

Soluble Urokinase Receptor (SuPAR) in COVID-19–Related AKI

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ABSTRACT

Background AKI commonly occurs in patients with coronavirus disease 2019 (COVID-19). Its pathogenesis is poorly understood. The urokinase receptor system is a key regulator of the intersection between inflammation, immunity, and coagulation, and soluble urokinase plasminogen activator receptor (suPAR) has been identified as an immunologic risk factor for AKI. Whether suPAR is associated with COVID-19–related AKI is unknown.

Methods In a multinational observational study of adult patients hospitalized for COVID-19, we measured suPAR levels in plasma samples from 352 adult patients that had been collected within 48 hours of admission. We examined the association between suPAR levels and incident in-hospital AKI.

Results Of the 352 patients (57.4% were male, 13.9% were black, and mean age was 61 years), 91 (25.9%) developed AKI during their hospitalization, of whom 25 (27.4%) required dialysis. The median suPAR level was 5.61 ng/ml. AKI incidence rose with increasing suPAR tertiles, from a 6.0% incidence in patients with suPAR <4.60 ng/ml (first tertile) to a 45.8% incidence of AKI in patients with suPAR levels >6.86 ng/ml (third tertile). None of the patients with suPAR <4.60 ng/ml required dialysis during their hospitalization. In multivariable analysis, the highest suPAR tertile was associated with a 9.15-fold increase in the odds of AKI (95% confidence interval [95% CI], 3.64 to 22.93) and a 22.86-fold increase in the odds of requiring dialysis (95% CI, 2.77 to 188.75). The association was independent of inflammatory markers and persisted across subgroups.

Conclusions Admission suPAR levels in patients hospitalized for COVID-19 are predictive of in-hospital AKI and the need for dialysis. SuPAR may be a key component of the pathophysiology of AKI in COVID-19.

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Over 7.5 million people worldwide have been infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with >425,000 deaths as of June of 2020 attributed to coronavirus disease 2019 (COVID-19).¹ Although initially thought of as a mainly respiratory disease, close to 50% of patients hospitalized with COVID-19 develop AKI.^{2–7} The burden of AKI in COVID-19 has placed significant strain on resources for RRT.⁸ In an observational study of 3235 hospitalized patients

with COVID-19 across the Mount Sinai Health System in New York, AKI occurred in 1406 patients (46%), of whom 280 (20%) required dialysis.⁷ Two-thirds of AKI cases were moderate to severe.⁷ The majority of patients had evidence of proteinuria.^{4,5} Other large studies from New York and China have reported similar findings.^{2–6} Most importantly, AKI is strongly associated with poor survival in COVID-19.^{4,6} Although attention has been directed to evidence of infection of renal tubular

epithelium and podocytes by the SARS-CoV-2 virus,^{9,10} the pathophysiology of AKI in COVID-19 is likely multifactorial and includes aggravation of prior risk factors, acute inflammation, cardiorenal syndrome, hemodynamic instability, and hypovolemia.^{11,12} The incidence of AKI in COVID-19 is similar to that reported in other pandemics, notably H1N1 influenza, suggesting that the systemic inflammatory response may be the main contributor to AKI in the setting of viral-related critical illness.^{13,14} There are no therapies or strategies to reduce the incidence of AKI in this patient population.^{15–17}

We have identified soluble urokinase plasminogen activator receptor (suPAR) as an immune mediator of kidney injury.^{18–28} The urokinase receptor system is a key regulator of the intersection between inflammation, immunity, and coagulation.²⁹ suPAR is produced by cleavage of membrane-bound uPAR in response to inflammatory stimuli such as viruses, and cardiovascular risk factors such as smoking and diabetes mellitus.^{30–32} High suPAR levels predispose patients to AKI in various clinical scenarios including critical illness, likely by modulating mitochondrial respiration and inducing reactive oxygen species generation in proximal tubular cells, sensitizing them to additional damage.^{20,33,34} Most importantly, adverse effects of suPAR on the kidneys are abrogated by the use of an anti-suPAR mAb in experimental models, suggesting that suPAR is a promising therapeutic target to mitigate AKI.^{19–21,35} suPAR levels are dramatically elevated in COVID-19 and may be a key mediator of COVID-19–related AKI.³⁶ We hypothesize that blood suPAR levels in patients hospitalized for COVID-19 are predictive of incident AKI. To test our hypothesis, we investigated the association between admission suPAR levels and incident AKI in patients hospitalized for COVID-19 enrolled in the International Study of Inflammation in COVID-19 (ISIC).

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Significance Statement

Nearly half of hospitalized patients with coronavirus disease 2019 (COVID-19) develop AKI, with 20% requiring dialysis. High levels of soluble urokinase plasminogen activator receptor (suPAR)—an immune mediator of kidney injury—predispose patients to AKI in various clinical scenarios, including critical illness. High suPAR levels modulate mitochondrial respiration and induce the generation of reactive oxygen species in proximal tubular cells, sensitizing them to additional insults. In a multicenter observational study, the authors measured plasma suPAR in 352 patients with COVID-19 within 48 hours of their hospitalization. They found suPAR levels to be strongly associated with incident AKI, independent of such clinical characteristics as kidney function and inflammatory biomarkers, and predictive of the need for dialysis. SuPAR may be a key component of the pathophysiology of AKI in COVID-19.

