ORIGINAL ARTICLE

Circulating suPAR associates with severity and in-hospital progression of COVID-19

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Abstract

Background: COVID-19 disease progression is characterized by hyperinflammation and risk stratification may aid in early aggressive treatment and advanced planning. The aim of this study was to assess whether suPAR and other markers measured at hospital admission can predict the severity of COVID-19.

Methods: The primary outcome measure in this international, multi-centre, prospective, observational study with adult patients hospitalized primarily for COVID-19 was the association of WHO Clinical Progression Scale (WHO-CPS) with suPAR, ferritin, CRP, albumin, LDH, eGFR, age, procalcitonin, and interleukin-6. Admission plasma suPAR levels were determined using the suPARnostic® ELISA and suPARnostic® Turbilatex assays.

Results: Seven hundred and sixty-seven patients, 440 (57.4%) males and 327 (42.6%) females, were included with a median age of 64 years. Log-suPAR levels significantly correlated with WHO-CPS score, with each doubling of suPAR increasing the score by one point ($p < .001$). All the other markers were also correlated with WHO-CPS score. Admission suPAR levels were significantly lower

in survivors (7.10 vs. 9.63, 95% CI 1.47–3.59, $p < .001$). A linear model (SALGA) including suPAR, serum albumin, serum lactate dehydrogenase, eGFR, and age can best estimate the WHO-CPS score and survival. Combining all five parameters in the SALGA model can improve the accuracy of discrimination with an AUC of 0.80 (95% CI: 0.759–0.836).

Conclusions: suPAR levels significantly correlated with WHO-CPS score, with each doubling of suPAR increasing the score by one point. The SALGA model may serve as a quick tool for predicting disease severity and survival at admission.

KEYWORDS
COVID-19, outcome, suPAR, WHO Clinical Progression Scale

1 | INTRODUCTION

Two years ago, the coronavirus SARS-CoV-2 was identified as the cause of an outbreak of severe acute respiratory illness (COVID-19) in Wuhan, China. Today, the infection has spread to millions worldwide. The novel coronavirus causes a wide spectrum of clinical manifestations, with a large fraction of patients developing a short period of mild or moderate clinical illness, while a small but substantial number of patients will experience severe pneumonia and acute respiratory distress syndrome.[1,2] Until now, several biomarkers have been studied in COVID-19, but their ability to discriminate risk and their clinical utility as triage tools needs further investigation.

The soluble urokinase plasminogen activator receptor (suPAR) is a protein found in blood and other body fluids. It is the soluble form of the cell membrane–bound protein urokinase plasminogen activator receptor (uPAR).[3-5] When expressed on the cell surface membrane, uPAR is involved in several critical cellular processes by regulating extracellular matrix degradation, such as proliferation, migration and adhesion, and in the inflammatory response.[3] Proteolytic cleavage of uPAR releases the soluble form, suPAR, to the bloodstream, especially upon an inflammatory stimulus. Although suPAR is generally low in healthy individuals, it is involved in numerous pathological inflammatory pathways and is elevated across a spectrum of diseases,[3,6-8] making it applicable as a prognostic marker. Indeed, the predictive ability of suPAR has been reported by many authors to be equal to or better than other scoring systems in patients admitted to the hospital.[4-7] These cumulative data suggest that high suPAR level at admission is an early marker of severe disease development.[8] COVID-19 is recognized as a hyperinflammatory syndrome with aberrant immune activation which may lead to cytokine storm and organ damage.[9] Research so far has shown that the early identification of COVID-19 individuals at low or high risk of serious illness may improve patient stratification, but, currently, admission blood biomarkers have only moderate predictive value for COVID-19 outcome and decision making in the clinical setting.[10] suPAR seems extremely promising as a COVID-19 prognostic marker and may assist in the early selection of patients who can be discharged and continue self-isolation at home or must be admitted to the hospital and/or intensive care unit.[10-13] In order to investigate the prognostic ability of suPAR in COVID-19, we designed the SPARCOL study to assess whether suPAR measured at hospital admission is associated with illness severity in adult patients hospitalized primarily for COVID-19.

