OBSERVATIONAL STUDY

OPEN

Biomarker Signatures of Severe Acute Kidney Injury in a Critically Ill Cohort of COVID-19 and Non-COVID-19 Acute Respiratory Illness

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IMPORTANCE: Kidney and lung injury are closely inter-related during acute respiratory illness, but the molecular risk factors that these organ injuries share are not well defined.

OBJECTIVES: We identified plasma biomarkers associated with severe acute kidney injury (AKI) during acute respiratory illness, and compared them to biomarkers associated with severe acute respiratory failure (ARF).

DESIGN, SETTINGS, AND PARTICIPANTS: Prospective observational cohort study enrolling March 2020 through May 2021, at three hospitals in a large academic health system. We analyzed 301 patients admitted to an ICU with acute respiratory illness.

MAIN OUTCOMES AND MEASURES: Outcomes were ascertained between ICU admission and day 14, and included: 1) severe AKI, defined as doubling of serum creatinine or new dialysis and 2) severe ARF, which included new or persistent need for high-flow oxygen or mechanical ventilation. We measured biomarkers of immune response and endothelial function, pathways related to adverse kidney and lung outcomes, in plasma collected within 24 hours of ICU admission. Severe AKI occurred in 48 (16%), severe ARF occurred in 147 (49%), and 40 (13%) patients experienced both. Two-fold higher concentrations of soluble tumor necrosis factor receptor-1 (sTNFR-1) (adjusted relative risk [aRR], 1.56; 95% CI, 1.24–1.96) and soluble triggering receptor on myeloid cells-1 (sTREM-1) (aRR, 1.85; 95% CI, 1.42–2.41), biomarkers of innate immune activation, were associated with higher risk for severe AKI after adjustment for age, sex, COVID-19, and Acute Physiology and Chronic Health Evaluation-III. These biomarkers were not significantly associated with severe ARF. Soluble programmed cell death receptor-1 (sPDL-1), a checkpoint pathway molecule, as well as soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular adhesion molecule-1 (sVCAM-1), molecules involved with endothelial-vascular leukocyte adhesion, were associated with both severe AKI and ARF.

CONCLUSIONS AND RELEVANCE: sTNFR-1 and sTREM-1 were linked strongly to severe AKI during respiratory illness, while sPDL-1, sICAM-1 and sVCAM-1 were associated with both severe AKI and ARF. These biomarker signatures may shed light on pathophysiology of lung-kidney interactions, and inform precision medicine strategies for identifying patients at high risk for these organ injuries.

KEY WORDS: acute kidney injury; acute respiratory failure; biomarkers; phenotypes; precision medicine

Lung and kidney organ dysfunction during critical illness are closely interrelated, exceedingly common, and associated with high mortality (1–3). Acute kidney injury (AKI) occurs in nearly half of patients with severe respiratory failure, making it the most prevalent extra-pulmonary organ

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KEY POINTS

Question: Among patients with acute respiratory illness, is there a biomarker signature related to severe acute kidney injury (AKI), and does it differ from the signature related to acute respiratory failure (ARF)?

Findings: In a prospective cohort study of patients with biomarkers of immune response and endothelial function measured at ICU admission, soluble tumor necrosis factor receptor-1 and soluble triggering receptor on myeloid cells-1 (biomarkers of early innate immune activation) were associated with severe AKI, but not severe ARF. Other biomarkers such as soluble programmed cell death receptor-1, soluble vascular adhesion molecule-1, and soluble intercellular adhesion molecule-1 were associated with both severe AKI and ARF.

Meaning: Distinguishing biomarkers associated with kidney dysfunction during respiratory illness, from those associated with both kidney and lung dysfunction, may guide approaches to tailor therapy during critical illness.

dysfunction in this group (3, 4). The majority of critically ill patients with respiratory failure die with such multiple organ failure, and relatively few from pulmonary dysfunction itself (5, 6). While many clinical risk factors for the development of AKI during respiratory failure have been identified, the biologic features remain incompletely understood (1, 7–9).

Biomarkers of inflammation and endothelial dysfunction have been linked to mortality in acute respiratory illnesses and are hypothesized to play a role in the development of AKI (10–13). However, these have rarely been studied in relation to incident or progressive AKI during acute respiratory illness, and it is unclear which are specific to the kidney, and which indicate underlying respiratory illness (1, 12, 14). Identifying a molecular signature specific for kidney outcomes, independent of worsening respiratory illness, could guide development and delivery of treatments designed to prevent AKI or improve kidney recovery. Similarly, a signature associated with both kidney and lung injury could be used to understand shared pathophysiology, and guide treatments hypothesized to mitigate injury in both organs.

Our primary objective was to identify novel plasma biomarkers associated with incident severe AKI in a cohort of critically ill patients with acute respiratory illness, focusing on biomarkers of immune response and endothelial cell dysfunction. Our cohort included a diverse set of respiratory conditions, with the predominant condition being COVID-19. Secondary objectives included: 1) determining which of these biomarkers were also associated with persistent or worsening respiratory illness and 2) comparing the molecular profiles of patients with prevalent kidney and lung injury at the time of ICU admission.

METHODS

Study Population and Design

We conducted a prospective cohort study of critically ill patients admitted to three hospitals affiliated with the University of Washington (Seattle, WA). Patients were enrolled between March 2020 and May 2021, during the COVID-19 pandemic (15–17). Patients were eligible if admitted to a medical ICU with signs or symptoms of acute respiratory illness, which included one of the following: 1) initiation of supplemental oxygen; 2) oxygen saturation less than 94% on ambient air; or 3) new opacities on chest radiograph. We excluded patients who were younger than 18 years, incarcerated, pregnant, or on chronic maintenance hemodialysis. Investigation was conducted in accordance with the 2008 Declaration of Helsinki. The University of Washington Human Subjects Division granted a waiver of informed consent given minimal risk, urgency of COVID-19 research in this period, and supply limitations in personal protective equipment preventing nonessential staff from approaching patients (STUDY No. 9763).