METHODS

The International Study of Inflammation in COVID-19

The ISIC is an ongoing multicenter observational study whose primary purpose is to characterize levels of various biomarkers of inflammation and their association with in-hospital outcomes of patients with COVID-19. Participating centers include: the University of Michigan in Ann Arbor, MI; Copenhagen University Hospital in Hvidovre, Denmark; Attikon University Hospital in Athens, Greece; the University of Thessaly, Greece; the University Hospital of Dusseldorf, Germany; and Charité University Medicine Berlin, Germany (Supplemental Material). Inclusion criteria were: (1) adult (≥ 18 years old) patients hospitalized primarily for COVID-19; (2) a confirmed SARS-CoV-2 infection diagnosed through RT-PCR test of nasopharyngeal or oropharyngeal samples; and (3) at least one blood sample collected during the hospitalization and stored for biomarker testing. Patients with confirmed SARS-CoV-2 infection who were not primarily admitted for COVID-19 were excluded. Institutional review board approval and consent procedures were obtained separately at each site according to local institutional policies.

The data collected were granular and extensive, including details at presentation, past medical history, home medications, inpatient medical therapy, hospitalization course, and outcomes. Clinical outcomes included several in-hospital events: respiratory failure, AKI, myocardial injury, thromboembolism, and coagulopathy, all accompanied by laboratory testing. We collected all biomarker data available including levels of C-reactive protein (CRP), D-dimer, ferritin, and lactate dehydrogenase (LDH). The data were extracted through manual chart review by at least two reviewers per site and entered in an online data repository managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Michigan.^{37,38} REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export

procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

Study Design and Definitions

For the purpose of this substudy of ISIC, we only included patients who had a blood sample collected within 48 hours of admission. Patients with a history of ESKD on dialysis, and those with AKI on admission (by comparing admission serum creatinine with measures within 1 year of admission), were excluded (Supplemental Figure 1). Overall, 352 participants of ISIC met inclusion criteria. The primary outcome was incident AKI during the hospitalization, defined on the basis of the Kidney Disease Improving Global Outcomes (KDIGO) criteria³⁹: AKI stage 1 was defined as a 1.5–1.9-fold increase in serum creatinine relative to the value on admission or a ≥ 0.3 mg/dl absolute increase in creatinine. Stage 2 AKI was defined as a 2.0–2.9-fold increase in serum creatinine compared with admission levels. Lastly, stage 3 AKI was defined as a threefold increase in serum creatinine compared with admission, a rise in creatinine to ≥ 4 mg/dl, or initiation of RRT.

Assessment of Kidney Function

Serum creatinine measurements on admission and all subsequent values during the index hospitalization were obtained from electronic medical records. The serum creatinine level at the time of suPAR measurement was used as the baseline value for all analyses. suPAR was measured on the day of admission in 327 (92.9%), and between 24 and 48 hours of admission in 25 (7.1%) patients. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.⁴⁰

Measurement of suPAR

suPAR was measured in plasma at participating centers using a commercially available ELISA (suPARnostic assay by Viro-Gates, Birkerød, Denmark) by experienced technicians blinded to the clinical data. The suPARnostic assay uses a double mAb sandwich assay to human suPAR. Kits have a lower detection limit of 100 pg/ml and intra- and interassay variation of 2.75% and 9.17%, respectively, as determined by the assay manufacturer.

Statistical Analyses

We first report cohort characteristics stratified by AKI and suPAR tertiles. Continuous variables are presented as means (\pm SD) or as medians (25th to 75th interquartile range [IQR]) for normally and non-normally distributed data, respectively. Categorical variables are presented as proportions (%). To compare patients with and without AKI, and across AKI stages or suPAR tertiles, we used ANOVA or Kruskal–Wallis for continuous variables, and chi-squared tests for categorical variables. We used Spearman–rank to assess correlations between suPAR and inflammatory biomarkers (CRP, D-dimer, ferritin, and LDH), and linear regression after log-transformation of the aforementioned markers (base 2, interpreted as per 100%

increase) to identify those that were independently associated with suPAR.

To identify determinants of in-hospital AKI, we used logistic regression with AKI as the binary dependent variable in models that incorporated age, sex, race, country of enrollment (United States versus Europe), body mass index (BMI), diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, oxygen saturation on admission, and eGFR derived from serum creatinine level obtained from the sample in which suPAR was measured. Each biomarker was evaluated in a separate model that included the aforementioned clinical characteristics in addition to suPAR.

We explored the association between suPAR and incident AKI using two approaches: binary logistic regression with in-hospital AKI as the dependent variable reporting odds ratio (OR), and modeling time to AKI using Cox regression hazards modeling reporting hazard ratio. Model 1 was unadjusted, including suPAR as tertiles with the first tertile being the reference. Model 2 was adjusted for age, sex, race, diabetes mellitus, hypertension, and eGFR to adjust for risk factors. Model 3 incorporated the aforementioned variables including oxygen saturation and CRP levels to adjust for disease severity.