2 | MATERIALS AND METHODS

2.1 | The SuPAR in adult patients with COVID-19 (SPARCOL) study

The SuPAR in Adult Patients With COVID-19 (SPARCOL) was an international, multi-centre, prospective, observational study (ClinicalTrials.gov Identifier: NCT04590794) whose primary aim was to characterize suPAR and its association with acute respiratory failure, admission to intensive care unit, organ injury and survival of patients with COVID-19. The study was designed in accordance with the Declaration of Helsinki and has been approved by the Institutional Review Board of the University Hospital of Larisa, under the reference number 17543. Participating centres included the following: University of Thessaly, Larisa, Greece; the Eginition University Hospital, Athens, Greece; the Hippokration University Hospital, Athens, Greece; the Hospital General Universitario Santa Lucía, Cartagena, Spain; the Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; the Hospital General Universitario Reina Sofía, Murcia, Spain; and the Copenhagen University Hospital Hvidovre, Hvidovre, Denmark. Patients presenting with

a positive SARS-CoV-2 test from November 1st 2020 to June 1st 2021 were systematically screened and enrolled if qualified.

The study was performed according to national and international guidelines. Institutional review board approval and consent procedures were obtained separately at each site according to local institutional policies. Reporting of the study conforms to broad EQUATOR guidelines.[14]

2.2 | Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) adult (≥18 years old) patients hospitalized primarily for COVID-19; (2) a confirmed SARS-CoV-2 infection diagnosed through reverse transcriptase polymerase chain reaction test of nasopharyngeal or oropharyngeal samples; and (3) at least one blood sample collected at admission and stored for biomarker testing. Patients with confirmed SARS-CoV-2 infection who were not primarily admitted for COVID-19 and patients with incomplete data were excluded.

2.3 | Blood sampling and laboratory measurements

In all patients, venous blood samples for biochemical analysis, complete blood count, and coagulation markers, including D-dimer, were collected at admission and analyzed in the participating laboratories. For measurement of suPAR, blood samples collected in tubes containing EDTA K3 as anticoagulant were centrifuged and plasma was subsequently frozen and stored at −80°C until testing.

Plasma suPAR levels were determined using the suPAR-nostic® ELISA (ViroGates, Denmark), which is a simplified double monoclonal antibody sandwich ELISA, or suPAR-nostic® TurbiLatex test (ViroGates, Denmark), which is a latex particle-enhanced turbidimetric immunoassay, by using Cobas analysers (Roche Diagnostics, Germany). The suPARnostic® TurbiLatex test is calibrated against an internal control verified with suPARnostic® ELISA and, according to manufacturer, the results are transferable between both assays. The suPARnostic® ELISA has a detection limit and quantification limit of 0.4 ng/ml, and a total coefficient of variation (imprecision) ranging from 2.3% to 6.0% for suPAR levels from 7.2 ng/ml to 2.3 ng/ml, as determined by the assay manufacturer. The suPARnostic® TurbiLatex assay has a detection and quantification limit of 1.20 ng/ml, and total coefficient of variation ranges from 3.5% to 3.9% for suPAR levels from 3.4 to 10.2 ng/ml, according to the manufacturer's data.

2.4 | Outcomes

The primary outcome measure was the association of WHO Clinical Progression Scale (WHO-CPS) with suPAR and other disease predictors. Secondary outcome measure was survival at hospital discharge.

2.5 | Data collection, monitoring and management

Manual chart review was used to gather details of patients who were followed until the 30th day post-discharge or death. Data analysis was based on predefined data points on a prospective data collection form. The staff was blinded to measurements until the end of the study and all data were analyzed. Clinical monitoring throughout the study was performed to maximize protocol adherence, while an independent Data and Safety Monitoring research staff monitored safety, ethical, and scientific aspects of the study. Data collection included patients' demographic details and medical history, comorbidities, medications, laboratory test results, suPAR level, hospitalization course, and outcomes. The goal of the clinical data management plan was to provide high-quality data by adopting standardized procedures to minimize the number of errors and missing data, and, consequently, to generate an accurate database for analysis. Remote monitoring was performed to signal early aberrant patterns, issues with consistency, credibility, and other anomalies. Any missing and outlier data values were individually revised and completed or corrected whenever possible.

