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Admission levels of Soluble Urokinase Plasminogen Activator Receptor (suPAR) are Associated with the Development of Severe Complications in Hospitalised COVID-19 Patients: A Prospective Cohort Study

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ABSTRACT

Objective: To examine the association between plasma levels of the soluble urokinase plasminogen activator receptor (suPAR) and the incidence of severe complications of COVID-19.
Methods: 403 RT-PCR-confirmed COVID-19 patients were recruited and prospectively followed-up at a major hospital in the United Arab Emirates. The primary endpoint was time from admission until the development of a composite outcome, including acute respiratory distress syndrome (ARDS), intensive care unit (ICU) admission, or death from any cause. Patients discharged alive were considered as competing events to the primary outcome. Competing risk regression was used to quantify the association between suPAR and the incidence of the primary outcome.
Results: 6.2% of patients experienced ARDS or ICU admission, but none died. Taking into account competing risk, the incidence of the primary outcome was 11.5% (95% confidence interval [CI], 6.7–16.3) in patients with suPAR levels >3.91 ng/mL compared to 2.9% (95% CI, 0.4–5.5) in those with suPAR ≤3.91 ng/mL. Also, an increase by 1 ng/mL in baseline suPAR resulted in a 58% rise in the hazard of developing the primary outcome (hazard ratio 1.6, 95% CI, 1.2–2.1, $p = 0.003$).
Conclusion: suPAR has an excellent prognostic utility in predicting severe complications in hospitalised COVID-19 patients.

Introduction

The novel coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has exerted enormous relentless pressures on the global healthcare systems. As of February 4, 2021, over 102 million people were infected with SARS-CoV-2, and more than 2.2 million have died since the start of the pandemic (WHO, 2020). The true number of cases may even exceed the number of diagnosed cases by more than 10-fold (Havers et al., 2020; Stringhini et al., 2020).

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; ICU, intensive care unit; LDH, lactate dehydrogenase; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; suPAR, soluble urokinase Plasminogen Activator Receptor; UAE, United Arab Emirates.

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Although the vast majority of COVID-19 cases are mild, a significant number of patients need hospitalisation and may require transfer to the intensive care unit (ICU) (Grasselli et al., 2020; Wu and McGoogan, 2020). Most patients with critical COVID-19 illness have underlying morbidity (Petrilli et al., 2020); however, critical illness has also occurred in otherwise healthy individuals. The current standard of care for triaging COVID-19 patients relies on routine clinical and laboratory assessment but offers limited prognostic information (Huang et al., 2020; Grasselli et al., 2020). Therefore, it is essential to accurately triage patients to identify those who may safely be discharged home for self-isolation, those who should be hospitalised, and those at risk of deterioration who may require ICU admission.

The plasmin-plasminogen system, which mediates several cellular pathways, depends on converting plasminogen to plasmin through either tissue-type plasminogen activator or urokinase-type plasminogen activator (Hamie et al., 2018). The urokinase-type plasminogen activator receptor (uPAR) is a glycosyl-phosphatidylinositol-linked membrane protein present on endothelial cells and other cells such as monocytes, activated T lymphocytes, macrophages, and megakaryocytes. The soluble form of uPAR (suPAR) originates from the cleavage and release of the membrane-bound uPAR, and depending on the degree of immune stimulation, can be found in blood, urine and cerebrospinal fluid.

As the urokinase receptor system is a crucial regulator of the intersection between inflammatory, immune, coagulation, and fibrinolytic responses, the role of suPAR has been assessed in the diagnosis, assessment, and prognosis of several infectious, autoimmune, and neoplastic disease processes (Desmedt et al., 2017). Therefore, we conducted this prospective cohort study with the aim of investigating the association between baseline plasma levels of suPAR and the incidence of severe complications in hospitalized COVID-19 patients, including acute respiratory distress syndrome (ARDS), ICU admission, and all-cause mortality.

Materials and methods

Setting

Al Ain Hospital is a 402-bed major public hospital and a designated COVID-19 response centre for the Eastern region of the Emirate of Abu Dhabi, United Arab Emirates (UAE).

