Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Soluble Urokinase Plasminogen Activator Receptor as a Decision Marker for Early Discharge of Patients with COVID-19 Symptoms in the Emergency Department

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□ **Abstract—Background: Severe acute respiratory syndrome coronavirus 2 (The Covid-19 pandemic) strains health care capacity. Better risk stratification, with discharge of patients with a predicted mild disease trajectory, can ease this burden. Elevated blood-soluble urokinase plasminogen activator receptor (suPAR) has previously been shown to be associated with risk of intubation in confirmed COVID-19 patients. Objective: To evaluate whether point-of-care measures of suPAR in patients presenting to the emergency department (ED) with symptoms of COVID-19 can identify patients that can be safely discharged. Methods: Observational cohort study including all patients in the ED with symptoms of COVID-19 from March 19 to April 3, 2020. SuPAR was measured at first presentation. Review of electronic patient records 14 days after admission was used to assess disease trajectory. Primary endpoints were mild, moderate, severe, or very severe trajectory. The predictive value of suPAR, National Early Warning Score (NEWS), C-reactive protein (CRP), and duration of symptoms was calculated using receiver operating characteristics (ROC). Results: Of 386 patients, 171 (44%) had a mild disease trajectory, 79 (20%) a moderate, 63 (16%) a severe, and 73 (19%) a very severe disease trajectory. Low suPAR was a strong marker of mild disease trajectory. Results suggest a cut-off for discharge for suPAR < 2.0 ng/mL if suPAR is used as a single parameter, and <3.0 ng/mL when combined with NEWS ≤ 4 and CRP < 10 mg/L. Conclusion: suPAR is a potential biomarker for triage and safe early discharge of patients with COVID-19 symptoms in the ED. suPAR can be used even before SARS-CoV-2 status is known. © 2021 Elsevier Inc. All rights reserved.**

□ **Keywords—Covid-19; ED overcrowding; Triage; Early discharge; Point-of-care test; suPAR; CRP; Early warning score**

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic places extraordinary pressure on the health care system and especially, hospital bed capacity (1,2). For optimal utilization of hospital resources, biomarkers of disease severity are urgently needed to ensure safe and quick discharge of patients who will not develop severe disease. Several routine biomarkers are associated with severe illness and mortality in patients with confirmed COVID-19. These include white blood cell count, alanine aminotransferase (ALAT), lactate dehydrogenase (LDH), and C-reactive protein (CRP) (3–5). However, examination

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of these biomarkers has focused solely on patients with confirmed SARS-CoV-2. Furthermore, these biomarkers are not always predictable, as they become abnormal only after a COVID-19 infection turns into a severe trajectory. Testing for SARS-CoV-2 has long latency, and many hospitals have struggled with limited supplies of test kits. With a large patient intake, physicians are often forced to decide whether a patient should be admitted or discharged before SARS-CoV-2 status is known. In combination with this, COVID-19 symptoms are broad and nonspecific, and safe discharge can therefore not be based on the SARS-CoV-2 status alone. In studies conducted prior to the COVID-19 pandemic pandemic, soluble urokinase plasminogen activator receptor (suPAR) has been shown to be a strong marker of readmission and mortality in all comers in the emergency department (ED) (6,7). suPAR is the soluble form of the membrane-bound urokinase-type plasminogen activator receptor (8). The precise physiological role of suPAR is not yet fully understood, but it is considered to reflect the level of chronic inflammation and immune activation (9). Elevated suPAR is found in a wide range of diseases: acute, chronic, noncommunicable, and infectious (9,10). SuPAR has been investigated in several viral infections, including human immunodeficiency virus, hepatitis B and C, Crimean-Congo hemorrhagic fever, and hantavirus. In all cases, elevated suPAR associates with clinical severity and mortality (11–16). Elevated suPAR has also been shown to be associated with increased severity in patients with respiratory diseases, such as pediatric lower respiratory tract infections, chronic obstructive pulmonary disease, and sepsis-related respiratory distress (17–19). In the general population, elevated suPAR is associated with the pace of biological aging and cognitive decline (20). Thus, suPAR seems to reflect the individual's health status and capacity to fight disease. The higher the suPAR concentration, the worse the prognosis. SuPAR is therefore a potential biomarker to aid decision-making for safe and early discharge of patients with COVID-19 symptoms in the ED. However, as SARS-CoV-2 is a novel virus, only a few studies have been conducted on suPAR in COVID-19 patients. Elevated baseline suPAR levels have been shown to be associated with risk of intubation and mechanical ventilation, as well as risk of acute kidney failure in confirmed COVID-19 patients (21,22). We aimed to evaluate whether suPAR can stratify patients presenting with symptoms of COVID-19 according to their risk of developing a mild, moderate, severe, or very severe disease trajectory, regardless of SARS-CoV-2 status. Furthermore, we tested the addition of suPAR to National Early Warning Score (NEWS) and CRP. NEWS is widely used in European hospitals to identify patients at risk of deterioration. It consists of a simple algorithm based on heart rate, systolic blood pressure, respiratory rate, oxygen saturation, oxygen supplement, temperature, and level of consciousness. Maximum aggregated score is 20, and an aggregated score of 0–4 is considered a low clinical risk (23). CRP is a widely recognized marker of inflammation, with commercially available point-of-care (POC) test (24). Both NEWS and CRP can thus be obtained without a central lab and could, therefore, be used in combination with POC suPAR at a very early stage.

