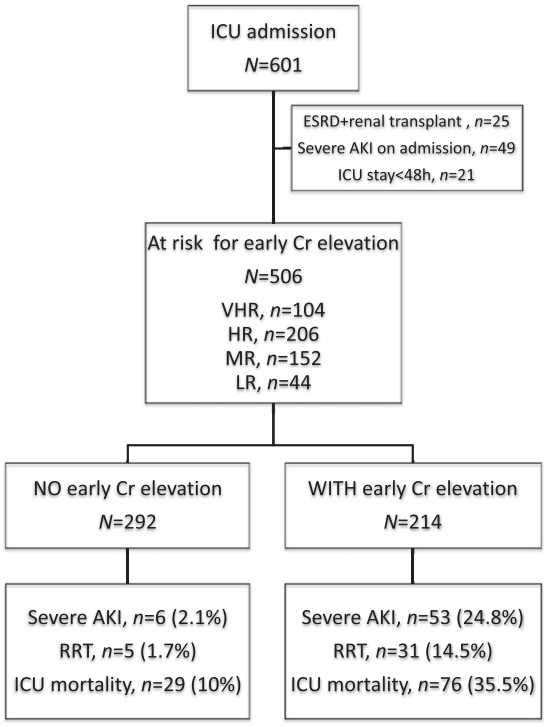

Figure 1. | Flow chart depicting patient screening and exclusions. HR, high risk; ICU, intensive care unit; LR, low risk; MR, moderate risk; RRT, renal replacement therapy; VHR, very high risk.

Table 2. Characteristics of the study population by hazard tier (tranche)

Variable	All	Hazard Tier 1: Very High Risk	Hazard Tier 2: High Risk	Hazard Tier 3: Moderate Risk	Reference Tier: Low Risk	*P* Value
N	506	104	206	152	44	—
Age (yr)	66 (52–76)	68 (53–76)	70 (58–77)	64 (49–76)	47 (26–59)	<0.001
Men	301 (59.5)	58 (55.8)	119 (57.8)	96 (63.2)	28 (63.6)	0.57
BMI (kg/m^2)	21.5 (19.3–24.1)	21.9 (18.8–24.1)	21.2 (19.1–24.1)	21.3 (19.7–24.3)	20.8 (19.4–22.4)	0.46
SAPS II	43 (35–53)	48 (40–59)	44 (37–55)	41 (32–49)	34 (28–41)	<0.001
SOFA	5 (3–7)	8 (7–10)	5 (3–7)	4 (2–5)	3 (2–5)	<0.001
APACHE II	18 (13–22)	20 (16–26)	18 (14–23)	15 (11–20)	12 (7–16)	<0.001
Serum creatinine, admission (mg/dl)	0.9 (0.7–1.2)	1.1 (0.8–1.4)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.8 (0.6–1.0)	<0.001
Urine output, ICU day 1 (ml/kg per hour)	1.2 (0.7–1.9)	1.3 (0.7–2.1)	1.2 (0.8–1.8)	1.2 (0.8–1.8)	1.5 (1.2–2.2)	0.14
Chronic major risk factors						
Age>70 yr	215 (42.5)	48 (46.2)	108 (52.4)	59 (38.8)	0 (0)	<0.001
Diabetes	92 (18.2)	23 (22.1)	48 (23.3)	21 (13.8)	0 (0)	0.001
Cardiovascular disease	48 (9.5)	8 (7.7)	23 (11.2)	16 (10.5)	1 (2.3)	0.27