Study design

After obtaining written informed consent, patients aged 18 years or above presenting with SARS-CoV-2 infection confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) were consecutively enrolled into the study and prospectively followed up until the occurrence of the primary outcome or hospital discharge. The primary endpoint was defined as the time interval between admission suPAR level and the development of a composite primary outcome including acute respiratory distress syndrome (ARDS), intensive care unit (ICU) admission, or all-cause mortality. ARDS was defined according to the Berlin criteria (ARDS Definition Task Force et al., 2012). Pregnant women and any patients experiencing any event from the primary outcome at presentation were excluded from the study.

Demographic, clinical, and laboratory information

Data on age, sex, ethnicity, height, body weight, body mass index (BMI), smoking status, and pre-existing morbidities were obtained at enrolment. Routine clinical and laboratory parameters were recorded, including blood pressure, respiratory rate, peripheral oxygen saturation, complete and differential blood cell counts, renal function test, serum electrolytes, liver function test, coagulation profile, serum creatine kinase, serum lactate dehydrogenase (LDH), serum ferritin, serum D-dimers, serum C-reactive protein (CRP), and SARS CoV-2 RT-PCR results. Grading of COVID-19 severity on computed tomography images of the chest was based on formal interpretative reports issued by radiologists.

SuPAR measurement

Plasma samples for suPAR were collected within 24 h of admission and were immediately transported to the research laboratory at UAE University and stored at −80 °C pending further analysis.

Plasma suPAR levels were measured using commercial Enzyme-linked Immunosorbent Assay (ELISA) kits (suPARnostic™ assay Virogates, Copenhagen, Denmark). The suPARnostic kit is designed to detect the full-length and cleaved forms of suPAR using a double monoclonal antibody sandwich assay. Plasma (25 μL) was mixed with 225 μL of horseradish peroxidase-labelled detection antibody (mouse anti-human suPAR antibody) in a white mixing plate provided with the kit. A total of 100 μL of this mix was then transferred to duplicate wells of optically clear microwell plate precoated with capture anti-suPAR antibody. The plates were incubated for one hour at room temperature. After washing procedures, 100 μL of the 3,3′,5,5′tetramethylbenzidine substrate were added to each well and incubated for 20 min under dark conditions. Colour development was stopped by adding sulphuric acid. A microplate reader was used to measure absorbance at 450 nm within 30 min of stopping the reaction. A calibration curve was prepared from the suPAR standard, and the plasma concentration of suPAR was determined by interpolation. The lower limit of detection of the assay was 0.1 ng/mL as determined by the manufacturer.

Statistical analyses

Baseline characteristics were summarized using descriptive statistics, including mean and standard deviation (SD) for continuous measures, and frequency tables for categorical variables. We compared categorical variables using the Chi-squared or Fisher's exact tests, and continuous variables using the unpaired t-test or its non-parametric equivalent (Wilcoxon rank sum test) in case the normality assumption is violated.

The primary endpoint was analysed using the time to event analysis (survival analysis). The survival time was defined as the time interval between the suPAR measurement upon hospital admission and the occurrence of any of the events from the primary outcome, i.e., ARDS, ICU admission, or death from any cause. Patients who were either lost to follow-up, withdrew informed consent, or did not experience any of the primary outcome events were right-censored. Patients who were discharged alive from the hospital were considered competing events to the primary endpoint. Survival curves were estimated using the cumulative incidence function that takes competing risks into account. Fine and Gray's proportional hazards model was used to investigate the association between admission suPAR level and the primary outcome adjusting for known risk factors (Fine and Gray, 1999). All statistical analyses were performed using R software (R: The R Project for Statistical Computing, n.d.). P values <0.05 were considered statistically significant.

Sample size calculation

We calculated the sample size using an advanced approach for a multivariable prediction model for binary and time to event outcome (Riley et al., 2019). The minimum sample size was chosen

to satisfy three criteria: (i) small optimism in predictor effect estimates as defined by a global shrinkage factor of ≥ 0.9, (ii) small absolute difference of ≤ 0.05 in the model's apparent and adjusted R^2 and (iii) precise estimation of the overall risk in the population. We used the R package *pmsampsize* to derive sample size. The minimum sample size was estimated to be 384 participants for building a prediction model that meets all the three criteria. We assumed a Cox-Snell R square to be around 0.15.

Ethical considerations

The study was approved by the National COVID-19 Research Ethics Committee (reference: DOH/CVDC/2020/835).