Materials and Methods

Study Participants and Study Design

A single-center observational cohort study at the ED at (Copenhagen University Hospital - Hvidovre) in the period from March 19 until April 3, and with follow-up until April 17, 2020. We included all patients (24/7) who were admitted to the ED with suspicion of COVID-19 during the study period. Patients had suPAR measured at admission, but test results were not available to the attending emergency physician. Hereafter, all patients followed routine patient courses through the ED and other hospital departments, regardless of suPAR values. Only patients > 18 years of age are referred to the ED. Patients were referred to the ED for hospital examination and observation after phone consultation with their general practitioner, the Medical Helpline 1813, or after examination by physicians in outpatient COVID-19 clinics handling patients with mild symptoms. The included patients were thus patients suspected of COVID-19 who could not be treated in the primary sector due to more severe symptoms or their general health status. Examination and treatment in the ED, as well as in the primary sector, are all covered by the universal public health care, without direct patient payment.

Clinical data at admission and patient trajectories were recorded after 14 days through the review of electronic health records (EHRs) by three emergency physicians associated with this study (MAS, IA, JT). Data were entered into a Research Electronic Data Capture program. A manual with definitions was developed a priori to ensure uniform data entry. Discrepancies were discussed and resolved by consensus among the three reviewers. The EHR covers medical records from all EDs in the Capital Region of (Capital Region of Denmark) and the Region of Zealand, as well as information on any drug prescriptions, and deaths in any part of Denmark.

Clinical Data at Admission

From the EHR we recorded the following data at admission: systolic and diastolic blood pressure, pulse, respiratory rate, oxygen saturation, body temperature, NEWS, results of routine blood tests, result of chest x-ray

study, smoking habits, length of COVID-19 symptoms prior to contact with the ED, and whether patients lived in nursing homes or received home assistance. In addition, we registered whether patients were diagnosed with infections including COVID-19 prior to admission. Further, we registered relevant comorbidities including heart and lung disease, previous strokes, and inflammatory diseases (Supplementary Table 1).

The following blood tests were routinely analyzed at admission at the Department of Clinical Biochemistry: white blood cell counts, hemoglobin, creatinine, CRP, ALAT, LDH, and bilirubin. White blood cell counts were analyzed using Sysmex-XN-9000 (Sysmex Corporation, Kobe, Japan). The remaining blood tests were analyzed using COBAS-8000 (Roche Diagnostics, Mannheim, Germany).

SuPAR Measurements

SuPAR was measured on-site using suPARnostic Quick Triage POC test (ViroGates, Birkerød, Denmark), according to the manufacturer's instructions (25). Blood (ethylenediaminetetraacetic acid, 4 mL) was drawn on arrival and centrifuged for 3 min. Ten microliters of plasma was mixed with 100 uL of the kit's accompanying dilution buffer and 60 μL of the mix applied to the POC test. Results were quantified using an aLF reader (QIAGEN, Hilden, Germany) after 20 min incubation. If results showed suPAR levels above the highest detection level (15 ng/mL), the plasma sample was further diluted, until results were $<$ 15 ng/mL, after which results were multiplied according to the dilution factor. The laboratory technician performing the POC test was blinded regarding the clinical status of the patients. According to the manufacturer, the suPAR concentration measured with POC test is within maximum $\pm$ 10% deviation from suPAR measured with enzyme-linked immunosorbent assay. The coefficient of variation (CV%) of POC suPAR test is 10–29%, with the highest variation at low suPAR concentration (25).