2.6 | Statistical analysis

WHO COVID-19 Clinical Progression Scale score was used as outcome score and was computed according to the criteria set forward by the WHO Working Group on the Clinical Characterization and Management of COVID-19 infection.[15] For the association of WHO-CPS score with measured biomarkers, we used ordinary least squares linear regression. Moreover, F-tests were utilized to check whether the addition of suPAR improved the previous models. Because suPAR level distribution was heavily skewed, suPAR data underwent a logarithmic transformation (with base 2) and log2 suPAR was used in all model computations. To assess whether the combined use of suPAR and the other studied factors increases the accuracy of the model, backward stepwise linear regression techniques were used. Mann-Whitney test was used to assess differences in different measurement levels. Spearman's method was used to correlate suPAR

levels and different clinical characteristics and laboratory results. The Benjamini-Hochberg false discovery rate correction was applied in the resulting p values to account for the multiple numbers of tests. Adjusted p-values less than 0.05 were deemed significant. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic value of the different models. Statistical analysis was performed using R v4.1. p-values less than 0.05 were deemed significant.

3 | RESULTS

Overall, 767 patients, 440 (57.4%) males and 327 (42.6%) females, were included in the study. Median age was 64 years, while 376 (49%) patients were older than 65 years (Table 1 and Table S1). During the course of hospitalization, 613 (79.9%) patients were discharged and 154 (20.1%) patients died. Admission blood count and biochemical profile are depicted according to survival in Table S2 and according to WHO-CPS score in Table S3. Because the study included only hospitalized individuals, all patients had a minimum score of 4 in the WHO-CPS. No one had a score of 9 (Table S4) because all patients needing dialysis or extracorporeal membrane oxygenation ultimately died.

Twenty-four patients with WHO-CPS score 8 [suPAR 7.55 ng/ml (IQR 5.4–9.75)] and 40 patients with WHO-CPS score 10 [suPAR 8 ng/ml (IQR 5.6–11.2)] received vasopressors. Also, 202 (26.3%) patients were admitted in the ICU [suPAR 8.4 ng/ml (IQR 5.7–11.3)], while 168 (22%) patients were intubated. Fifty-one (6.6%) patients had arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2) ratio less than 200 [suPAR 6.9 ng/ml (IQR 5.35–8.65)].

3.1 | Primary outcome

Log-suPAR levels significantly correlated with WHO-CPS score. For each doubling of suPAR (i.e., one unit increase in log-suPAR), an increase of one point in the score was expected ($p < .001$). suPAR levels markedly increased with increasing WHO-CPS score from 4 to 7 (representing mechanical ventilation), but maintained a constant level in scores 7, 8 (mechanical ventilation with $PaO_2/FiO_2 < 150$), and 10 (death) (Figure 1).

Besides suPAR, six other predictors were tested separately for association with WHO-CPS score using linear regression. Those predictors were serum ferritin, C-reactive protein (CRP), serum albumin, serum lactate

TABLE 1 Clinical characteristics at admission and duration of hospitalization

	Median	1st Quartile	3rd Quartile
Age (years)	64	53	73
Body mass index (kg/m^2)	27	25	29
Temperature (°C)	38	37.7	39
Glasgow Coma Scale	15	14	15
Systolic arterial pressure (mmHg)	129	116	140
Diastolic arterial pressure (mmHg)	75	65	73
Mean arterial pressure (mmHg)	92.33	81	100
Heart rate (bmp)	81	67	95
Respiratory rate (per min)	24	21	27
SpO$_2$ (%)	86	83	89
FiO$_2$ (%)	21	21	21
SaO$_2$ (%)	91	87	94
pH	7.48	7.45	7.51
PaO$_2$ (mmHg)	60	52	67
PaCO$_2$ (mmHg)	33	31	35
HCO$_3$ (mmol/L)	25.8	24	28
APACHE II	6	5	7
SOFA	2	2	3
ICU length of stay (d)	13	7	20
Hospital length of stay (d)	10	6	17