For visualization, we plotted the daily percentage change in creatinine from admission stratified by suPAR tertiles using locally weighed smoothing. To assess suPAR's effect on risk discrimination, we plotted receiver operating characteristic curves and computed the area under the curve (AUC) for model 0 incorporating age, sex, race, and admission eGFR, and for model 1 which includes variables from model 0 in addition to suPAR. We compared the AUCs for both models using DeLong's test.⁴¹

Lastly, we investigated the possibility of effect modification attributed to differences in baseline characteristics. We tested for interaction and computed ORs for the association between suPAR levels and AKI in relevant subgroups. Two-tailed *P* values ≤ 0.05 were considered statistically significant. Analyses were performed using SPSS 24 (IBM, NY) and R (R Core Team, 2014).⁴²

RESULTS

Cohort Characteristics

Among 873 participants of ISIC, 352 met inclusion criteria for our study (Supplemental Figure 1). One hundred and 48 patients (42.0%) were admitted at the University of Michigan, and 204 (57.9%) at European centers (Supplemental Tables 1 and 2). Overall, the cohort had a mean age of 61 (range, 19–95) and consisted of 57.4% male and 13.9% Black patients (Table 1). The mean admission eGFR was 80 ml/min per 1.73 m², and 25.6% of patients had an eGFR < 60 ml/min per 1.73 m². A total of 91 (25.9%) patients developed AKI during the hospitalization, among whom 43 (47.3%) had at least moderate AKI (stage 2 or 3 KDIGO), and 25 (27.5%) required RRT. The mean admission serum creatinine in patients with AKI was

1.3 mg/dl (SD 0.9), whereas the mean peak creatinine was 2.8 mg/dl (SD 2.0). All patients requiring dialysis were in the intensive care unit. The median number of days on RRT was 5 (range, 1–12). Biomarkers of inflammation including CRP, ferritin, D-dimer, and LDH were significantly higher in patients with AKI compared with those without AKI (Table 1). In multivariable analysis, male sex and eGFR were independently associated with AKI. Younger age, lower eGFR, and lower oxygen saturation were associated with incident RRT. Among the biomarkers, only suPAR and CRP were independently associated with AKI (Table 2).

suPAR Level and Its Determinants

The median suPAR level in the entire cohort was 5.61 ng/ml (IQR, 4.00–7.88), close to threefold higher than that of healthy individuals (2.1 ng/ml).⁴³ Patients in the highest suPAR tertile were more likely to be men, to be Black, and to have higher BMI, diabetes mellitus, hypertension, congestive heart failure, and lower eGFR on admission (Supplemental Table 3). suPAR levels correlated positively with CRP, D-dimer, ferritin, and LDH, independently of clinical characteristics (Supplemental Tables 4 and 5). Only congestive heart failure and eGFR were independently associated with suPAR levels (Supplemental Table 5).

suPAR and In-Hospital AKI in Patients with COVID-19

Patients who developed AKI during their hospitalization had a median suPAR level 61.6% higher than that of patients who did not develop AKI (Table 1). We found a step-wise rise in the

incidence of AKI with increasing suPAR tertiles, from a 6% incidence in patients with suPAR < 4.60 ng/ml (first tertile), to a 45.8% incidence of AKI in patients with suPAR levels > 6.86 ng/ml (Figure 1A). Severity of in-hospital AKI correlated with admission suPAR levels: patients with KDIGO stage 2–3 AKI had significantly higher suPAR levels compared with those with mild AKI (Figure 1B). Serum creatinine levels steadily increased in patients with suPAR levels in the second and third tertiles, whereas they declined in patients in the first tertile (Figure 2). None of the patients with suPAR < 4.60 ng/ml (first tertile) needed dialysis. Among those who required dialysis ($n=25$), we found a strong correlation between suPAR levels and the duration of RRT ($r=0.74$, $P<0.001$). The median duration of RRT in the third suPAR tertile (>6.86 ng/ml) was 6 days (IQR 3–8), compared with 3 days (IQR 1–3) in the second suPAR tertile (4.60–6.86 ng/ml), $P=0.03$.

Multivariable and Sensitivity Analyses

In unadjusted analysis, patients in the second and third suPAR tertiles had a 5.42-fold (95% confidence interval [95% CI], 2.27 to 12.93) and a 13.26-fold (95% CI, 5.69 to 30.88) increase in the odds of developing AKI, respectively, compared with the first tertile (Figure 3A). The highest suPAR tertile remained strongly associated with incident AKI (aOR, 9.15; 95% CI, 3.64 to 22.93) after adjusting for age, sex, race, and eGFR. Although the second tertile of suPAR was not associated with incident RRT (OR, 5.18; 95% CI, 0.60 to 45.0), patients in the third suPAR tertile had a 22.26-fold increase in the odds of requiring RRT (95% CI, 2.93 to 169.29). The association