CKD	31 (6.1)	11 (10.6)	11 (5.3)	9 (5.9)	0 (0)	0.08
Chronic minor risk factors						
Hypertension	228 (45.1)	46 (44.2)	117 (56.8)	59 (38.8)	6 (13.6)	<0.001
BMI>30 kg/m^2	34 (6.7)	4 (3.8)	17 (8.3)	13 (8.6)	0 (0)	0.11
Bilirubin>2 mg/dl	41 (8.1)	9 (8.7)	22 (10.7)	8 (5.3)	2 (4.5)	0.23
Cerebrovascular accident	216 (42.7)	49 (47.1)	99 (48.1)	58 (38.2)	10 (22.7)	0.01
AIDS	3 (0.6)	2 (1.9)	0 (0)	1 (1)	0 (0)	0.20
Cancer	52 (10.3)	9 (8.7)	23 (11.2)	19 (12.5)	1 (2.3)	0.23
Acute risk factors						
Hypotension	162 (32)	104 (100)	51 (24.8)	7 (4.6)	0 (0)	<0.001
Vasoactive therapy	112 (22.1)	104 (100)	7 (3.4)	1 (0.7)	0 (0)	<0.001
Sepsis	129 (25.5)	37 (35.6)	79 (38.3)	13 (8.6)	0 (0)	<0.001
Mechanical ventilation	380 (75.1)	98 (94.2)	156 (75.7)	99 (65.1)	27 (61.4)	<0.001
High-risk surgery	171 (33.8)	46 (44.2)	92 (44.7)	33 (21.7)	0 (0)	<0.001
Nephrotoxin exposure	134 (26.5)	38 (36.5)	88 (42.7)	8 (5.3)	0 (0)	<0.001
ICU outcomes						
Early Cr elevation (%)	214 (42.3)	94 (90.4)	77 (37.4)	43 (28.3)	0 (0)	<0.001
Severe AKI (%)	59 (11.7)	21 (20.2)	26 (12.6)	10 (6.6)	2 (4.5)	0.004
RRT (%)	36 (7.1)	11 (10.6)	17 (8.3)	6 (3.9)	2 (4.5)	0.17
Mortality (%)	105 (20.8)	42 (40.4)	39 (18.9)	21 (13.8)	3 (6.8)	<0.001
Severe AKI or death	129 (25.5)	50 (48.1)	50 (24.3)	25 (16.4)	4 (9.1)	<0.001
Length of ICU stay (d)	6 (3–14)	7 (4–14)	7 (3–16)	5 (2–14)	4 (2–7)	0.003