Results

Baseline characteristics

Overall, 403 RT-PCR-confirmed COVID-19 patients were enrolled from May 10, 2020, through August 24, 2020, and followed up until the occurrence of the primary outcome, hospital discharge, or transfer to another healthcare facility (See flowchart for patients selection and follow-up in Figure 1).

Table 1 shows the baseline demographic, clinical, and radiological features of COVID-19 patients. Most patients were males (72.7%, 293/403) and originally of non-Arab Asian ethnicity (65%, 262/403). The mean age at presentation was 49.3 years (SD 11.9).

In total, 6.2% (25/403) of patients experienced the primary outcome (ARDS or ICU admission), 68.7% (277/403) were discharged alive, and 25.1% (101/403) were right-censored because they were still hospitalised at the end of the study or transferred to another healthcare facility. No patient died, was lost to follow-up, or withdrew consent during the study period.

Compared with patients who were discharged, those who experienced the primary outcome had higher prevalence of diabetes mellitus (72.0% vs 44.4%, $p = 0.014$) and hypertension (76.0% vs 47.6%, $p = 0.011$). However, no statistically significant differences were observed with respect to age, sex, BMI, smoking status, education, ethnicity, other morbidities, baseline blood pressure measurements, and peripheral oxygen saturation.

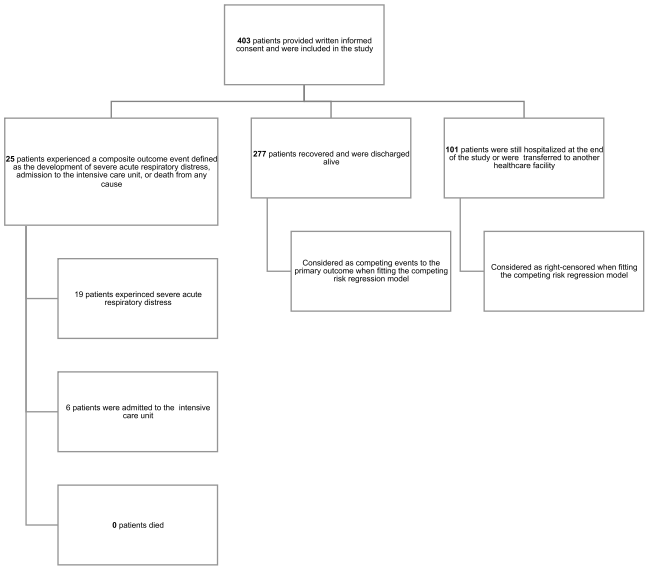

Figure 1. Flowchart showing selection of patients with COVID-19 for inclusion in the study.
Patients aged 18 years or above presenting with SARS-CoV-2 infection confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) were consecutively enrolled into the study and prospectively followed up until the occurrence of the primary outcome or hospital discharge.

Unfavourable laboratory profiles at admission were observed in patients who experienced the primary outcome compared to those who did not (Table 2). These include higher levels of CRP (63.3 ± 55.4 mg/L vs 31.8 ± 39.7 mg/L, $p < 0.001$), serum creatinine (99.0 ± 61.1 μmol/L vs 81.6 ± 64.1 μmol/L, $p = 0.005$), serum LDH (326.3 ± 81.0 mmol/L vs 279.2 ± 122.2 mmol/L, $p = 0.002$), serum ferritin (823.5 ± 584.3 ng/mL vs 556.9 ± 598.1 ng/mL, $p = 0.005$), and neutrophil-to-monocyte ratio (14.1 ± 8.1 vs 8.6 ± 5.2, $p < 0.001$).

The association between plasma suPAR levels and the primary outcome

Patients who experienced the primary outcome had higher baseline plasma suPAR levels than those discharged alive (5.5 ng/mL vs 4.1 ng/mL, $p < 0.0001$). Furthermore, 80% of those who experienced the primary outcome had suPAR levels >3.91 ng/mL compared to 47% in those who did not develop it. The distribution of admission plasma suPAR levels across the two groups is shown in Figure 2.

The incidence of the primary outcome was 7.5% (95% confidence interval [CI], 4.6%–10.3%) after allowing for right-censored observations and competing events. This incidence was 11.5% (95% CI, 6.7%–16.3%) in patients with suPAR levels above the median (i.e. >3.91 ng/mL) compared to 2.9% (95% CI, 0.4%–5.5%) in patients with suPAR levels below the median ($\leq$3.91 ng/mL). Figure 3 displays the cumulative incidence function of the primary outcome according to the median suPAR level of 3.91 ng/mL.