Biomarker Measurements

Biomarkers were measured in EDTA plasma collected within 24 hours of ICU admission, originally for a study comparing molecular risk factors for mortality in critically ill patients with and without COVID-19 respiratory illness (15, 16). Among measurements available throughout the cohort, we selected a priori 12 biomarkers related to immune response and/or endothelial function that have previously been linked to poor outcomes in respiratory illness or AKI

pathophysiology. Biomarkers included interleukin (IL)-6 and procalcitonin, measured using an Food and Drug Administration authorized clinical assay (Roche Elecsys Immunoassay, Cobas e411 analyzer, Indianapolis, IN). Other biomarkers were measured with electrochemiluminescence-based immunoassays (Meso Scale Discovery, Rockville, MD), and included IL-10, soluble triggering receptor on myeloid cells-1 (sTREM-1), soluble tumor necrosis factor receptor-1 (sTNFR-1), soluble programmed cell death receptor-1 (sPDL-1), IL-8, monocyte chemoattractant protein-1 (MCP-1), C-reactive protein, serum amyloid A, soluble intercellular adhesion molecule-1 (sICAM-1), and soluble vascular adhesion molecule-1 (sVCAM-1).

Clinical Data Collection and Outcome Definitions

Clinical data were extracted from electronic health records into standardized case report forms. Our primary outcome was severe AKI within 14 days, defined as initiation of renal replacement therapy (RRT) or doubling of serum creatinine from ICU admission (18). All patients with Kidney Disease: Improving Global Outcomes (KDIGO) stages 0–3 AKI at ICU admission were potentially at risk for developing this outcome and included in this analysis, while patients who received RRT on the day of ICU admission or earlier were excluded (18). If patients died before day 14, they were classified as having severe AKI only if they met serum creatinine or RRT criteria prior to death. In a sensitivity analysis, we examined time to severe AKI as an outcome, and accounted for death as a competing risk.

To identify risk factors specific to severe AKI, we sought to contrast which biomarkers were and were not related to incident respiratory outcomes. We defined a secondary outcome of severe acute respiratory failure (ARF) within 14 days, which included new needs for advanced respiratory support (high-flow oxygen or mechanical ventilation) or a persistent need for advanced support through day 14 among patients already on high-flow oxygen or mechanical ventilation at admission. Patients who died before day 14 were classified as having severe ARF if they required advanced respiratory support at the time of death. Patients on advanced respiratory support at admission who were weaned off, and patients who never needed such support were classified as not experiencing severe ARF.

We also compared the molecular features of patients with and without prevalent AKI, at the time of ICU admission. We defined prevalent AKI by KDIGO stages 1–3, and used the lowest serum creatinine prior to admission as the baseline (18). To understand how the molecular features of AKI overlap with severe respiratory illness at the time of ICU admission, we stratified patients by prevalent ARF (receiving advanced respiratory support).

Statistical Analysis

In our primary analysis, we estimated relationships between each biomarker and risk of severe AKI using relative risk regression, with a Poisson distribution and robust SEs (19). We adjusted for age, sex, COVID-19, and Acute Physiology and Chronic Health Evaluation-III (APACHE-III) score, which included chronic kidney disease and initial serum creatinine measurements, among other measures of physiologic illness severity (20). Biomarker concentrations were log-2 transformed due to right-skew. A relationship was considered statistically significant if Benjamini-Hochberg corrected false discovery rate (FDR) was less than 0.05. We also repeated this analysis in key subgroups. Notably, we examined patients with respiratory illness related to COVID-19, and patients with other forms of respiratory illness. We also examined the subgroup of patients with KDIGO stages 0–1 AKI, who may be more amenable to intervention than patients who have already developed later stages of AKI. In the sensitivity analysis examining time to severe AKI, we used a Fine-Gray model to account for death as a competing risk (21).

For secondary analyses assessing relationships between each biomarker and risk of severe ARF, we used the primary methods described above. To compare biomarker profiles by prevalent organ dysfunction, we used Mann-Whitney *U* and Kruskal-Wallis tests.

Finally, to further explore the clinical relevance of these biomarkers, we aimed to develop parsimonious models with age, sex, and just a single biomarker that predicted risk for severe AKI. We split the cohort randomly 70%/30% into training and test sets, and fit logistic regression models in the training set with age (as a continuous variable),

sex (binary variable), and log-2 transformed biomarker (continuous variable). We compared biomarker models to clinical models with age, sex, and either APACHE-III or creatinine (as continuous variables), using area under the receiver operating characteristic (AUROC) curve to assess discrimination. Predictors reflected data within 24 hours of ICU admission. Since all patients had complete clinical data, we used complete-case analysis to build models. We reported methods and results according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement (**Supplementary Appendix**, http://links.lww.com/CCX/B221 for completed TRIPOD checklist).

STATA (StataCorp, College Station, TX) Version 17.0 was used for all analyses.

RESULTS

Cohort Description

We included 301 patients at risk for severe AKI in our primary analysis, all of whom had plasma collected within 24 hours of ICU admission (**Fig. 1**). An additional nine patients, who were initiated emergently on RRT prior to sample collection, were included in secondary analyses of prevalent organ dysfunction. At the time of ICU admission, 63% of the cohort was male; 19% had AKI; 22% were on high-flow oxygen or noninvasive mechanical ventilation; and 45% were on invasive mechanical ventilation (**Table 1**). Primary reasons for ICU admission are in **Table S1** (http://links.lww.com/CCX/B221), with 64% having COVID-19.