Categorical variables are expressed as *n* (%). Continuous variables are expressed as median (interquartile range). BMI, body mass index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation I; ICU, intensive care unit; RRT, renal replacement therapy.

Characteristics of the entire cohort are shown in Table 2. The mean age was 62.1±17.3 years, and 59.5% of patients were men. The majority of patients (n=355; 70%) had no known underlying kidney disease; 11 (2.2%) patients were known to have CKD stages 1 and 2 with proteinuria and/or microhematuria, 24 (4.7%) patients were known to have CKD stages 3–5, and prior renal history was not available in 116 (22.9%) patients. Overall, severe AKI occurred in 59 (11.7%) patients (AKIN stage 2, 2.6%; AKIN stage 3, 9.1%), and all-cause ICU mortality occurred in 105 (20.8%) patients. Of 59 patients with severe AKI, 35 (59% of severe AKI) patients died in the ICU. The median ICU length of stay of the entire cohort was 6 (IQR=3–14) days.

Hazard Tiers or Tranches for AKI

Of 506 patients, 104 (20.6%) patients were classified as VHR, 206 (40.7%) patients were classified as HR, 152 (30%) patients were classified as MR, and 44 (8.7%) patients were

Table 3. Characteristics of the study population by presence or absence of early Cr elevation

Variable	No Early Cr Elevation	With Early Cr Elevation	P Value
N	292	214	
Age (yr)	61 (47–74)	69 (59–78)	<0.001
Men	163 (55.8)	138 (64.5)	0.05
BMI (kg/m^2)	21.2 (19.1–23.6)	21.2 (19.4–24.4)	0.23
SAPS II	41 (33–50)	46 (39–55)	<0.001
SOFA	4 (2–6)	7 (4–9)	<0.001
APACHE II	16 (12–20)	20 (15–25)	<0.001
Serum creatinine, admission (mg/dl)	0.8 (0.6–1.0)	1.2 (0.8–1.5)	<0.001
Serum urea, admission (mg/dl)	34 (23–48)	54 (33–80)	<0.001
Urine output, ICU day 1 (ml/kg per hour)	1.2 (0.8–1.9)	1.2 (0.7–1.9)	0.22
Bilirubin, admission (mg/dl)	0.7 (0.5–1.0)	0.7 (0.5–1.1)	0.22
Number of risk factors for AKI			
Number of chronic major risk factors	1 (0–2)	1 (0–2)	<0.001
Number of chronic major risk factors≥2	79 (27.1)	91 (42.5)	<0.001
Number of chronic minor risk factors	1 (0–2)	1 (1–2)	0.12
Number of chronic minor risk factors≥2	90 (30.8)	77 (36)	0.25
Number of acute risk factors	1 (0–1)	2 (1–2)	<0.001
Number of acute risk factors≥2	68 (23.3)	115 (53.7)	<0.001
Hazard tier			
Very high risk	10 (3.4)	94 (43.9)	<0.001
High risk	129 (44.2)	77 (36.0)	<0.001
Moderate risk	109 (37.3)	43 (20.1)	<0.001
Chronic major risk factors			
Age>70 yr	111 (38)	104 (48.6)	0.01
Diabetes	48 (16.4)	44 (20.6)	0.24
Cardiovascular disease	97 (33.2)	110 (51.4)	<0.001
CKD	4 (1.4)	27 (12.6)	<0.001
Chronic minor risk factors			
Hypertension	121 (41.4)	107 (50)	0.06
BMI>30 kg/m^2	21 (7.2)	13 (6.1)	0.72
Bilirubin>2 mg/dl	17 (5.8)	24 (11.2)	0.03
Cerebrovascular accident	124 (42.5)	92 (43)	0.93
AIDS	1 (0.3)	2 (0.9)	0.58
Cancer	31 (10.6)	21 (9.8)	0.88
Acute risk factors			
Hypotension	48 (16.4)	114 (53.3)	<0.001
Vasoactive therapy	14 (4.8)	98 (45.8)	<0.001
Sepsis	55 (18.8)	74 (34.6)	<0.001
Mechanical ventilation	206 (70.5)	174 (81.3)	0.01
High-risk surgery	95 (32.5)	76 (35.5)	0.51
Nephrotoxin exposure	66 (22.6)	68 (31.8)	0.02
ICU outcomes			
Severe AKI	6 (2.1)	53 (24.8)	<0.001
RRT	5 (1.7)	31 (14.5)	<0.001
Mortality	29 (9.9)	76 (35.5)	<0.001
Severe AKI or death	31 (10.6)	98 (45.8)	<0.001
Length of ICU stay (d)	4 (2–11)	8 (4–16)	<0.001

Categorical variables are expressed as n (%). Continuous variables are expressed as median (interquartile range). BMI, body mass index.