Patient Trajectory

After 14 days follow-up, we recorded the length of hospitalization, readmissions, SARS-CoV-2 status, diagnoses of other infections during follow-up, use of antibiotics, supplemental oxygen, continuous positive air pressure (CPAP), noninvasive ventilation (NIV), transfer to the intensive care unit (ICU), acute organ failure, referral to palliative care, and mortality. Acute organ failure was defined as: acute kidney failure (if acute dialysis was applied); liver failure (if new onset of international normalized ratio $>$ 1.6 for patients not receiving antiplatelet therapy or ALAT $>$ 400); lung failure (if patient respiration frequency $\geq$ 28 breaths/min and the patient received $>$ 10 L of oxygen for $>$ 1 h, or the patient needed NIV treatment or intubation and mechanical ventilation); and heart failure (if cardiac troponin T $>$ 100, or reduced ejection fraction, or worsening of known reduced ejection fraction identified by echocardiography).

SARS-CoV-2 Testing

SARS-CoV-2 testing was performed on all patients, as part of routine diagnostics, and analyzed at the Department of Clinical Microbiology using a RealStar® SARS-CoV-2 RT-PCR Kit RUO (Altona Diagnostics, Hamburg, Germany) adapted to a Roche flow system. The lower limit of detection was reported to be 50 copies of RNA.

Primary Endpoints

Primary endpoints were defined as mild, moderate, severe, and very severe disease trajectory. Very severe disease trajectory was defined as one or more of: acute organ failure, admission to ICU, palliative care, or death.

Severe disease trajectory was defined as no indication of very severe disease trajectory and one or more of: hospitalization more than 5 days, ongoing hospitalization at end of follow-up, CPAP, NIV, or high-flow oxygen.

Moderate disease trajectory was defined as no indication of very severe or severe disease trajectory and hospitalization for more than 24 h or readmission.

Mild disease trajectory was defined as no indication of very severe, severe, or moderate disease trajectory; that is, hospitalization $<$ 24 h, without readmission, high-flow oxygen, CPAP, NIV, acute organ failure, admission to ICU, palliative care, or death.

Statistical Analysis

Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as number (n) and percentages (%). Variables were stratified according to primary endpoints and suPAR levels, and differences assessed by the Kruskal–Wallis or chi-squared test.

The ability of suPAR to predict disease trajectory was evaluated by receiver operating characteristics (ROC), with a mild, as well as a mild or moderate, disease trajectory compared with all other outcomes. To ensure safe discharge, optimal cut-off values were based on optimizing the certainty of a "mild trajectory," as well as the certainty of a "mild or moderate trajectory." We therefore prioritized maximum specificity when calculating cut-offs. In other words, we calculated the probability of having a suPAR value below the cut-off if the patients had a "mild trajectory" as well as the probability of having

a suPAR value below the cut-off if the patients had a "mild or moderate trajectory." To evaluate changes in optimal cut-off at high specificity, we calculated cut-offs for specificity in increments of 0.01 in the range of 0.90 to 0.99.

To evaluate the effect of suPAR in combinations with parameters routinely used in patient allocation, a logistic regression model was fitted for a mild disease trajectory and for a mild or moderate disease trajectory compared with all others, with log2 suPAR, CRP (≤10/>10), NEWS (≤4/>4), and symptoms duration (≤5/>5 days) as independent variables. The linear predictor from this model was used in an ROC analysis calculating cut-offs at specificity 0.90–0.99. suPAR values equivalent to the linear predictor cut-off values were calculated for all combinations of independent variables.

R 3.60 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis and to create the figures. A p-value < 0.05 was considered statistically significant.

Ethics

The database and collection of clinical data were approved by the (Danish) Data Protection Agency (record no. P-2020-513) and by the (Danish Patient Safety Authority) Patient Safety Authority (record no. 31-1521-319). No changes to routine clinical practice or treatment were applied. The study did not cause any delay in treatment or diagnostics.

Results

Inclusion

We screened 415 patients and included 386. Reasons for exclusion were: no COVID-19 suspicion (n = 19), no suPAR test in the ED (n = 9), and technical reasons (n = 1). We had no loss to follow-up.