Table 1. Clinical characteristics and inflammatory markers stratified by AKI

Characteristic	Cohort (n=352)	No AKI (n=261)	AKI (n=91)	P Value ^a
Clinical characteristics				
Age in yr, mean (SD)	61 (16)	60 (17)	65 (15)	0.011
Male, n (%)	202 (57.4)	138 (52.9)	64 (70.3)	0.004
Black, n (%)	49 (13.9)	27 (10.3)	22 (24.2)	0.001
Enrolled in the United States, n (%)	148 (42.0)	95 (36.4)	53 (58.2)	<0.001
BMI kg/m ² , mean (SD)	30 (7)	30 (7)	32 (7)	0.03
Diabetes mellitus, n (%)	91 (25.9)	54 (20.7)	37 (40.7)	<0.001
Hypertension, n (%)	169 (48.0)	110 (42.1)	59 (64.8)	<0.001
Coronary artery disease, n (%)	34 (9.7)	22 (8.4)	12 (13.2)	0.19
Congestive heart failure, n (%)	29 (8.2)	14 (5.4)	15 (16.5)	0.001
Admission eGFR ml/min per 1.73 m ² , mean (SD) ^b	80 (27)	85 (25)	67 (29)	<0.001
Admission eGFR < 60 ml/min per 1.73 m ² , n (%) ^b	90 (25.6)	51 (19.5)	39 (42.9)	<0.001
Oxygen saturation on admission, %	94 (6)	95 (5)	92 (7)	<0.001
Required mechanical ventilation, n (%)	77 (21.9)	22 (8.4)	55 (60.4)	<0.001
Required dialysis, n (%)	25 (7.1)	0 (0.0)	25 (27.5)	<0.001
Biomarkers^c				
suPAR ng/ml, median (IQR)	5.61 (4.00–7.88)	5.05 (3.51–6.70)	7.38 (5.50–10.38)	<0.001
CRP mg/dl, median (IQR)	5.70 (2.58–12.50)	4.90 (2.00–9.80)	14.25 (7.80–22.80)	<0.001
Ferritin ng/ml, median (IQR)	495 (234–1160)	465 (205–998)	595 (299–1350)	0.01
D-dimer mg/L, median (IQR)	0.72 (0.44–1.71)	0.63 (0.40–1.23)	1.10 (0.56–2.17)	0.005
LDH IU/L, median (IQR)	322 (232–472)	295 (220–407)	427.00 (313–592)	<0.001

^aP value for the comparison between groups with and without AKI.

^bCalculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

^cCRP levels were available in 301 participants, ferritin in 207 participants, D-dimer in 204 participants, and LDH in 256 participants.

Table 2. Determinants of incident AKI and need for dialysis in hospitalized patients with COVID-19

Characteristic	AKI (n=91)		RRT (n=25)	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Model 0: clinical characteristics				
Age, per 10 yr	0.91 (0.71 to 1.15)	0.42	0.56 (0.37 to 0.86)	0.007
Male	3.00 (1.65 to 5.46)	<0.001	1.77 (0.65 to 4.82)	0.27
Black	1.99 (0.88 to 4.46)	0.10	3.77 (0.58 to 24.43)	0.16
Institution (United States versus Europe)	0.57 (0.30 to 1.08)	0.08	14.49 (2.40 to 87.58)	0.004
BMI, per 5 kg/m ²	1.03 (0.83 to 1.27)	0.80	0.91 (0.61 to 1.36)	0.66
Diabetes mellitus	1.46 (0.78 to 2.72)	0.24	2.30 (0.80 to 6.58)	0.12
Hypertension	1.13 (0.59 to 2.14)	0.72	1.53 (0.48 to 4.87)	0.47
Coronary artery disease	0.74 (0.29 to 1.92)	0.54	0.61 (0.11 to 3.47)	0.57
Congestive heart failure	1.35 (0.51 to 3.58)	0.55	0.76 (0.13 to 4.58)	0.76
eGFR, per 5 ml/min per 1.73 m ²	0.87 (0.81 to 0.92)	<0.001	0.81 (0.72 to 0.91)	<0.001
Oxygen saturation, per 1%	0.96 (0.91 to 1.00)	0.06	0.91 (0.86 to 0.97)	0.002
Models 1–5: biomarkers ^a				
suPAR, per 100% increase ^b	2.47 (1.60 to 3.79)	<0.001	4.01 (2.01 to 7.99)	<0.001
CRP, per 100% increase	1.37 (1.09 to 1.72)	0.04	1.11 (0.81 to 1.53)	0.53
Ferritin, per 100% increase	1.02 (0.81 to 1.27)	0.89	1.23 (0.78 to 1.94)	0.37
D-dimer, per 100% increase	1.09 (0.87 to 1.36)	0.46	1.01 (0.68 to 1.50)	0.97
LDH, per 100% increase	1.17 (0.69 to 2.00)	0.56	2.06 (0.89 to 4.77)	0.07

^aEach biomarker was evaluated in a separate model that included the listed clinical characteristics in addition to suPAR.

^bSerum creatinine–derived eGFR measured at the time of suPAR sample collection was used in Model 1 assessing the association between suPAR and AKI. eGFR was measured at the time of suPAR collection. CRP levels were available in 301 participants, ferritin in 207 participants, D-dimer in 204 participants, and LDH in 256 participants.

between suPAR and RRT was not attenuated by adjusting for age, male sex, race, and eGFR (aOR, 22.86; 95% CI, 2.77 to 188.75). When examined as a continuous variable, a doubling of suPAR was associated with a 3.18-fold increase in the odds of developing AKI (95% CI, 2.18 to 4.63), and 3.28-fold odds

of requiring RRT (95% CI, 1.93 to 5.57). The association was mildly attenuated after adjusting for clinical characteristics including eGFR (Model 2) and CRP (Model 3). Findings were consistent in a time-to-event analysis (Figure 3B). None of the other inflammatory biomarkers were associated