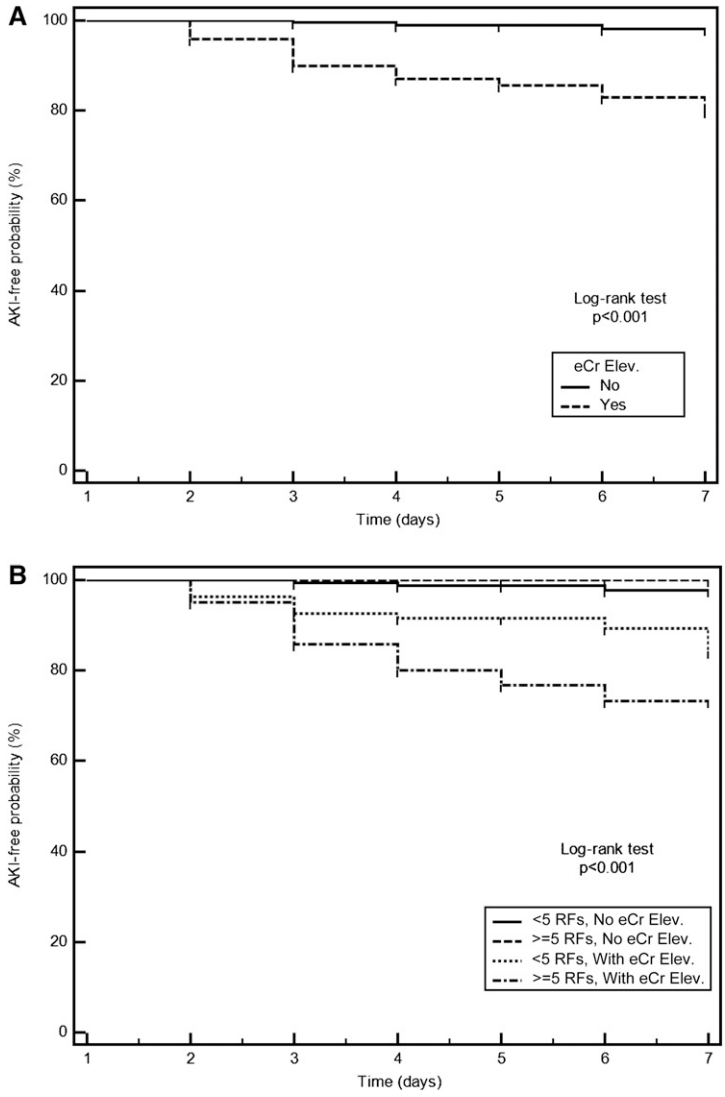

Figure 2. | **Survival curves showing patients with early Cr elevation were more likely to evolve to severe AKI.** (A) In the entire cohort; (B) when subgrouped by number of AKI risk factors. The value of five was the best cutoff for number of AKI risk factors on receiver operating characteristic curve analysis. eCr Elev., early creatinine elevation; RFs, risk factors.

classified as low risk (Figure 1). Characteristics are shown in Table 2. As is expected from the definitions of the hazard tiers, all acute risk factors and most chronic major risk factors were significantly more common in the VHR and HR groups. Among the chronic minor risk factors, hypertension and cerebrovascular accident were less common in the low-risk group. Early creatinine elevation developed in 94 (90.4%), 77 (37.4%), and 43 (28.3%) patients in the VHR, HR, and MR groups, respectively (Figure 1). Occurrence of severe AKI and ICU mortality was also highest in the VHR group, intermediate in the HR and MR groups, and lowest in the low-risk group. Need for RRT was not significantly different among the hazard tiers.

Those patients with creatinine elevation were significantly older, had more CVD, CKD, and sepsis, and had higher severity of illness scores on admission. They had more acute risk factors, except for high-risk surgery, and more chronic major risk factors, particularly CVD and CKD. Overall, creatinine elevation occurred on ICU day 2 (IQR=2–3.5 days).

In terms of the primary end point, the creatinine elevation group was more likely to evolve to severe AKI in the entire cohort or when subgrouped by number of AKI risk factors or hazard tier (Figure 2). They also had significantly higher rates of severe AKI in the ICU, need for RRT, and death during their ICU stay (Figure 1, Table 3). In this group, the creatinine elevation preceded severe AKI by a median of 2 (IQR=1–6) days. The measures of performance of creatinine elevation as a test for severe AKI within 7 days are shown in Table 4. Overall, the sensitivity was 92% and the specificity was 62%. The sensitivity was comparable across all hazard tiers (≥92%), but the specificity was low in the VHR group (11%). Negative predictive value (NPV) was excellent (99%) overall and ranged from 83% to 100% across all hazard tiers. Positive predictive value was low (<20% for all). Similar trends were seen for severe AKI at any time in the ICU (Table 4).

On univariate analysis, creatinine elevation was strongly associated with severe AKI (OR, 18.84; 95% confidence interval [95% CI], 5.71 to 62.15) along with nonrenal SOFA score, serum creatinine on admission, number of AKI risk factors, and hazard tier (Table 5). There was a weaker association for nonrenal APACHE II (OR, 1.02; 95% CI, 0.97 to 1.07) and nonrenal SAPS II (OR, 1.01; 95% CI, 0.99 to 1.04) with severe AKI; therefore, SOFA was used in the subsequent models. On adjusted analysis, the association between creatinine elevation and severe AKI was attenuated (ORs, 10.96 to 12.86) but remained highly significant. The addition of creatinine elevation to clinical models led to a significant increase in the area under the receiver operating characteristic curve for AKI prediction (Figure 3). On sensitivity analyses, qualitatively similar results were obtained when either APACHE II or SAPS II was used in the model in place of SOFA.