During the 14 days following ICU admission, 16% of patients (n = 48) experienced severe AKI (Table 1). Median time from ICU admission to severe AKI was 4 days (interquartile range, 2–7 d). Patients who developed severe AKI were more likely to have AKI, COVID-19 and higher APACHE-III at ICU admission. Among the 48 patients who developed severe AKI, 40 (83%) also had severe ARF.

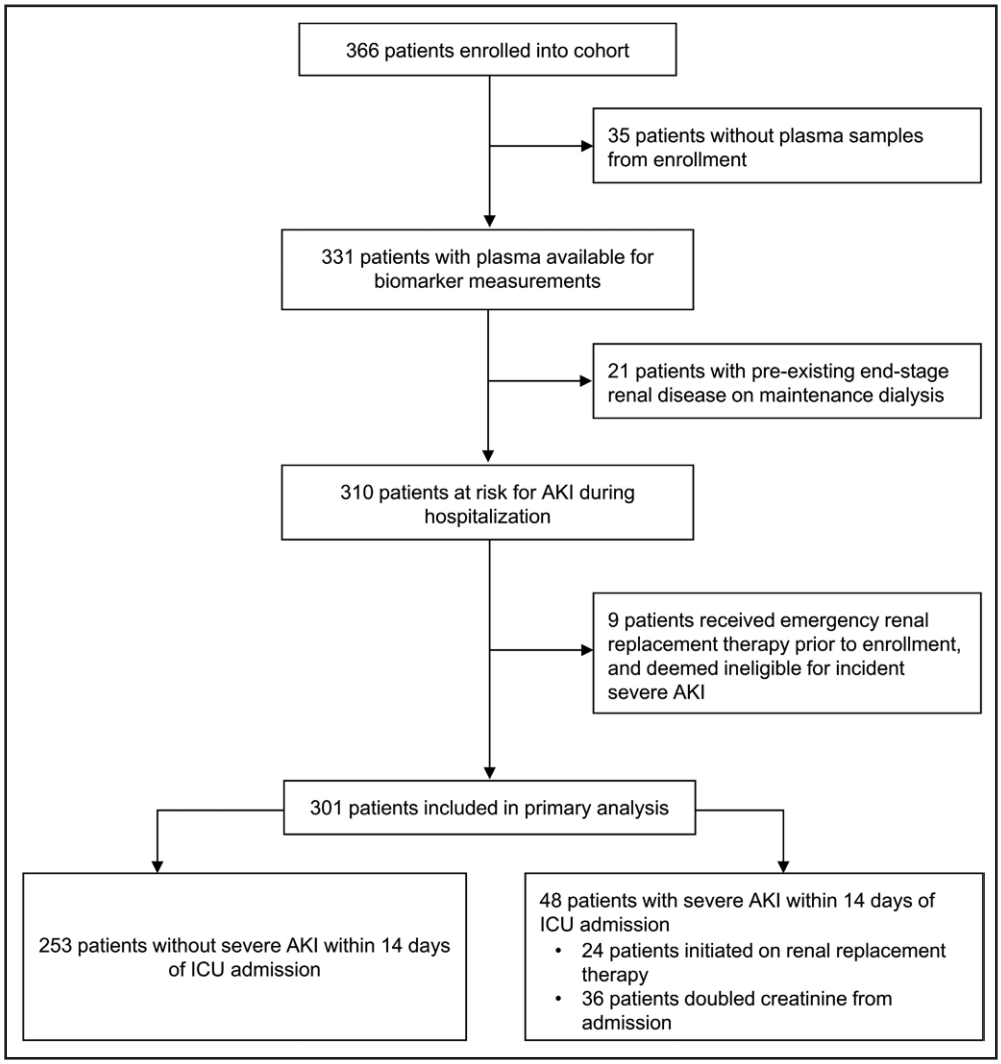

Figure 1. Study flow chart. Patients with severe acute kidney injury (AKI) may have experienced both doubling of creatinine and initiation of renal replacement therapy.

Biomarkers Associated With Severe AKI

Overall, all biomarkers were higher in patients who developed severe AKI, compared with those who did not (**Table S2**, http://links.lww.com/CCX/B221). We then estimated risk of severe AKI associated with doubling of biomarker concentrations (i.e., twofold higher), adjusting for age, sex, COVID-19, and APACHE-III. Doubling of sTREM-1 and sTNFR-1, biomarkers in pathways of early innate immune activation, were associated with