Note: Abbreviations: FiO$_2$, fraction of inspired oxygen; HCO$_3$, bicarbonate; ICU, intensive care unit; PaO$_2$, arterial partial pressure of oxygen; PaCO$_2$, arterial partial pressure of carbon dioxide; SaO$_2$, arterial oxygen saturation; SpO$_2$, peripheral capillary oxygen saturation.

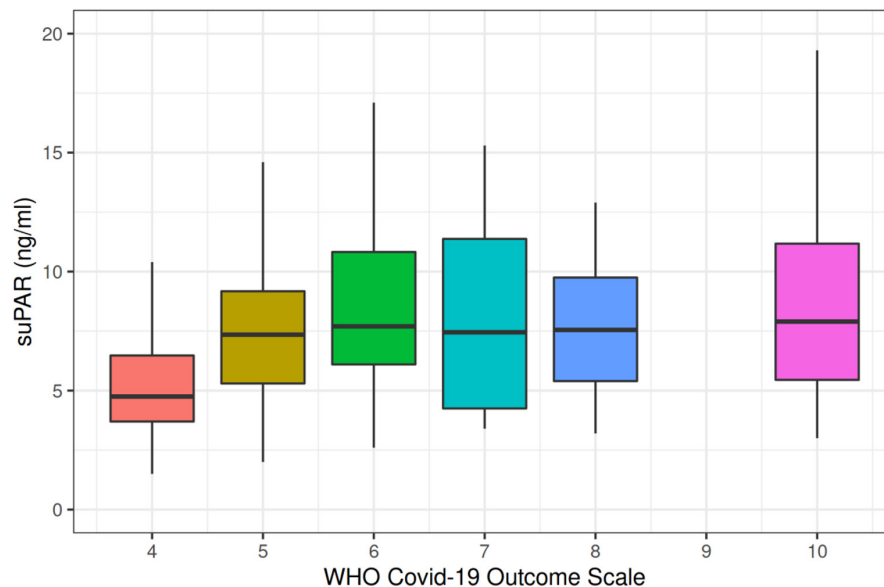**FIGURE 1** Box plot of suPAR levels categorized by WHO COVID-19 Outcome scale score

TABLE 2 Linear regression models with WHO-CPS score as dependent variable

	Beta coefficient	p-value
Ferritin (ng/ml)	1.588×10^{-4}	.016
CRP (mg/dl)	0.0648	<.001
Albumin (g/dl)	−1.058	<.001
LDH (IU/L)	0.00343	<.001
eGFR (ml/min/1.73 m^2)	−0.0269	<.001
Age (Years)	0.0478	<.001
Procalcitonin (ng/ml) ($n = 248$)	1.055	.001
IL−6 (pg/ml) ($n = 254$)	0.00292	<.001

Note: Abbreviations: CPR, c-reactive protein; LDH, lactate dehydrogenase; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6.

dehydrogenase, estimated glomerular filtration rate (eGFR, computed with CKD-EPI equation), and age. All these predictors had a statistically significant corellation with the WHO-CPS score, as presented in Table 2. Procalcitonin and interleukin-6 levels were also assessed, but only in a subset of patients with complete data, and were significantly associated with WHO-CPS score (Table 2).

To examine the usefulness of suPAR as an additional parameter in the aforementioned predictors, we added the log-suPAR and compared the new models with the respective predictors. As depicted in Table 3, the addition of suPAR made a statistically significant improvement in all models. Moreover, to investigate whether the use of all or a subgroup of the above parameters can better estimate the WHO-CPS score, we constructed a linear model including all terms and sequentially removed the non-significant terms. The final model (named SALGA)

contains as terms suPAR, serum albumin, serum lactate dehydrogenase, eGFR, and age (Table 4).