Discussion

Identifying individuals at higher risk for developing AKI in the hospital is of increasing interest, which led to the proposed term of "renal angina." This concept represents a combination of patient risk factors and subtle changes in sCr and urine output (as the equivalent of chest pain) as a methodology to predict evolving AKI (13). In a patient with multiple AKI risk factors, one would need a smaller change in sCr and urine output to raise clinical suspicion for evolving AKI (analogous to the diabetic man with heartburn). However, in another patient with fewer risk factors, it would take a bigger change in sCr to reach that same level of suspicion. Hence, the thresholds for increase in sCr and duration of oliguria were smallest in VHR patients, intermediate for HR, and largest in MR patients (Table 1) in the original proposal (13). The second hypothesis of RA is that, like cardiac angina, it should be very sensitive and have a high NPV. The third hypothesis of RA is that when AKI biomarkers are used in patients with RA, the diagnostic performance of those biomarkers will improve, similar to troponin use in cardiac angina. Although an attractive concept, these hypotheses have not yet been tested in an adult ICU population.

In our multicenter study, we assessed the performance of the one component of the aRA concept using only the originally proposed creatinine thresholds (13) in a cohort of critically ill adults and showed that early creatinine elevation is a good predictor of severe AKI. Indeed, 24.8% of patients with creatinine elevation developed severe AKI during the ICU stay compared with only 2.1% of the no creatinine elevation group. Creatinine elevation was strongly associated with development of severe AKI within 7 days after adjustment for hazard tier/AKI risk factors, nonrenal SOFA score, and sCr. The addition of creatinine elevation to clinical models significantly improved prediction of the primary end point.

Our data reveal a high overall sensitivity (89%–92%) and reasonable specificity (62%–64%) for AKI within 7 days and throughout the ICU stay. For the primary end point, sensitivity was >90% across all hazard tiers. As described, RA is desired to be highly sensitive and have a good NPV, which is confirmed in this study using the definition of creatinine elevation. As evidenced by the high overall

Table 4. Measures of diagnostic test accuracy of early Cr elevation for severe AKI

Endpoint	Number of Events	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	Diagnostic Odds Ratio (95% CI)
Severe AKI within 7 d								
All	38[a]	0.92 (0.78 to 0.98)	0.62 (0.57 to 0.66)	0.16 (0.12 to 0.22)	0.99 (0.97 to 1.00)	2.41 (2.08 to 2.79)	0.13 (0.04 to 0.38)	18.8 (5.7 to 62.1)
Very high risk	16	1.00 (0.76 to 1.00)	0.11 (0.06 to 0.20)	0.17 (0.10 to 0.26)	0.83 (0.74 to 0.90)	1.13 (1.05 to 1.22)	0 (NA)	NA
High risk	12	0.92 (0.60 to 0.96)	0.66 (0.59 to 0.73)	0.14 (0.08 to 0.25)	0.86 (0.75 to 0.92)	2.69 (0.08 to 3.49)	0.13 (0.02 to 0.83)	21.3 (2.7 to 168.8)
Moderate risk	8	1.00 (0.60 to 1.00)	0.76 (0.68 to 0.82)	0.19 (0.09 to 0.34)	1.00 (0.96 to 1.00)	4.11 (3.08 to 5.49)	0 (NA)	NA
Severe AKI in ICU								
All	59[a]	0.89 (0.79 to 0.95)	0.64 (0.59 to 0.68)	0.25 (0.19 to 0.31)	0.98 (0.95 to 0.99)	2.50 (2.14 to 2.9)	0.16 (0.07 to 0.34)	15.7 (6.6 to 37.3)
Very high risk	21	1.00 (0.81 to 1.00)	0.12 (0.06 to 0.21)	0.22 (0.15 to 0.32)	1.00 (0.66 to 1.00)	1.14 (1.05 to 1.23)	0 (NA)	NA
High risk	26	0.88 (0.69 to 0.97)	0.70 (0.63 to 0.76)	0.30 (0.20 to 0.42)	0.98 (0.93 to 0.99)	2.95 (2.27 to 3.84)	0.16 (0.06 to 0.48)	17.9 (5.2 to 62.1)
Moderate risk	10	0.90 (0.54 to 0.99)	0.76 (0.68 to 0.83)	0.21 (0.11 to 0.36)	0.99 (0.94 to 0.99)	3.76 (2.63 to 5.38)	0.13 (0.02 to 0.85)	28.6 (3.5 to 233.8)

95% CI, 95% confidence interval; NA, not applicable.
[a]Two severe AKI events occurred in the low-risk tranche (both within first 7 ICU days).