The multivariate Fine-Gray competing risk model was fitted to examine the association between plasma suPAR levels and the incidence of the primary outcome while adjusting for potential risk factors including age, sex, smoking, diabetes, hypertension, BMI, creatinine, C-reactive protein, ferritin, lactate dehydrogenase and the neutrophil-to-monocyte ratio (Table 3). In this model, baseline suPAR levels were significantly associated with the incidence of the primary outcome even after adjusting for potential risk factors. An increase in suPAR level by 1 ng/mL would lead to 58% increased hazard for developing the primary outcome (adjusted hazard ratio [HR] 1.6, 95% CI: 1.2–2.1, $p = 0.003$). Furthermore, inflammatory markers such as CRP or ferritin were not independent predictors of the primary outcome. On the other hand, the neutrophil-to-monocyte ratio remained a significant independent predictor of the primary outcome (HR: 1.6, 95% CI: 1.2–2.1, p <0.001).

Discussion

We investigated the association between suPAR level and the incidence of severe complications in COVID-19 patients, including ARDS, ICU admission, and death from any cause. Our study's results demonstrate that patients who experienced these complications had higher baseline suPAR level than those without. Furthermore, a competing risk analysis showed that the higher the level of suPAR at baseline, the higher the risk of experiencing COVID-19 complications, even after adjusting for potential demographic, clinical and laboratory parameters. More specifically, for every increase of 1 ng/mL in suPAR level at baseline, there is a corresponding increase of 58% in the hazard of experiencing COVID-19 complications.

SuPAR levels have previously been shown to be significantly higher in patients with fatal outcomes than survivors in a myriad of critical illnesses, including systemic inflammatory response syndrome and invasive bacterial bloodstream infections (Hoenigl et al., 2013; Huttunen et al., 2011; Koch et al., 2011; Mölkänen et al.,

Table 1
Demographic, clinical, and radiological features of hospitalised COVID-19 patients.

Characteristic	Total	Primary outcome[a]		*P*-value[c]
		No[b]	Yes	
Number (%)	403 (100)	378 (94)	25 (6)	
Age (years) mean (SD[d])	49.31 (11.93)	49.12 (11.82)	52.16 (13.36)	0.339
Sex *n* (%)				
Female	110 (27.30)	106 (28.04)	4 (16.00)	0.281
Male	293 (72.70)	272 (71.96)	21 (84.00)	
Ethnicity *n* (%)				
Arab	134 (33.25)	126 (33.33)	8 (32.00)	0.774
Non-Arab Asian	262 (65.01)	245 (64.81)	17 (68.00)	
Other	7 (1.74)	7 (1.85)	0 (0.00)	
Body mass index mean (SD)	28.39 (5.25)	28.37 (5.34)	28.68 (3.83)	0.410
Smoking status *n* (%)				
Current or ex-smoker	87 (21.59)	82 (21.69)	5 (20.00)	1.000
Non-smoker	316 (78.41)	296 (78.31)	20 (80.00)	
Diabetes mellitus *n* (%)				
No	217 (53.85)	210 (55.56)	7 (28.00)	0.014
Yes	186 (46.15)	168 (44.44)	18 (72.00)	
Hypertension *n* (%)				
No	204 (50.62)	198 (52.38)	6 (24.00)	0.011
Yes	199 (49.38)	180 (47.62)	19 (76.00)	
Respiratory disease *n* (%)				
No	352 (87.34)	331 (87.57)	21 (84.00)	0.835
Yes	51 (12.66)	47 (12.43)	4 (16.00)	
Cardiovascular disease *n* (%)				
No	252 (62.53)	237 (62.70)	15 (60.00)	0.955
Yes	151 (37.47)	141 (37.30)	10 (40.00)	
Chronic kidney disease *n* (%)				
No	371 (92.06)	349 (92.33)	22 (88.00)	0.694
Yes	32 (7.94)	29 (7.67)	3 (12.00)	
Cancer *n* (%)				
No	361 (89.58)	338 (89.42)	23 (92.00)	0.943
Yes	42 (10.42)	40 (10.58)	2 (8.00)	
Liver disease *n* (%)				
No	375 (93.05)	352 (93.12)	23 (92.00)	1.000
Yes	28 (6.95)	26 (6.88)	2 (8.00)	
Systolic blood pressure mmHg, mean (SD)	130.27 (15.54)	130.34 (15.38)	129.27 (18.12)	0.317
Diastolic blood pressure mmHg, mean (SD)	77.27 (9.64)	77.15 (9.67)	79.14 (9.08)	0.342
Respiratory rate, mean (SD)	18.25 (1.33)	18.21 (1.22)	18.86 (2.38)	0.152
Peripheral oxygen saturation mean (SD)	98.35 (1.48)	98.39 (1.46)	97.68 (1.52)	0.011
Grade of peripheral oxygen saturation *n* (%)				
<90%	1 (0.25)	1 (0.26)	0 (0.00)	0.818
90–94%	5 (1.24)	5 (1.32)	0 (0.00)	
>94%	397 (98.51)	372 (98.41)	25 (100.00)	
Computed tomography scan of the chest *n* (%)				
Mild	109 (27.18)	105 (27.93)	4 (16.00)	0.184
Moderate	274 (68.33)	253 (67.29)	21 (84.00)	
Severe	18 (4.49)	18 (4.79)	0 (0.00)	