Subsequently, ROC curve analysis was performed to evaluate survival prediction models after hospital admission. Combining all five parameters in the SALGA model can improve the accuracy of discrimination (AUC=0.80, 95% CI: 0.759–0.836; Figure 2). Additionally, the combined model can predict the need for oxygen therapy (AUC=0.78, 95% CI 0.744–0.821; Figure 3) and mechanical ventilation (AUC = 0.77, 95% CI 0.726–0.803; Figure S1).

3.2 | Secondary outcome

We investigated the association of admission suPAR levels with overall mortality. Admission suPAR levels were significantly lower in patients who survived compared to those who died (5.8 ng/ml vs. 8.2 ng/ml). The difference was statistically significant ($p < .001$).

4 | DISCUSSION

In this international, multi-centre, prospective, observational study with 767 COVID-19 patients, suPAR levels significantly correlated with WHO-CPS score; for each doubling of suPAR, an increase of one point in the score was expected. Also, ferritin, CRP, albumin, LDH, eGFR, age, procalcitonin, and interleukin-6 were associated with WHO-CPS score, but the addition of suPAR significantly improved their predictive ability. The present study clearly shows that suPAR is associated with severe disease, while the SALGA model can best estimate the WHO-CPS score and may be used as a quick tool at admission

	Residual sum of squares	Difference of Sum of squares	*F*-statistic	*p*-value
Ferritin	3813.21			
+ log-suPAR	3425.16	388.05	81.12	<.001
CRP	3701.48			
+ log-suPAR	3423.44	278.04	58.88	<.001
Albumin	3760.15			
+ log-suPAR	3462.15	298	64.64	<.001
LDH	3822.39			
+ log-suPAR	3506.47	315.92	68.2	<.001
eGFR	3644.76			
+ log-suPAR	3413.74	231.02	51.5	<.001
Age	3671.86			
+ log-suPAR	3413.83	258.02	57.67	<.001
Procalcitonin	652.68			
+ log-suPAR	604.45	48.23	19.55	<.001
IL-6	685.08			
+ log-suPAR	630.34	54.74	21.8	<.001

Note: Abbreviations: CPR, c-reactive protein; LDH, lactate dehydrogenase; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6.

TABLE 4 Linear regression model (SALGA) for WHO-CPS score

	Coefficient	*p*-value
Log-suPAR (ng/ml)	0.488	<.001
Age (years)	0.02	.001
LDH (IU/L)	0.002	<.001
eGFR (ml/min/1.73 m^2)	−0.013	<.001
Albumin (g/dl)	−0.434	.002

Note: Abbreviations: LDH, lactate dehydrogenase; eGFR, estimated glomerular filtration rate.
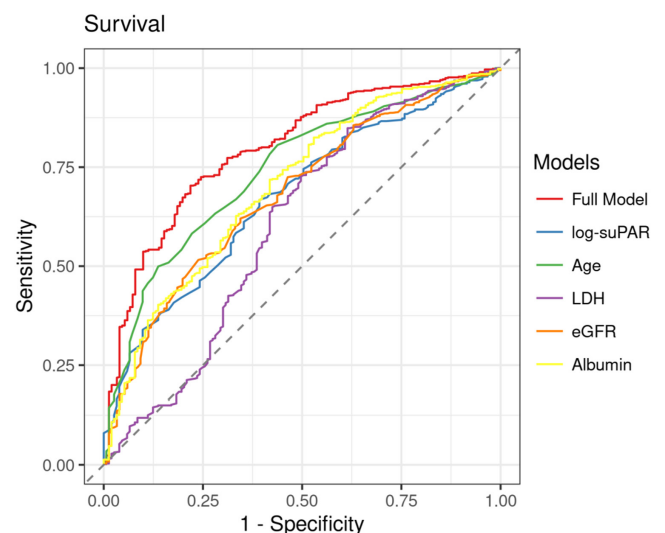

FIGURE 2 Receiver operating characteristic curves for prediction of survival after hospital admission. Different curves present the ability of five independent variables and their combined model to predict survival

for predicting disease progression in hospitalized patients with COVID-19.