TABLE 1.
Cohort Description by Incident Severe Acute Kidney Injury

Cohort Features	Total ($n = 301$)	No Severe AKI ($n = 253$)	Severe AKI ($n = 48$)	p
Demographics				
Age, yr	55 (16)	55 (17)	54 (16)	0.63
Male	191 (63%)	160 (63%)	31 (65%)	0.86
Race				0.077
White	183 (61%)	155 (61%)	28 (58%)	
Asian	33 (11%)	28 (11%)	5 (10%)	
Black	45 (15%)	41 (16%)	4 (8%)	
Native American	14 (5%)	10 (4%)	4 (8%)	
Pacific Islander	5 (2%)	2 (1%)	3 (6%)	
Other	2 (1%)	2 (1%)	0 (0%)	
Unknown	19 (6%)	15 (6%)	4 (8%)	
Ethnicity				0.92
Non-Hispanic	214 (71%)	172 (71%)	42 (72%)	
Hispanic	73 (24%)	60 (24%)	13 (25%)	
Unknown	14 (5%)	11 (5%)	3 (5%)	
Chronic conditions				
Diabetes	84 (28%)	66 (26%)	18 (38%)	0.11
Coronary artery disease	39 (13%)	36 (14%)	3 (6%)	0.13
Chronic kidney disease	52 (17%)	40 (16%)	12 (25%)	0.12
Cirrhosis	23 (8%)	19 (8%)	4 (8%)	0.84
Heart failure	49 (16%)	41 (16%)	8 (17%)	0.94
Chronic obstructive pulmonary disease	45 (15%)	37 (15%)	8 (17%)	0.72
ICU conditions at admission				
COVID-19	193 (64%)	156 (62%)	37 (77%)	0.041
Acute respiratory distress syndrome, based on Berlin criteria	122 (41%)	91 (36%)	31 (65%)	< 0.001
Vasopressors	127 (42%)	98 (39%)	29 (60%)	0.005
Acute Physiology and Chronic Health Evaluation-III	79 (49–106)	74 (45–98)	108 (74–125)	< 0.001
AKI, stage 1 or greater	56 (19%)	36 (14%)	20 (42%)	< 0.001
KDIGO stage 1	30 (10%)	27 (11%)	3 (6%)	
KDIGO stage 2	7 (2%)	3 (1%)	4 (8%)	
KDIGO stage 3	19 (6%)	6 (2%)	13 (27%)	
High-flow oxygen or noninvasive mechanical ventilation	67 (22%)	60 (24%)	7 (15%)	0.16
Invasive mechanical ventilation	136 (45%)	107 (42%)	29 (60%)	0.021
Hospital outcomes				
Severe acute respiratory failure	147 (49%)	107 (42%)	40 (83%)	< 0.001
Hospital mortality	92 (31%)	57 (23%)	35 (73%)	< 0.001

AKI = acute kidney injury, KDIGO = "Kidney Disease: Improving Global Outcomes" work group.
Severe AKI and acute respiratory failure ascertained between day 1 and day 14 after ICU admission. ICU conditions ascertained on first day of ICU admission. Age expressed as mean (SD), and other continuous variables are expressed as median (interquartile range). All categorical variables are expressed as number (%). p values correspond to t test, Mann-Whitney U tests, and χ^2 tests as appropriate.

85% (adjusted relative risk [aRR], 1.85; 95% CI, 1.42–2.41) and 56% (aRR, 1.56; 95% CI, 1.24–1.96) higher risk for severe AKI at FDR less than 0.05, respectively (**Fig. 2*A***; and **Table S3**, http://links.lww.com/CCX/B221). Doubling of sPDL-1, an immune checkpoint molecule, was also associated with higher risk for severe AKI (aRR, 1.44; 95% CI, 1.22–1.71). Finally, doubling of sICAM-1 and sVCAM-1, soluble forms of two endothelial cell adhesion molecules, were associated with over 20% higher risk for severe AKI (sICAM-1: aRR, 1.23; 95% CI, 1.05–1.43 and sVCAM-1: aRR, 1.29; 95% CI, 1.12–1.49). Results were similar when modeling death as a competing risk (**Table S4**, http://links.lww.com/CCX/B221).

To further assess robustness of these results, we repeated analyses in key subgroups. Among patients with COVID-19, sTREM-1, sTNFR-1, sPDL-1, sICAM-1, and sVCAM-1 were all at least nominally associated with severe AKI, similar to the results in our primary analysis (**Table S5**, http://links.lww.com/CCX/B221). Effect sizes for these biomarkers were also similar among patients without COVID-19, although their significance was attenuated in this smaller sample (**Table S6**, http://links.lww.com/CCX/B221). Finally, we examined patients with stages 0–1 AKI at baseline, and determined associations between biomarkers and severe AKI were strongest in this subgroup (**Table S7**, http://links.lww.com/CCX/B221).

Biomarkers Associated With Severe ARF

Next, we assessed which of these biomarkers were also related to severe ARF within 14 days. Approximately half of the patients (n = 147) experienced this outcome, which included 34 patients who had new needs for advanced respiratory support between admission and day 14; 66 patients with persistent need for advanced respiratory support from admission through day 14; and 47 patients who died by day 14 while needing advanced respiratory support (**Tables S8** and **S9**, http://links.lww.com/CCX/B221). Patients with severe ARF had far higher illness severity, hospital mortality, and elevated biomarker concentrations compared with patients who did not have this outcome (Table S8, http://links.lww.com/CCX/B221; **Table S10**, http://links.lww.com/CCX/B221).

In adjusted models, three biomarkers associated with severe AKI were also associated with severe ARF: sPDL-1, sICAM-1, and sVCAM-1 (**Fig. 2*B***; and **Table S11**, http://links.lww.com/CCX/B221). Conversely, sTREM-1 and sTNFR-1, which were both associated with higher risk for severe AKI, were not associated with severe ARF at FDR less than 0.05 (sTREM-1:

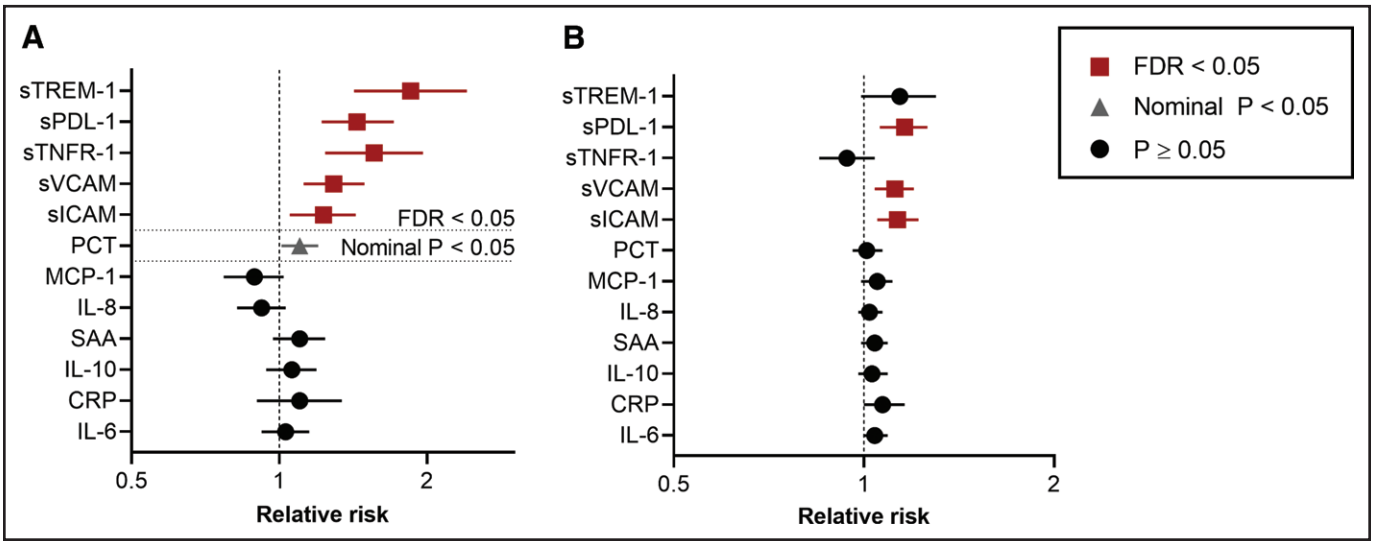

Figure 2. Relationships between biomarkers and risk for severe acute kidney injury (AKI) and acute respiratory failure (ARF). *Plots* indicate relative risk of each outcome associated with two-fold higher biomarker concentrations. **A**, Plots relative risk of severe AKI. **B**, Plots relative risk for severe ARF. CRP = C-reactive protein, FDR = false discovery rate, IL = interleukin, MCP-1 = monocyte chemoattractant protein-1, PCT = procalcitonin, SAA = serum amyloid A, sICAM = soluble intercellular adhesion molecule, sPDL-1 = soluble programmed cell death receptor-1, sTNFR-1 = soluble tumor necrosis factor receptor-1, sTREM-1 = soluble triggering receptor on myeloid cells-1, sVCAM = soluble vascular adhesion molecule.

aRR, 1.14; 95% CI, 0.99–1.30 and sTNFR-1: aRR, 0.94; 95% CI, 0.85–1.04).

Recognizing the heterogeneity in our severe ARF outcome, we performed exploratory analyses examining how the presence of Berlin acute respiratory distress syndrome (ARDS) at admission affected our findings. Of 122 patients with ARDS at admission, 71% qualified for the severe ARF outcome (through death or persistent need for advanced oxygen support, while 29% improved and did not qualify). In this subgroup, sPDL-1 and sICAM-1 still had the strongest adjusted associations with severe ARF with nominal statistical significance (**Table S12**, http://links.lww.com/CCX/B221). We also examined the 147 patients originally classified as severe ARF, and determined whether patients with and without ARDS had differences in biomarker measurements. Interestingly, ARDS patients had baseline elevations in several biomarkers not associated with incident ARF, such as IL-6, MCP-1, sTREM-1, and sTNFR-1 (**Table S13**, http://links.lww.com/CCX/B221).

Biomarkers by Prevalent AKI and ARF

As a secondary analysis, we compared biomarker profiles between patients with and without AKI at the time of ICU admission (prevalent AKI). Several biomarkers involved in immune response were higher among patients with AKI than those without, with the greatest differences in sTREM-1, sTNFR-1, and procalcitonin (**Fig. 3**; and **Table S14**, http://links.lww.com/CCX/B221).

We also examined how these AKI biomarker profiles differed by ARF at admission. We stratified patients into four groups: 1) a reference group without ARF or AKI; 2) ARF without AKI; 3) AKI and ARF; and 4) AKI without ARF (**Table S15**, http://links.lww.com/CCX/B221). Overall, patients with both prevalent AKI and ARF had the highest biomarkers, compared with those with just one or neither organ dysfunction.

Using Top Biomarkers for Prediction of Severe AKI

Because sTREM-1, sPDL-1, or sTNFR-1 had the strongest associations with severe AKI, we explored how they could be used in parsimonious models to identify highest risk patients. In training data, we found biomarker models all had moderate discrimination for incident severe AKI and did not significantly differ from a model based on APACHE-III (**Fig. 4*A***). In test data, a model with sTREM-1 (AUROC, 0.87; 95% CI, 0.79–0.95) had significantly higher discrimination than a model with APACHE-III (AUROC, 0.68; 95% CI, 0.50–0.86; DeLong test $p = 0.03$) (**Fig. 4*B***). We also compared biomarker-based models to a model with age, sex, and serum creatinine (**Table S16**, http://links.lww.com/CCX/B221). The creatinine-based model had poor discrimination for the outcome