[a] Includes the development of acute respiratory distress syndrome, intensive care unit admission, or death from any cause.
[b] Includes patients who were right-censored or were discharged alive.
[c] Categorical variables were compared using the Chi-squared or Fisher's exact tests, and continuous variables were compared using the unpaired t-test or the Wilcoxon rank-sum test.
[d] Standard deviation.

2011; Raggam et al., 2014; Wittenhagen et al., 2004). They were also found to be immune mediators for developing acute and chronic kidney disease, and more recently predictive of in-hospital acute kidney injury and the need for dialysis in COVID-19 hospitalised patients (Azam et al., 2020; Hayek et al., 2020, 2015). A potential role for suPAR in triaging patients attending emergency departments has been highlighted (Schultz et al., 2019; Uusitalo-Seppälä et al., 2012). It is essential to emphasise that suPAR levels not only reflect underlying infections but also are influenced by pre-existing comorbidities like diabetes mellitus, chronic inflammation and others. Thus, suPAR may more or less reflect the overall susceptibility profile of an individual for developing severe diseases rather than only diagnose the acute event, such as COVID-19 or other infections. For triage purposes, it is essential to categorize the patient based on chronic conditions as well as based on the acute event in various risk categories. suPAR may be a promising biomarker in this setting as currently only very few COVID-19 triage scores are published (Giannella et al., 2020) and are often based on retrospective study designs, often including various variables that are either difficult to assess (e.g., SOFA Score) or have limited availability (e.g., interleukin testing). With suPAR testing, we may overcome at least some of these limitations and provide a single, simple and fast biomarker for risk stratification in COVID-19 patients.

Our study is one of a few investigating the association between suPAR levels and COVID-19 complications. Recently, a small study of 57 COVID-19 patients conducted in Greece showed that a suPAR serum level ≥6 ng/mL was the best predictor for the development of severe respiratory failure, defined as PO_2/FiO_2 ratio <150 requiring mechanical ventilation or continuous positive airway pressure, and outperformed established markers like CRP (Rovina et al., 2020). In our study, we observed similar findings, with suPAR

Table 2
Laboratory features of hospitalised COVID-19 patients.