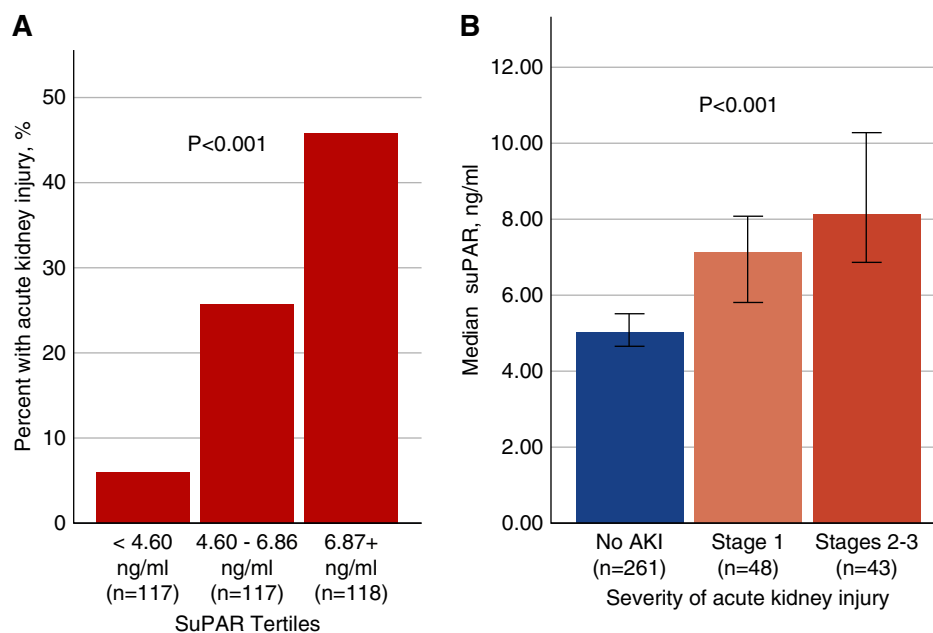


Figure 1. AKI stratified by suPAR levels. Bar graphs showing (A) the percentage of patients with incident AKI stratified by suPAR tertiles, and (B) the median suPAR levels across AKI stages. Note: stages 2–3 AKI here exclude patients on dialysis, which are shown in a separate bar graph. P value is derived from the chi-squared test in (A) and Kruskal–Wallis test in (B).

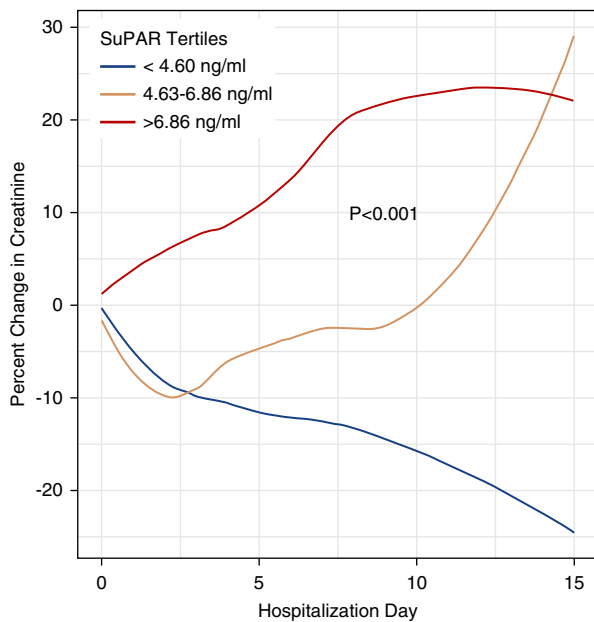


Figure 2. Percent change in creatinine throughout the hospitalization stratified by suPAR tertiles. We plotted the daily percentage creatinine change relative to admission creatinine stratified by suPAR tertiles using locally weighted smoothing. *P* value derived from linear mixed model examining the interaction between the creatinine slope and suPAR tertiles. Patients in second and third tertiles had steadily increasing creatinine levels compared with patients in the first suPAR tertile.

with incident AKI (Table 2). The AUC for suPAR in predicting AKI was 0.741 (95% CI, 0.684 to 0.798), whereas the AUC for admission eGFR was 0.675 (95% CI, 0.609 to 0.740) (Supplemental Figure 2). Addition of suPAR to a model including age, sex, race, and admission eGFR significantly improved the AUC for predicting AKI (Δ AUC 0.065, $P < 0.001$; Figure 4).

In sensitivity analyses, the association between suPAR and AKI did not differ according to day of sample collection ($P = 0.71$), and persisted across relevant subgroups (Figure 5), but was notably stronger in obese patients ($\text{BMI} > 30 \text{ kg/m}^2$, interaction P value = 0.05) and nonhypertensive patients (interaction P value = 0.02). Exclusion of patients in whom suPAR levels were measured 24–48 hours after admission yielded similar findings (Supplemental Table 6).

DISCUSSION

A characterizing feature of severe COVID-19 is the induction of the innate immune response and massive cytokine release, including suPAR.³⁶ We report for the first time the association between suPAR and AKI in a multinational cohort of patients hospitalized for COVID-19. We found admission suPAR levels in these patients to be a strong predictor of in-hospital AKI. Patients in the lowest suPAR tertile ($< 4.60 \text{ ng/ml}$) had a low

incidence of AKI (6%), with none requiring dialysis, whereas patients in the third tertile ($> 6.86 \text{ ng/ml}$) had an incidence of AKI of 45.8% with 16.1% requiring dialysis. The association was independent of eGFR, disease severity, or other biomarkers of inflammation and persisted across subgroups. In light of recent studies showing a role for suPAR as an immune-mediator of kidney injury, our findings highlight suPAR as a potential contributor to the large burden of AKI in COVID-19.