Soluble urokinase plasminogen activator receptor is a signalling glycoprotein and a marker of the level of chronic systemic inflammation. It is an immune mediator involved in numerous physiological and pathological pathways and its levels in circulation reflect the ability of the patient to cope with diseases.[16,17] An increase in suPAR levels can be triggered by various stimuli, including SARS-CoV-2, and suPAR is highly expressed in lung tissue,[18] which may be critical for disease progression. Indeed, suPAR has been recently implicated in the evolution of COVID-19 and its associated complications[12,19,20] and represents the inflammatory biomarker that is most reflective of the hyperinflammatory state in patients with comorbidities.[3,12,21]

The WHO-CPS score was developed in response to the needs of the rapidly evolving COVID-19 outbreak,

including a measure of viral burden, a measure of patient survival, and a measure of patient progression.[15] Nevertheless, the evidence on the association of suPAR with the WHO-CPS is scarce. In the SAVE-MORE double-blind, randomized controlled trial that evaluated the efficacy and safety of anakinra in patients with COVID-19 and suPAR ≥6 ng/ml, 57.2% of patients with severe pneumonia had a plasma suPAR ≥6 ng/ml and those who were randomized to Anakinra had better 28-day
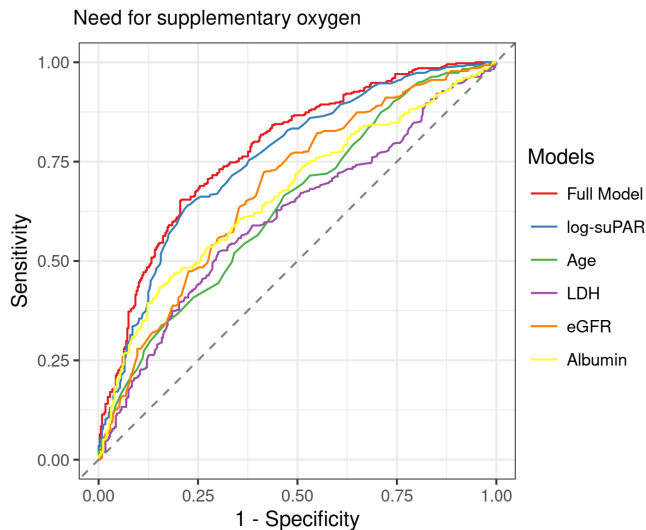
FIGURE 3 Receiver operating characteristic curves for prediction of the need for supplemental oxygen therapy after hospital admission. Different curves present the ability of five independent variables and their combined model to predict the need of oxygen therapy

WHO-CPS score compared to placebo. However, the baseline correlation between suPAR and WHO-CPS was not investigated.[22] In the present multi-centre study, which is one of the largest studies assessing suPAR in COVID-19, suPAR levels significantly correlated with WHO-CPS score, with each doubling of suPAR increasing the score by one point. Also, admission suPAR levels were significantly lower in survivors. Considering that COVID-19 has a wide spectrum of clinical manifestations and predicting the course of disease and outcome is difficult, the use of suPAR appears promising in identifying patients with severe disease progression.

To date, several biomarker studies have been published, but the clinical utility of the tested biomarkers in predicting COVID-19 mortality needs further investigation. The present study revealed a significant association between the tested clinical and biochemical prognostic markers, i.e., ferritin, CRP, albumin, LDH, eGFR, age, procalcitonin, and interleukin-6, and WHO-CPS score. These markers are commonly measured in clinical practice to estimate the prognosis and clinical course of patients with COVID-19, but their use is based on small studies that have measured them at inconsistent time points during the hospitalization and have examined them in association with mortality alone or respiratory failure as the endpoint.[23-25] On the contrary, the important characteristics of suPAR favour its use in patients with COVID-19. suPAR is a key regulator of inflammation and immunity and its levels are higher in patients with known risk factors for severe COVID-19.[3,8,18,21] In addition, suPAR levels may improve risk stratification of critically ill patients, especially

in those with moderate organ dysfunction (SOFA score ≤7).[26] The median SOFA score in our study was ≤7 as well, but we included both critically and non-critically ill patients.