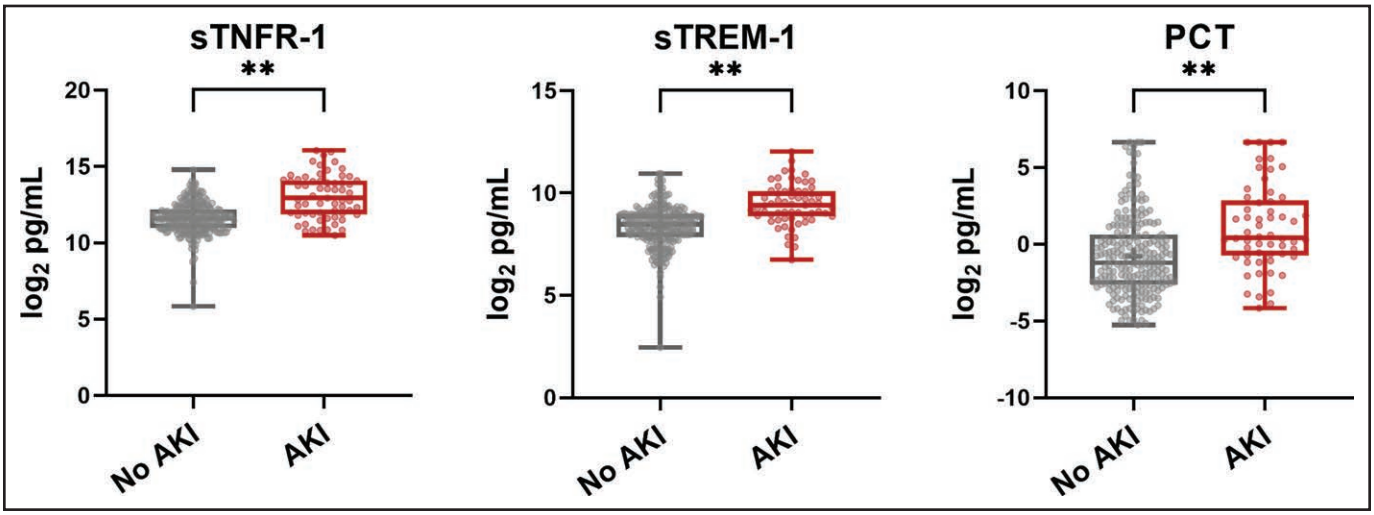

Figure 3. Biomarker concentrations by prevalent acute kidney injury. Acute kidney injury (AKI) defined as Kidney Disease: Improving Global Outcomes stage 1 or greater on the day of admission to the ICU. *Boxes* indicate median and interquartile range for biomarker concentrations, *whiskers* indicate minimum and maximum values, and *dots* represent individual measurements. Comparisons by groups performed with Mann-Whitney *U* tests, and biomarkers were sorted by *p* values, with top three biomarkers shown here. **False discovery rate < 0.05. PCT = procalcitonin, sTNFR-1 = soluble tumor necrosis factor receptor-1, sTREM-1 = soluble triggering receptor on myeloid cells-1.