Baseline Characteristics

Mean age was 64 years (IQR 46–77), and 165 patients (43%) were male (Table 1). When baseline characteristics were stratified according to primary endpoints, significant differences were seen for suPAR, gender, age, white blood cell count, CRP, ALAT, creatinine, NEWS, number of comorbidities, home assistance, nursing home, and new x-ray study abnormalities (Table 1).

Disease Trajectories After 14 Days Follow-Up

Of 386 patients, 171 (44%) had a mild disease trajectory, 79 (20%) a moderate, 63 (16%) a severe, and 73 (19%) a very severe disease trajectory (Table 1). The median suPAR level at admission was 3.1 ng/mL (IQR 2.4–4.45) for patients with a mild disease trajectory and 5.8 ng/mL (IQR 4.3–9.8) for patients with a very severe disease trajectory (Table 1). Of the included, 19 (4.9%) were confirmed SARS-CoV-2 positive prior to visit to the ED (Table 1), and 80 were confirmed positive during admission to the ED or other hospital departments. Patients with low suPAR were more often COVID-19 negative, received less oxygen treatment, and had lower readmission rate and lower mortality (Table 2). Patients with a mild disease trajectory were COVID-19 positive in 15% of cases, compared with 48% of patients with very severe disease trajectory. Only 1.2% of patients with mild disease trajectories had COVID-19 combined with another infection, compared with 22% with very severe disease trajectory (Table 3).

Treatment During Hospitalization

Seven patients (4.1%) with mild disease trajectories received oxygen. All 7 received non-high-flow oxygen through a conventional face mask or nasal cannula (Table 4). Thirteen patients (7.6%) with a mild disease trajectory received antibiotics (Table 4). For patients with very severe disease trajectory, 71% received oxygen through a conventional mask or nasal cannula, 16% received mechanical ventilation, and 66% received antibiotics (Table 4). No patients with suPAR levels below 4.0 ng/mL (n = 196) were transferred to the ICU (Table 3).

SuPAR as a Single Predictor of Disease Trajectory

For patients with mild disease trajectory (n = 36, 9%), ROC analysis showed that specificity for suPAR < 2.0 ng/mL was 93%, and specificity for suPAR < 3.0 ng/mL was 82% (Figure 1, Table 5). For patients with either mild or moderate disease trajectory (n = 120, 31%), specificity for suPAR < 2.0 ng/mL was 96% and specificity for suPAR < 3.0 was 88% (Figure 2, Table 5). Negative predictive value (NPV) for very severe disease trajectory was 100% for suPAR < 2 ng/mL and 94% for suPAR < 3 ng/mL (Table 5).

SuPAR as a Predictor of Disease Trajectory in Combination with NEWS, CRP, and Duration of Symptoms

For patients with mild disease trajectory, ROC analysis showed that specificity for the combination of suPAR < 3 ng/mL CRP ≤ 10 and NEWS ≤ 4 was 93% (Figure 1, Table 5). In patients with either mild or moderate disease trajectories, specificity for the combination was 99% (Figure 2, Table 5). For patients with suPAR < 3 ng/mL CRP ≤ 10 and NEWS ≤ 4, NPV was 100% for very

Table 1. Baseline Data at Admission Stratified According to Disease Trajectory After 14 Days