Table 5. Multivariable analysis for severe AKI within 7 days

Variable	Unadjusted		Adjusted							
			Clinical Model 1		Model 1		Clinical Model 2		Model 2	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Early Cr elevation	18.84 (5.71 to 62.15)	<0.001	—		10.96 (3.15 to 38.06)	<0.001	—		12.86 (3.52 to 46.97)	<0.001
Nonrenal SOFA	1.18 (1.07 to 0.32)	0.002	1.11 (0.99 to 1.25)	0.06	1.05 (0.94 to 1.18)	0.37	1.09 (0.95 to 1.24)	0.21	1.09 (0.95 to 1.25)	0.21
sCr, admission	5.65 (3.01 to 10.61)	<0.001	4.70 (2.33 to 9.50)	<0.001	3.12 (1.50 to 6.50)	0.002	4.84 (2.53 to 9.25)	<0.001	2.98 (1.50 to 5.91)	0.002
No. of AKI risk factors	1.28 (1.08 to 1.51)	0.004	1.04 (0.85 to 1.26)	0.73	0.98 (0.80 to 1.20)	0.87	—		—	
Hazard tier	1.74 (1.16 to 2.63)	0.008	—		—		1.20 (0.73 to 1.99)	0.46	0.77 (0.44 to 1.32)	0.34

Exploratory univariate analysis for several variables was first performed to identify possible confounders associated with severe AKI for potential inclusion in the multivariable analysis. Because all factors significant in univariate analysis were part of the definition for the hazard tranches, the final models included early Cr elevation, nonrenal SOFA score (per 1-point increase), admission sCr (transformed to the natural log), and either the number of AKI risk factors or hazard tier. A multivariable logistic regression analysis was then performed, and variables were forced into the model (enter mode). Sensitivity analyses using nonrenal APACHE II or SAPS II in place of nonrenal SOFA yielded similar results. OR, odds ratio; sCr, serum creatinine.

NPV (99%), patients throughout all the tiers that did not have creatinine elevation are very unlikely to progress to severe AKI. Our findings are consistent with a recent pediatric study, in which a low RA index (RA index<8) had NPV of 92%–99% (28). It should be noted that NPVs were more modest (83%–86%) in the VHR and HR subgroups.

To our knowledge, this is the first study evaluating the creatinine elevation and risk groups in an adult ICU population. Other than AKI, we also observed that patients who had early creatinine elevation were more likely to have other adverse outcomes, such as need for RRT, death, and longer ICU stay. Our study has several strengths. This large multicenter cohort of critically ill patients represents a wide range of patient ages, comorbidities, and illness severities. The multicenter nature of our study minimizes single center bias for RRT initiation and ICU admission and discharge policies. We also had sufficient patient-level detail to allow calculation of daily changes in sCr throughout the ICU stay. Indeed, we noted a high rate of early creatinine elevation in the VHR group, which is likely related to the very low threshold for sCr increase (0.1 mg/dl) needed to qualify within this subgroup. We were also able to adjust for severity of illness and organ dysfunction scores to estimate the independent association between creatinine elevation and severe AKI.

We acknowledge certain limitations in our study. This secondary analysis of data from an observational study has the inherent limitations common to all observational studies. As such, we do not have access to information beyond the original data collection. For instance, data on hourly urine output were not available. Because the urine output criteria for aRA involve the duration of oliguria (1, 3, or 5 hours) (9), we were not able to incorporate these data into the present study. AKI biomarkers were not measured in the original study, precluding evaluation of a directed AKI biomarker testing strategy in the current study. Additionally, we acknowledge a modest number of severe AKI events. Serum creatinine was used to identify risk groups and was also used to define AKI.