Characteristic	Total	Primary Outcome[a] No[b]	*P*-value[c] Yes	Characteristic
Plasma suPAR[d] level ng/mL mean (SD[e])	4.16 (1.67)	4.07 (1.62)	5.51 (1.80)	<0.001
Serum creatinine μmol/L mean (SD)	82.65 (63.96)	81.59 (64.07)	99.04 (61.12)	0.005
Serum ferritin ng/mL mean (SD)	573.72 (600.04)	556.94 (598.11)	823.48 (584.28)	0.005
Serum lactate dehydrogenase mmol/L mean (SD)	282.08 (120.57)	279.17 (122.25)	326.35 (80.96)	0.002
Neutrophil-to-monocyte ratio mean (SD)	8.96 (5.58)	8.63 (5.22)	14.11 (8.14)	<0.001
Serum C-reactive protein, mg/L mean (SD)	33.71 (41.46)	31.80 (39.75)	63.30 (55.37)	<0.001
Serum D-Dimers mg/L mean (SD)	0.66 (0.91)	0.68 (0.94)	0.50 (0.45)	0.348
Serum potassium mmol/L mean (SD)	4.01 (0.46)	4.01 (0.46)	3.88 (0.44)	0.131
Serum sodium mmol/L mean (SD)	137.48 (3.72)	137.56 (3.74)	136.29 (3.32)	0.055
Serum urea mmol/L mean (SD)	4.46 (2.38)	4.41 (2.35)	5.35 (2.64)	0.033
Total white blood cells $\times 10^9$/L mean (SD)	6.27 (2.33)	6.28 (2.33)	6.13 (2.26)	0.670

[a] Includes the development of development of acute respiratory distress syndrome, intensive care unit admission, or death from any cause.
[b] Includes patients who were right-censored or were discharged alive.
[c] Categorical variables were compared using the Chi-squared or Fisher's exact tests, and continuous variables were compared using the unpaired t-test or the Wilcoxon rank-sum test.
[d] Soluble urokinase plasminogen activator receptor.
[e] Standard deviation.

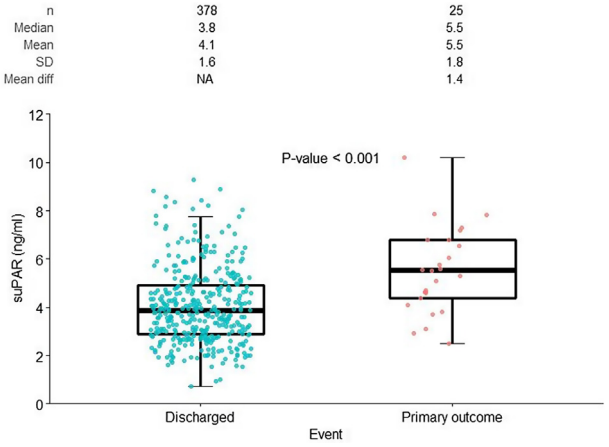

Figure 2. The boxplot of baseline plasma levels of the soluble urokinase plasminogen activator receptor (suPAR) in COVID-19 patients according to the primary outcome.
The primary outcome is the development of acute respiratory distress syndrome, admission to intensive care unit, or death from any cause. The p-value provided corresponds to the unpaired t-test comparing the average level of suPAR between those who experienced the primary outcome and those who did not.

being the dominant predictor for severe COVID-19 associated complications; however, absolute plasma suPAR levels were lower in our study. This may be explained by the younger age in our cohort compared to the Greek study cohort and the consequently lower proportion of underlying disease associated with elevated baseline suPAR levels. Additionally, a logistic regression model rather than a competing risk regression modelling was used to investigate the association.

We showed that COVID-19 patients with plasma suPAR levels >3.9 ng/mL had unfavourable serum creatinine, CRP, ferritin, LDH, and neutrophil-to-monocyte ratio profiles. However, only the neutrophil-to-monocyte ratio remained a significant independent predictor of the primary outcome in the multivariate competing risk regression model. It has been observed that lymphocyte and monocyte populations decrease while neutrophil counts increase in COVID-19 (Zhao et al., 2020), and more recent research showed a link between neutrophil-to-monocyte ratio and COVID-19 in-hospital mortality (Rizo-Téllez et al., 2020).

This study's major strength is the relatively large number of suPAR samples collected (compared to other studies) and the inclusion of information on a broad range of demographic, clinical and laboratory characteristics in the multivariate regression model. The limitation of this study is the relatively moderate number of events composing the primary outcome. This was