suPAR is the circulating form of uPAR, a glycosyl-phosphatidylinositol-anchored (GPI) three-domain (D_I , D_{II} , and D_{III}) receptor protein encoded by the *PLAUR* gene, and expressed on a variety of cells, including immune cells, endothelial cells, and podocytes.^{19,44,45} The specific physiologic role of suPAR is unclear. Its levels in circulation reflect the aggregate activity of the uPAR system with respect to innate immune activity, proteolysis, and extracellular matrix remodeling.^{44,46,47} Although expressed at low levels in normal conditions, uPAR is induced during leukocyte activation and differentiation in response to environmental stimuli such as smoking and certain RNA viruses.^{48–50} Several proinflammatory conditions with high suPAR levels have a high incidence of kidney disease, including cardiovascular risk factors, autoimmune diseases, lung disease, atherosclerosis, cancer, heart failure, and critical illness.^{51–57} High levels of suPAR in circulation are strongly predictive of progressive kidney dysfunction, with prolonged exposure directly affecting the kidneys *via* pathologic activation of $\alpha v \beta 3$ integrin expressed on podocytes, which induces small GTPase signaling (Rac-1) and podocyte foot process effacement leading to proteinuria and eventually chronic kidney dysfunction.^{18,19,21,28} Transgenic mice over-expressing suPAR develop proteinuric kidney disease and more-severe AKI after contrast injection.^{20,21,28} We found suPAR levels in COVID-19 to be almost threefold higher than in healthy persons (2.1 ng/ml),⁴³ and as high as in critically ill patients who subsequently develop AKI.²⁵

The pathophysiology of AKI in COVID-19 is unclear.⁵⁸ Autopsy reports in patients with COVID-19 have revealed significant proximal tubular injury, and glomerular thrombi with lymphocyte and macrophage infiltration.⁹ Although a hypercoagulable state and microangiopathy are thought to be common mechanisms for both respiratory failure and AKI, D-dimer levels were not independently associated with AKI in our cohort. Direct infection of the kidney has also been shown, but its contribution to injury is unclear.^{9,58,59} Nevertheless, AKI in the setting of sepsis is complex and multifactorial, involving both intrinsic (risk factors and comorbidities) and extrinsic processes (viral infection, hypovolemia, nephrotoxic drugs), with the immune system and acute inflammation having a central role and suPAR being one potential mediator.^{11,60}

suPAR may be implicated in the pathogenesis of COVID-19-related AKI through multiple mechanisms. It has been previously shown to facilitate viral entry into kidney cells through $\alpha v \beta 3$ integrin in hemorrhagic fever secondary to hantavirus, leading to disruption in cell permeability and

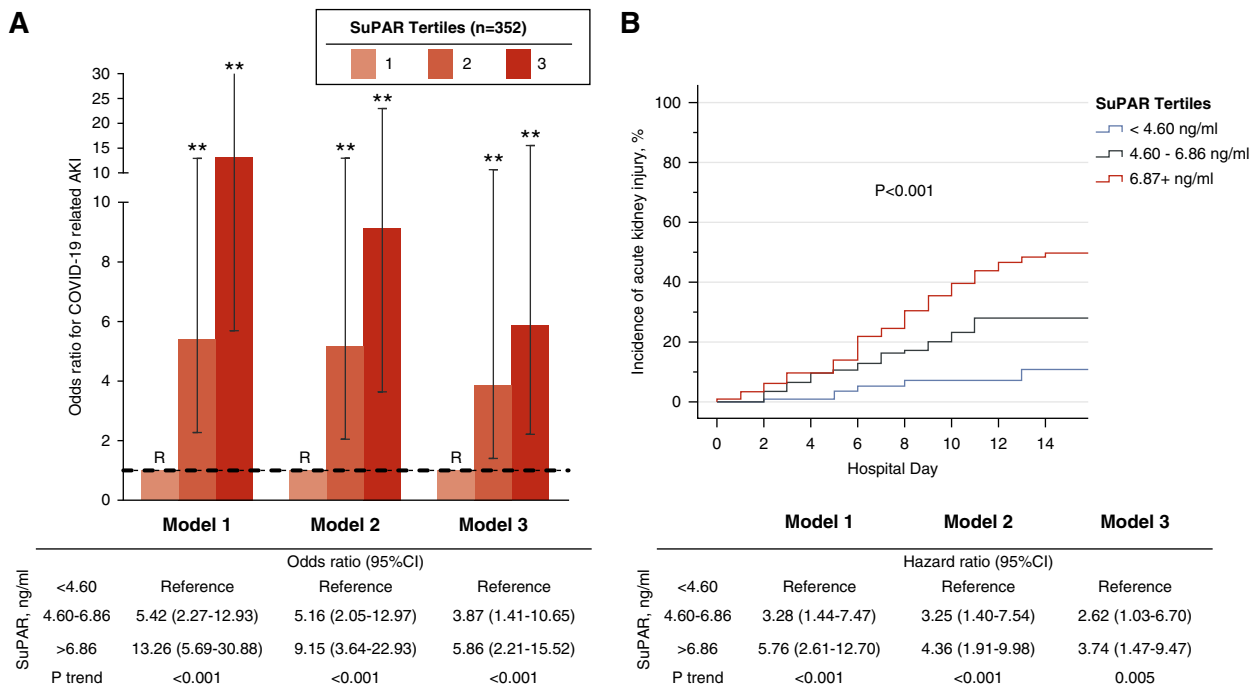


Figure 3. SuPAR and odds of COVID-19–related AKI. (A) Bar graph depicting ORs and 95% CIs for AKI according to admission suPAR tertiles. (B) Kaplan–Meier curves showing cumulative incidence of AKI stratified by suPAR tertiles with log-rank *P* value. Cox regression modeling hazard ratios are reported in the accompanying table. Model 1 was unadjusted. Model 2 was adjusted for age, sex, race, diabetes mellitus, hypertension, and eGFR at the time of sample collection for suPAR. Model 3 incorporated the aforementioned variables including oxygen saturation and CRP levels. Tertile 1 was the reference (R) group in all models. ***P* < 0.001. Data for model 3 were available in 301 participants.