In summary, we evaluated the RA concept in a heterogeneous multicenter cohort of critically ill adult patients and we found that early creatinine elevation and risk grouping have good predictive capacity and excellent potential as a screening test to identify patients at low risk for severe AKI in whom AKI biomarker testing could be expected to have low yield. If confirmed and validated in other cohorts, our results will be more generalizable and represent an important step to a better understanding of the optimal mode to use AKI biomarkers. We propose the development and validation of a quantitative RA index for adults, as well as evaluation of the efficacy and cost-effectiveness of a selective or directed biomarker testing strategy using risk grouping.

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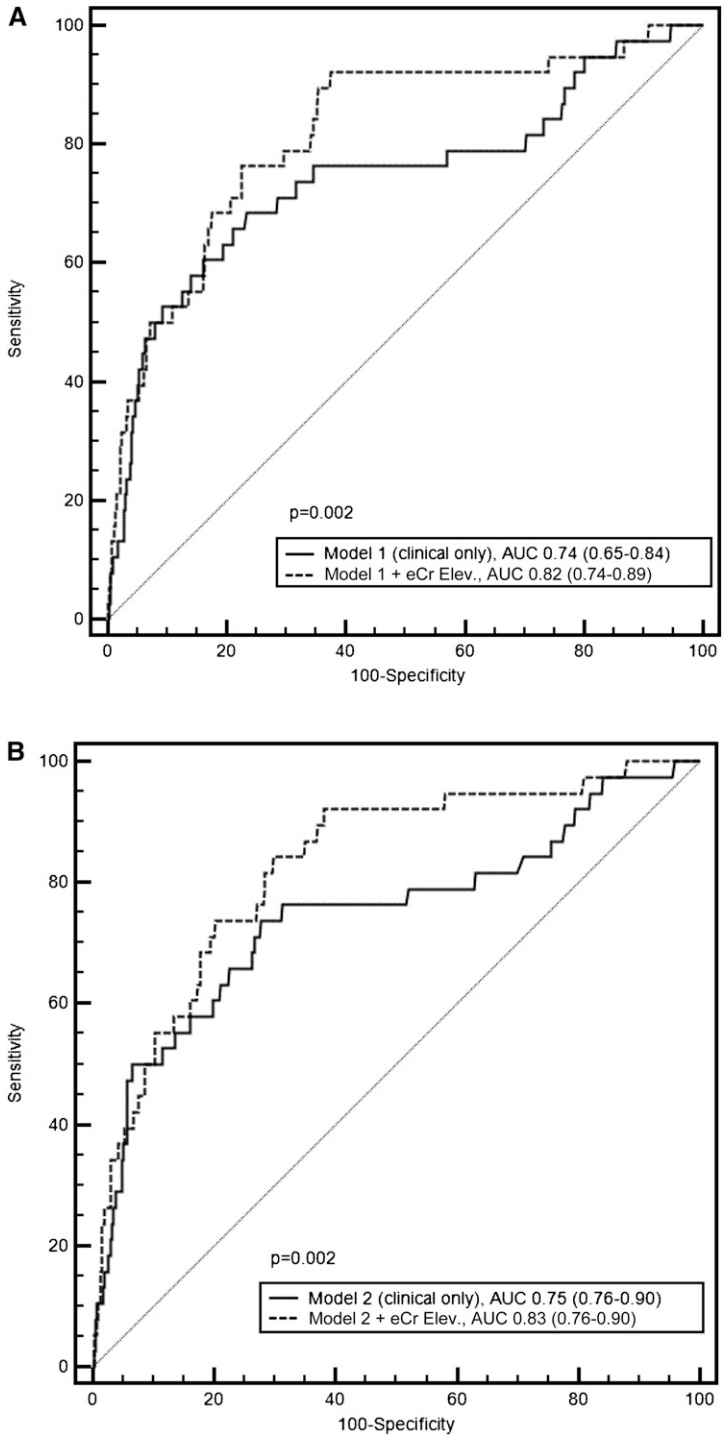

Figure 3. | **Evaluation of the performance of prediction models with the addition of early Cr elevation.** (A) Clinical model 1 includes number of AKI risk factors (total), nonrenal Sequential Organ Failure Score (SOFA), and admission serum creatinine. (B) Clinical model 2 includes hazard tier (tranche), nonrenal SOFA, and admission serum creatinine. AUC, area under the receiver operating characteristic curve; eCr Elev., early creatinine elevation.

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Disclosures

None.

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