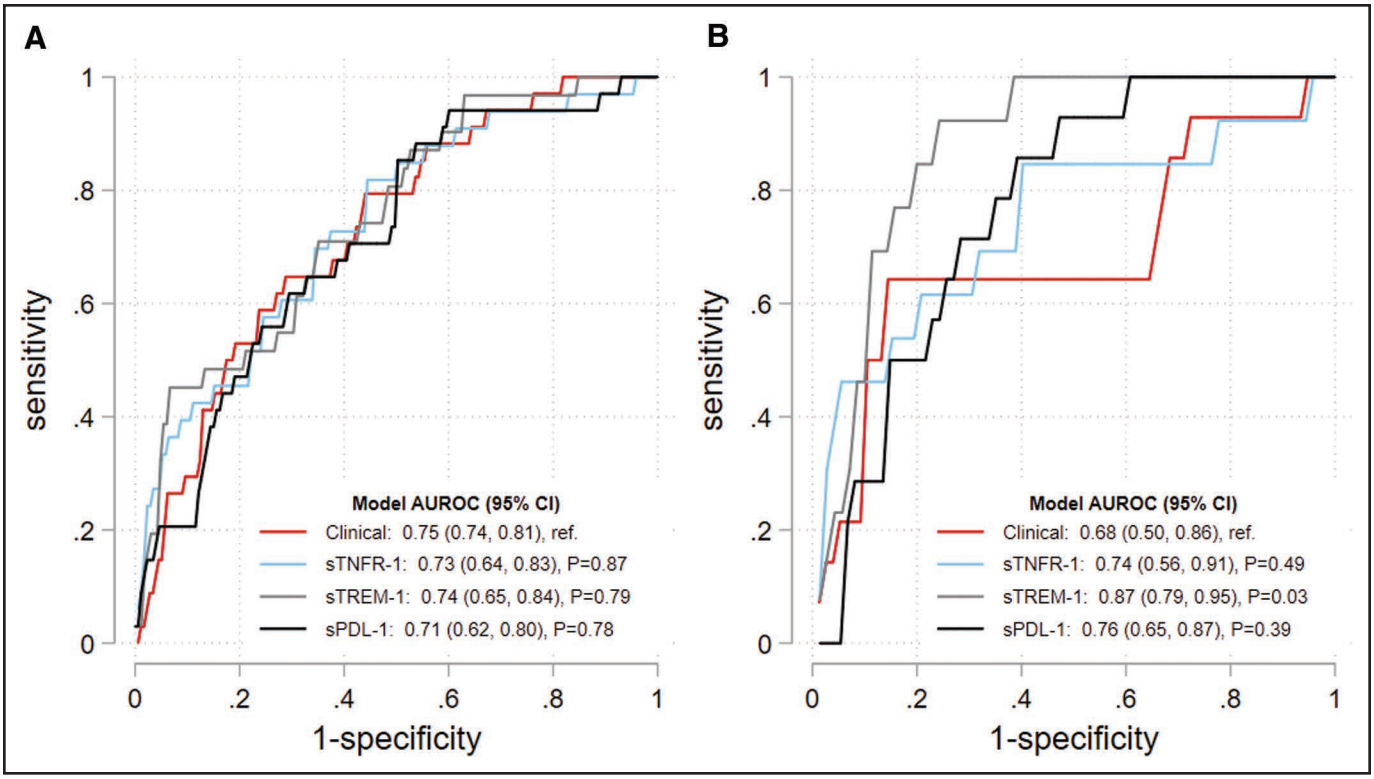

Figure 4. Comparison of area under the receiver operating characteristic (AUROC) curves of biomarker and clinical models. **A**, Training set, *n* = 211, of which *n* = 34 had severe acute kidney injury (AKI). **B**, Test set, *n* = 90, of which *n* = 14 had severe AKI. Clinical model includes age, sex, and Acute Physiology and Chronic Health Evaluation-III score. Biomarker models include age, sex, and the specified biomarker. *p* values are for DeLong tests comparing equality of AUROC of each biomarker model to the clinical model. sPDL-1 = soluble programmed cell death receptor-1, sTNFR-1 = soluble tumor necrosis factor receptor-1, sTREM-1 = soluble triggering receptor on myeloid cells-1.

in training (AUROC, 0.65; 95% CI, 0.55–0.75) and test (AUROC, 0.59; 95% CI, 0.40–0.77) data. The sTREM-1 based model again had significantly higher AUROC in test data ($p = 0.02$).

We then examined how many patients would be considered high-risk for severe AKI using the best clinical (APACHE-III) and biomarker (sTREM-1) models, and how well this classification captured the primary outcome (**Table 2**). We examined thresholds of 5%, 10%, 20%, and 30%—a range which optimized each model's negative and positive predictive values (NPV, PPV). Both models had thresholds with sensitivity and NPV exceeding 90% in training and test sets. At a threshold of 5%, both sTREM-1 and APACHE-III models captured most instances of severe AKI and had at least moderate NPV in the test data; however, the APACHE-III model flagged nearly all patients as high-risk and had lower specificity. At a threshold of 10%, the sTREM-1 model still captured all instances of severe AKI in the test data, while the APACHE-III model missed a higher proportion of cases. Neither model offered robust PPV at any threshold.

DISCUSSION

In a cohort of critically ill patients with acute respiratory illness, we identified unique patterns of immune response and endothelial biomarkers across phenotypes of kidney and respiratory organ dysfunction. Consistent with prior epidemiologic work, we found AKI is common during respiratory illness, and frequently related to persistent or worsening respiratory dysfunction (3, 4). Select immune response biomarkers, including sTREM-1, sTNFR-1, and sPDL-1, and endothelial function biomarkers, such as sICAM-1 and sVCAM-1, were associated with risk for severe AKI in the first 2 weeks after ICU admission. Although the majority of patients who developed severe AKI also experienced severe ARF, only sPDL-1, sICAM-1 and sVCAM-1 were associated with a higher risk for both outcomes. Taken together, this study identifies

TABLE 2.

Performance Characteristics of Soluble Triggering Receptor on Myeloid Cells-1 and Acute Physiology and Chronic Health Evaluation-III Models to Predict Severe Acute Kidney Injury

Dataset	Model Threshold	[a]Patients at High/ Low Risk	Outcomes Identified/ Not Identified	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Training	sTREM-1 model						
	≥ 5%	169/27	30/1	97 (83–100)	16 (11–22)	18 (12–24)	96 (81–100)
	≥ 10%	115/81	27/4	87 (70–96)	47 (39–55)	24 (16–32)	95 (88–99)
	≥ 20%	45/151	15/16	48 (30–67)	82 (75–87)	33 (20–49	89 (83–94)
	≥ 30%	23/173	12/19	39 (22–58)	93 (88–97)	52 (31–73)	89 (83–93)
	APACHE-III model						
	≥ 5%	187/9	31/0	100 (89–100)	6 (3–10)	17 (12–23)	100 (66–100)
	≥ 10%	118/78	27/4	87 (70–96)	45 (37–53)	23 (16–32)	95 (87–99)
	≥ 20%	59/137	18/13	58 (39–76)	75 (68–82)	31 (19–44)	91 (84–95)
	≥ 30%	26/170	10/21	32 (17–51)	90 (85–94)	39 (20–59)	88 (82–92)
Test	sTREM-1 model						
	≥ 5%	64/19	13/0	100 (75–100)	27 (17–39)	20 (11–32)	100 (82–100)
	≥ 10%	41/42	13/0	100 (75–100)	60 (48–72)	32 (18–48)	100 (92–100)
	≥ 20%	21/62	10/3	77 (46–95)	84 (74–92)	48 (26–70)	95 (87–99)
	≥ 30%	12/71	6/7	46 (19–75)	91 (82–97)	50 (21–79)	90 (81–96)
	APACHE-III model						
	≥ 5%	78/5	12/1	92 (64–99)	6 (2–14)	15 (8–25)	80 (28–100)
	≥ 10%	48/35	8/5	62 (32–86)	43 (31–55)	17 (8–30)	86 (70–95)
	≥ 20%	20/63	8/5	62 (32–86)	83 (72–91)	40 (19–64)	92 (82–97)
	≥ 30%	9/74	3/10	23 (5–54)	91 (82–97)	33 (8–70)	87 (77–93)

APACHE-III = Acute Physiology and Chronic Health Evaluation-III, sTREM-1 = soluble triggering receptor on myeloid cells-1.

[a]Patients at high/low risk indicates the number of patients predicted to be above/below the specified threshold.