AKI.^{61–64} Whether SARS-CoV-2 infects kidney cells more readily in the presence of high suPAR needs to be explored. suPAR was initially thought to be involved in FSGS.^{18,19} Interestingly, histopathologic findings of FSGS and severe proteinuria have been reported in Black patients with COVID-19 and specifically those with high-risk homozygous *APOL1* variants.^{10,65,66} We have previously shown that high suPAR levels and high-risk homozygous *APOL1* variants are synergistic in activating $\alpha\beta3$ integrins and in their association with the progression of kidney disease in two cohorts of Black patients.²³ The same mechanism may be at play in patients with severe COVID-19. suPAR also affects proximal tubular cells, altering mitochondrial respiration and inducing oxidative stress.²⁰ Other reports have suggested that high suPAR promotes fibrosis of the tubules in an integrin-dependent manner.^{19,21,67,68} These deleterious changes to podocytes and tubular cells have been abrogated by the use of anti-uPAR monoclonal antibodies in experimental models.^{18–20,69} Ultimately, only an in-human intervention assessing the effect of lowering suPAR on the incidence of AKI can provide definitive conclusion on its role as an immune-mediator of kidney injury.

The study has several strengths. It is a multinational study that relied on granular collection of clinical, laboratory, and outcome data throughout the COVID-19 hospitalization. Patients with a positive COVID-19 test who were not primarily admitted for COVID-19 were excluded from this cohort,

allowing us to derive conclusions specifically related to severe COVID-19. We acknowledge a few limitations to the study. Patients from European centers were not consecutively

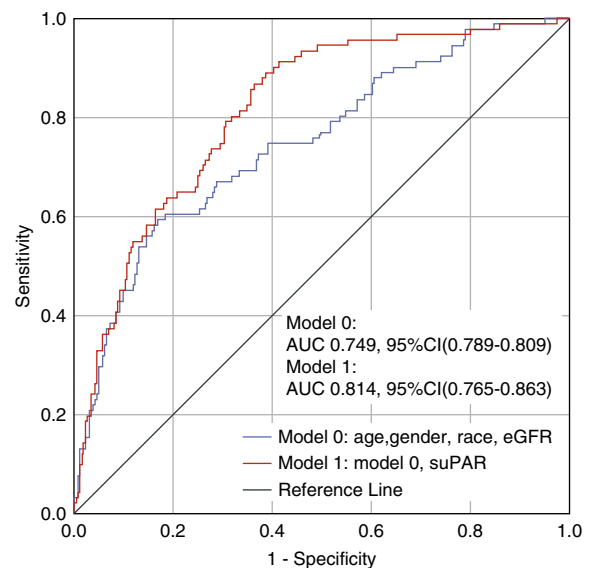


Figure 4. Addition of suPAR improves the AUC for predicting AKI. Receiver operating characteristic curve for predicting AKI. Model 0 includes age, sex, race, and creatinine-derived eGFR at the time of suPAR measurement. Model 1 includes all aforementioned characteristics in addition to suPAR as a continuous variable.