It is worthy of note that suPAR is not an acute phase reactant, has no circadian variation, and remains stable during episodes of acute stress.[3,8,17] Based on the specific characteristics of suPAR and the other markers, a multi-level approach using key clinical and laboratory data could improve prediction at hospital admission.[27] Thus, we constructed the SALGA model that can best estimate the WHO-CPS score. The SALGA includes suPAR, serum albumin, serum lactate dehydrogenase, eGFR, and age, which were identified as the most significant parameters. The SALGA model addresses an unmet need in the COVID-19 care continuum and could serve as a quick tool at admission for predicting the severity of illness and disease progression. The available point-of-care bedside suPAR testing contributes to a quick triage.

Although the SALGA model predicted the need for mechanical ventilation and oxygen therapy in hospitalized patients, our findings seem applicable in the out-of-hospital setting as well. A recent study funded by Médecins Sans Frontières (MSF) evaluated a clinical prediction model including age, sex, peripheral oxygen saturation, and suPAR to assist with the assessment of patients with COVID-19, categorized by the WHO-CPS, in high-patient-throughput resource-limited settings.[28] The primary outcome was development of oxygen requirement within 14 days of enrolment, and the authors found suPAR and interleukin-6 to be the best predictors for need of oxygen. The combination of prehospital MSF model with the in-hospital SALGA model may prove the best strategy to decompress overstretched healthcare systems and reduce healthcare costs by supporting clinicians to identify which patients with COVID-19 will deteriorate throughout the continuum of the disease. The weekly number of new hospitalizations due to COVID-19 and the capability of the Omicron variant to evade the protective effects of antibodies elicited by vaccination or natural infection illustrate the potential for widespread impact of this combination, especially in lower- and middle-income countries.

The present study has several strengths. It is a large multi-centre study that relied on collection of clinical, laboratory and outcome data throughout the COVID-19 hospitalization. Data collection was systematic and all centres included consecutive patients, thus limiting the risk of selection bias. Our sample was limited to patients primarily hospitalized for COVID-19, and we included a diverse population from different COVID-19 waves. The major limitation of the present study is its observational nature. Despite the careful data collection and analysis, it may be not possible to fully account for all potential confounders.

5 | CONCLUSIONS

suPAR levels significantly correlated with WHO-CPS score, with each doubling of suPAR increasing the score by one point. The SALGA model can best estimate the WHO-CPS score and could serve as a quick tool at admission for predicting the severity of illness and disease progression in patients with COVID-19.

CONFLICT OF INTEREST
AC, AS, NP, EL, KT, AP, AM, NN, MM, DR, EBM, ICL, LGDGR, KG and IP report no conflicts of interest. JEO is a co-founder, shareholder and CSO of ViroGates A/S and is mentioned inventor on patients on suPAR owned by Copenhagen University Hospital Hvidovre, Denmark.

AUTHOR CONTRIBUTIONS
Conceptualization: AC. Data curation: AC, AS, NP, EL, KT, AP, AM, NN, MM, DR, EBM, ICL, LGDGR, JEO, KG, IP. Formal analysis: AC, IP, NP, AS. Methodology: AC, IP, EL, JEO. Project administration: AC. Visualization: AC, NP, IP, JEO. Writing—original draft: AC. Writing—review and editing: AC, AS, NP, EL, KT, AP, AM, NN, MM, DR, EBM, ICL, LGDGR, JEO, KG, IP.

PATIENT CONSENT FOR PUBLICATION
Not applicable.

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APPENDIX

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