Model thresholds indicate probabilities calculated from logistic regression model. Outcomes identified/not identified indicates the number of patients with the severe acute kidney injury outcome captured in the high/low risk classifications. All counts and estimates determined in subset with sTREM-1 measurements ($n = 196$ in training data, $n = 83$ in test data). Biomarker model parameters given by the following equation: log(odds) = 0.00005 + 0.99 × Age (in yr) + 0.67 × Male sex + 2.73 × sTREM-1 (log-2 pg/mL). Clinical model parameters given by the following equation: log(odds) = 0.039 + 0.99 × Age (in yr) + 0.77 × Male sex + 1.02 × APACHE-III.

novel molecular risk factors for kidney outcomes, aims to differentiate which are and are not linked to concurrent respiratory outcomes, and, in turn, offers data to inform precision medicine studies of AKI during respiratory illness.

Both sTREM-1 and sTNFR-1 were consistently related to both prevalent and incident AKI, as they were elevated among patients with AKI at ICU admission and associated with risk of severe AKI. Both biomarkers reflect early innate immune activation and mediate immune-mediated tubular and glomerular injury in experimental models (22–24). sTNFR-1 is an strong emerging predictor of kidney outcomes in other populations, but fewer studies have examined it during respiratory illness (12, 16, 25, 26). The largest study in respiratory illness was a secondary analysis of older trial data in ARDS, which identified sTNFR-1, among other plasma biomarkers of inflammation, endothelial dysfunction, and epithelial injury, as the strongest predictor of AKI within 4 days (12). Our work extends the findings in the ARDS study by examining a longer time frame after development of acute respiratory illness, incorporating RRT into the outcome, analyzing overlap between AKI and ARF, and using more

contemporary patients across a wider range of illness severity. More recent studies have identified sTNFR-1 as a predictor of AKI in smaller COVID-19 populations, including work from our group which included a subset of patients in the present study (16, 26). Furthermore, we believe this is the first study to show sTREM-1s association with incident AKI during respiratory illness, with prior work focusing on sTREM-1 to diagnose sepsis-associated AKI (27, 28). Beyond AKI, there is a large body of evidence showing sTNFR-1 and sTREM-1 are associated with mortality in patients with sepsis, pneumonia, COVID-19, and ARDS (26, 29–34). Given that sTNFR-1 and sTREM-1 were associated with AKI but not ARF, we hypothesize the relationship between mortality and these biomarkers may be mediated through kidney-related outcomes, rather than respiratory outcomes.

Next, we developed models using top biomarkers to predict severe AKI in order to help prospectively identify patients at highest risk for this outcome. These models, each of which included age, sex and a single biomarker, had several strengths. First, they qualitatively had better discrimination than a clinical model with age, sex, and serum creatinine, consistent with work showing that creatinine is a delayed indicator of kidney function (25). Second, the biomarker-based models had similar discrimination to one using APACHE-III, but APACHE-III is a complex score that can be cumbersome in clinical practice, relying on greater than 15 physiologic and laboratory variables, as well as knowledge of past medical history that is not always available early in critical illness (20). These biomarker models need validation in other datasets, and their performance is untested against more robustly developed clinical models; however, our findings provide proof-of-concept on how biomarkers may support prognostic enrichment in clinical trials. In particular, the model with sTREM-1 (for which a commercial assay is under development) achieved good NPV and may help screen out patients unlikely to develop incident AKI. Identifying high-risk patients remains challenging in AKI research, and future work should aim to further understand how sTREM-1, other biomarkers, and clinical variables might all be used for earlier AKI diagnosis, prognostication, and intervention (35, 36).

Finally, our work highlights biologic features that connect kidney and lung outcomes. We determined sPDL-1, sVCAM-1, and sICAM-1 were associated with AKI and ARF, suggesting these biomarkers could reflect pathophysiologic derangements compromising both organs. ICAM-1 and VCAM-1 are cell adhesion molecules that mediate leukocyte-endothelial cell interactions and are expressed on injured lung and kidney tissues in COVID-19 and other forms of acute illness (37–41). They have also been linked to mortality in these settings, but their relationship to AKI is inconsistent (12, 42–44). sPDL-1 is the soluble form of a checkpoint molecule whose role in respiratory illness is not well-established. Our group has previously shown that sPDL-1 is associated with mortality and ventilator-free days in this population, but we are unaware of studies linking it to AKI (15). These biomarkers can potentially be used to identify patients at risk for multiple organ dysfunction and may represent appealing targets for future pathophysiologic study of kidney-lung interactions during critical illness.

This study has important limitations. First, many patients entered the cohort having already developed respiratory failure, so our severe ARF outcome included a diverse set of patients with either nonresolving or worsening respiratory illness; in rare cases, this included patients with transient worsening from baseline. We chose to define severe ARF this way to capture illness trajectories that could benefit from intervention at admission, and indeed patients with this trajectory experienced high mortality; however, these issues may limit our ability to identify risk factors for incident ARF and delineate them from risk factors for AKI. Second, though we enrolled a diverse set of patients across three hospitals, it is a moderate-sized single-center study, so generalizability may be limited. In particular, our prediction models should be evaluated in other datasets, as their performance characteristics were strong though imprecise in the small test dataset. Third, the study is observational, so we cannot determine whether biomarkers were causally linked to outcomes, and their biologic roles in critical illness are not consistently understood. Fourth, the non-COVID-19 population in our study was relatively small and heterogeneous, which may have underpowered and attenuated our subgroup analysis. Although we found similar relationships between biomarkers and severe AKI regardless of COVID-19, our findings may differ in populations with a different composition of respiratory illness.

CONCLUSIONS

sTREM-1 and sTNFR-1, biomarkers of innate immune activation, were associated with severe AKI, while sPDL-1, sVCAM-1, and sICAM-1 were associated with both severe AKI and severe ARF. These biomarkers may represent important molecular risk factors for kidney outcomes during respiratory illness and be used to study pathophysiology of kidney-lung interactions and to individualize care.

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