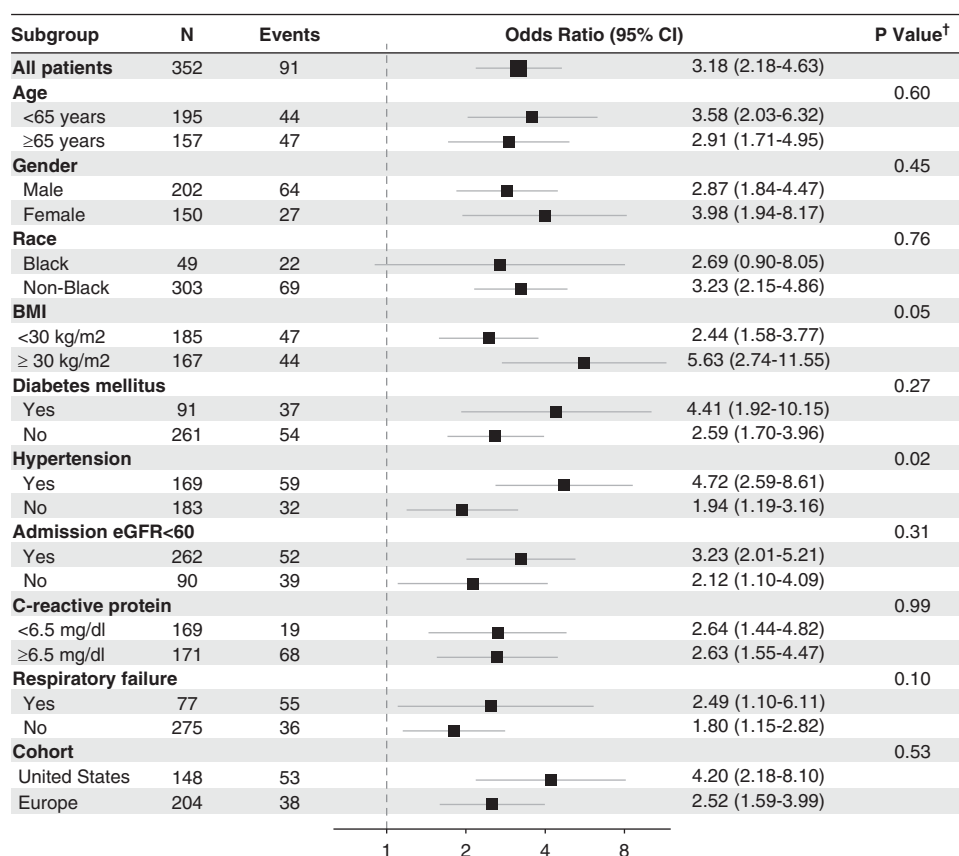


Figure 5. SuPAR and AKI across subgroups. Forest plot depicting the risk of AKI on the basis of suPAR levels as a continuous variable according to subgroups. suPAR levels were log-transformed (base 2) given their skewed distribution. †P value for the interaction between subgroups.

enrolled, lending a risk of selection bias. However, the range of suPAR levels in this cohort was wide, thus limiting the effect of a selection bias on the validity of the association between suPAR and AKI. The association between suPAR and AKI was also similar when examining the European and the University of Michigan cohorts separately. Although COVID-19 is associated with a high incidence of proteinuria, we could not assess urine protein systematically assessed in ISIC.

In conclusion, suPAR levels were independently associated with incident AKI in patients hospitalized for COVID-19. In light of recent experimental data suggesting that suPAR is an immune-mediator of kidney injury, targeting suPAR should be considered as a strategy to mitigate AKI in COVID-19 and other patient populations at high risk of AKI.

DISCLOSURES

O. Anderson and J. Eugen-Olsen are named inventors on patents related to suPAR. J. Eugen-Olsen is a cofounder, shareholder, and chief scientific officer of ViroGates. J. Eugen-Olsen has a patent suPAR as a marker of low-grade inflammation issued to ViroGates. J. Reiser is cofounder of TrisAQ, a biotechnology company developing drugs targeting suPAR. S. Hayek and J. Reiser are members of the scientific advisory board of TrisAQ. J. Reiser has a patent

US20110212083—Role of soluble uPAR in the Pathogenesis of Proteinuric Kidney Disease with royalties paid to TrisAQ, a patent US9867923—Reducing Soluble urokinase Receptor in the Circulation with royalties paid to Miltenyi, a patent JP2016530510—Non-Glycosylated suPAR Biomarkers and Uses thereof with royalties paid to TrisAQ, a patent US20160296592—Methods/Compositions for the Treatment of Proteinuric Diseases with royalties paid to TrisAQ, a patent US9144594—Dynamin Mediated Diseases with royalties paid to TrisAQ, and a patent US8809386—Dynamin Ring Stabilizers with royalties paid to TrisAQ. All remaining authors have nothing to disclose.

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Dr. Salim S. Hayek designed the study. Dr. Tariq U. Azam, Dr. Husam R. Shadid, Dr. Penelope Blakely, Dr. Patrick O'Hayer, Dr. Hanna Berlin, Dr. Michael Pan, Dr. Izzet Altintas, Dr. Jens Tingleff, Dr. Maria-Evangelia Adami, Dr. Nicky Solomonidi, Dr. Maria Tsilika, Dr. Pinkus Tober-Lau, Dr. Eleni Arnaoutoglou, Dr. Athanasios Chalkias, and Dr. Sven H. Loosen collected the data and performed quality control. Dr. Salim S. Hayek and Dr. Lili Zhao analyzed the data. Dr. Salim S. Hayek wrote the first draft of the manuscript. Dr. Tariq U. Azam, Dr. Husam R. Shadid, Dr. Penelope Blakely, Dr. Patrick O'Hayer, Dr. Salim S. Hayek, Dr. Subramaniam Pennathur, Dr. Rodica Pop-Busui, Ove Andersen, Dr. Frank Tacke, Dr. Athanasios Chalkias, Dr. Sven H. Loosen, Dr. Evangelos J. Giamarellos-Bourboulis, Dr. Jesper Eugen-Olsen, and Dr. Jochen Reiser provided expert interpretation of the findings, and provided critical revisions to the manuscript. All coauthors had full access to the data and take responsibility for the integrity and accuracy of the data analysis. All authors approved the final version of the manuscript.

DATA SHARING STATEMENT

Data from ISIC can be made available upon request through a collaborative process. Please contact penegonz@med.umich.edu for additional information.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at <http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020060829/-/DCSupplemental>.

ISIC Investigators.

Supplemental Figure 1. Patient selection flowchart.

Supplemental Figure 2. ROC curves for suPAR and admission eGFR.

Supplemental Table 1. Participating centers and number of patients included in the substudy.

Supplemental Table 2. Clinical characteristics and inflammatory biomarkers stratified by continent of enrollment.

Supplemental Table 3. Clinical characteristics and inflammatory biomarkers stratified by suPAR tertiles.

Supplemental Table 4. Correlation between suPAR and inflammatory biomarkers.

Supplemental Table 5. Determinants of suPAR levels.

Supplemental Table 6. Determinants of incident acute kidney injury and need for dialysis in hospitalized patients with COVID-19 after excluding 25 patients with suPAR levels measured 24–48 hours after admission.

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