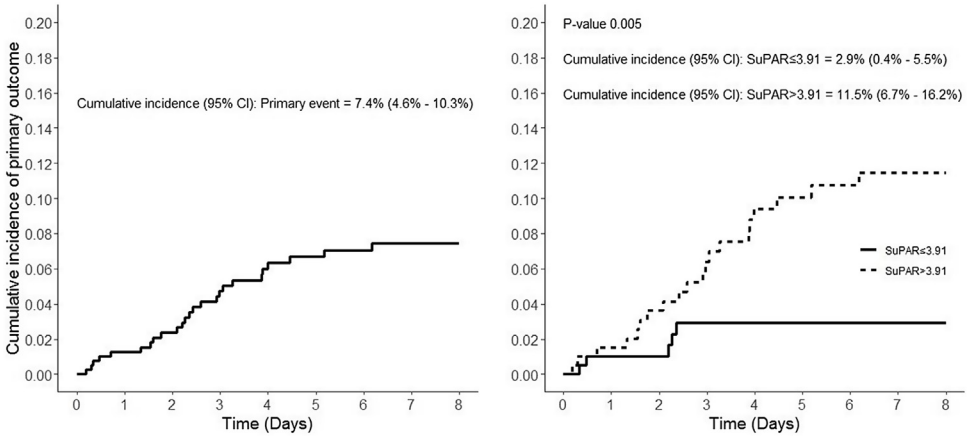

Figure 3. The cumulative incidence of the primary outcome stratified by the median soluble urokinase Plasminogen Activator Receptor (suPAR) in hospitalized COVID-19 patients.
The primary outcome is the development of acute respiratory distress syndrome, admission to intensive care unit, or death from any cause. The cumulative incidence function takes into account recovery as a competing risk. The p-value provided in the right-hand plot corresponds to the log rank test accounting for competing risk.

Table 3
The multivariate Fine-Gray competing risk regression model for predicting the primary outcome for COVID-19 complications consisting of the development of acute respiratory syndrome, intensive care admission, or death from any cause.

Characteristic	Hazard ratio (95% confidence interval)	*P*-value
Age (years)	0.81 (0.48–1.35)	0.41
Sex		
Male	Reference	–
Female	0.71 (0.34–1.46)	0.35
Body mass index	1.06 (0.68–1.65)	0.8
Smoking status		
Non-smoker	Reference	–
Current or ex-smoker	0.74 (0.46–1.19)	0.21
Diabetes mellitus		
No	Reference	–
Yes	1.66 (0.92–2.99)	0.093
Hypertension		
No	Reference	–
Yes	1.34 (0.67–2.71)	0.41
Serum lactate dehydrogenase	1.13 (0.83–1.55)	0.44
Serum ferritin	1.16 (0.83–1.61)	0.38
Serum C-reactive protein	1.08 (0.79–1.47)	0.64
Neutrophil-to-monocytes ratio	1.6 (1.24–2.06)	<0.001
Soluble urokinase Plasminogen Activator Receptor (suPAR)	1.58 (1.17–2.14)	0.003

because we included any patient admitted to the hospital for COVID-19 regardless of disease severity at baseline. We learned over the last months that hospital admission strategies varied significantly between countries. If we excluded less severe patients from the study, the frequency of the primary outcome would probably have increased. Still, the purpose of this study was to investigate suPAR as a prognostic biomarker in people admitted to the hospital, hence including all hospitalized patients in the analysis is important for the applicability of this biomarker. As a consequence, we observed that suPAR levels in mild COVID-19 cases are much lower than those found in severe cases.

Conclusions

We found plasma suPAR and neutrophil-to-monocyte ratio to be significantly associated with severe COVID-19 complications. Future studies might consider integrating plasma suPAR and other clinical and laboratory biomarkers into prognostic models to improve risk prediction accuracy, allowing them to perform treatment interventions based on the given risk for severe complications. A reliable prediction tool would allow more research into individualised treatment and better utilisation and hospital resources management.

Ethics approval and consent to participate

The United Arab Emirates' National COVID-19 Research Ethics Committee approved the study (DOH/CVDC/2020/835, date: 29/04/2020).

Consent for publication

Not applicable as no identifiable personal information is being presented.

Availability of data and materials

The data underlying this article are presented within the manuscript.

Competing interests

The authors have no conflicts of interests to declare.

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Authors' contribution

AO and ARA designed the study and coordinated data collection. AO and FA developed and implemented the data capture system using RedCap software. ZB, JP and HS contributed to the study design. HG, SK, SA, YK, FK recruited study participants and coordinated data collection. JG performed suPAR measurements. AO and AS performed all statistical analysis. AO drafted the first version of the manuscript. AO, ARA, ZB, JP and HS contributed to manuscript writing. All authors read and approved the final version of the manuscript. AO is the guarantor of the study.

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