	Mild Disease Trajectory	Moderate Disease Trajectory	Severe Disease Trajectory	Very Severe Disease Trajectory	*p*-Value	Total
N	171	79	63	73		386
Age, years, n, median (IQR)	52 (35–65)	64 (46–77)	71 (61.5–79)	77 (70–85)	< 0.001	64 (46–77)
Female,* n (%)	117 (68.4%)	38 (48.1%)	28 (44.4%)	38 (52.1%)		221 (57.3%)
Male,* n (%)	54 (31.6%)	41 (51.9%)	35 (55.6%)	35 (47.9%)	< 0.001	165 (42.7%)
0–5 days, n (%)	78 (46.4%)	42 (55.3%)	38 (62.3%)	43 (62.3%)		201 (53.7%)
6–10 days, n (%)	36 (21.4%)	14 (18.4%)	11 (18%)	13 (18.8%)	0.425	74 (19.8%)
11–15 days, n (%)	30 (17.9%)	12 (15.8%)	6 (9.8%)	6 (8.7%)		54 (14.4%)
$>$ 15 days, n (%)	24 (14.3%)	8 (10.5%)	6 (9.8%)	7 (10.1%)		45 (12%)
suPAR level ng/mL, median (IQR)	3.1 (2.4–4.45)	3.9 (2.7–5.05)	5.4 (3.8–7.05)	5.8 (4.3–9.8)		4 (2.7–5.9)
Leukocyte count (10^9/L)	7.8 (5.85–9.4)	8.6 (6.7–12.2)	9.2 (6.3–13.1)	10.1 (5.4–11.6)	< 0.001	8.25 (6.1–10.9)
CRP (ug/mL)	3.8 (1.1–16)	20 (3.5–53)	68 (15.5–140)	52.5 (19.75–132.5)	0.00176	15.5 (2.4–65.75)
LDH (U/L)†	184 (169–204)	205 (177.5–246)	260 (186–309)	237 (206–332)	< 0.001	199 (176–251)
ALAT (U/L)	22 (16–30)	25 (17–35)	26 (18–40)	25 (18–41)	< 0.001	23 (17–35)
Creatinine (μmol/L)	69 (60–82)	77 (62–95)	81.5 (65–108)	97 (79–139)	0.0283	77 (62–96.5)
HgB (mmol/L)	8.5 (8–9.2)	8.6 (7.8–9)	8.2 (7.1–9.05)	8.1 (6.9–9.1)	< 0.001	8.4 (7.6–9.1)
EWS score at admission, median (IQR)	1 (0–2)	1 (0–3)	4 (1.5–6)	5 (2–7)	0.0225	2 (0–4)
New chest x-ray study abnormality, n (%)	25 (14.7%)	27 (34.6%)	26 (44.8%)	50 (69.4%)	< 0.001	128 (33.9%)
No new chest x-ray study abnormality, n (%)	119 (70%)	45 (57.7%)	30 (51.7%)	20 (27.8%)		214 (56.6%)
No chest x-ray study performed, n (%)	26 (15.3%)	6 (7.7%)	2 (3.4%)	2 (2.8%)		36 (9.5%)
Known asthma, n (%)	29 (17%)	15 (19%)	5 (7.9%)	6 (8.2%)		55 (14.2%)
Known COPD, n (%)	22 (12.9%)	13 (16.5%)	16 (25.4%)	20 (27.4%)	0.0819	71 (18.4%)
Total number of comorbidities, median (IQR)	1 (0–2.5)	2 (1–3)	3 (2–4)	3 (1–4)	0.0215	2 (1–3)

(*continued on next page*)

Table 1. (*continued*)

	Mild Disease Trajectory	Moderate Disease Trajectory	Severe Disease Trajectory	Very Severe Disease Trajectory	*p*-Value	Total
N	171	79	63	73		386
Active smoker, n (%)	45 (27.1%)	15 (20%)	10 (16.1%)	14 (19.2%)	< 0.001	84 (22.3%)
Ex-smoker, n (%)	46 (27.7%)	29 (38.7%)	28 (45.2%)	37 (50.7%)	0.0215	140 (37.2%)
Never smoked, n (%)	75 (45.2%)	31 (41.3%)	24 (38.7%)	22 (30.1%)		152 (40.4%)
Unknown smoking history, n (%)	5 (2.9%)	4 (5.1%)	1 (1.6%)	0 (0.0%)		10 (2.6%)
Receiving home assistance,‡ n (%)	28 (16.4%)	20 (25.3%)	30 (47.6%)	40 (54.8%)		118 (30.6%)
Living in nursing home, n (%)	6 (3.6%)	9 (11.4%)	10 (15.9%)	26 (35.6%)	< 0.001	51 (13.3%)
Confirmed SARS-CoV-2 prior to admission, n (%)	5 (2.9%)	5 (6.3%)	6 (9.5%)	3 (4.1%)	< 0.001	19 (4.9%)
Diagnosed with other infection(s) prior to admission, n (%)	6 (3.5%)	11 (13.9%)	6 (9.5%)	3 (4.1%)	0.191	26 (6.7%)

Baseline data are defined as data available in the patient's admission file of first contact to the emergency department (ED) with Coronavirus disease 2019 (COVID-19) symptoms. Disease trajectory was assessed after 14 days, and baseline data were hereafter stratified according to disease trajectory. For details on definition of disease trajectory groups, please see the materials and methods section. *p*-Value compares differences in baseline data among the different groups of disease trajectory.

* Defined according to biological sex.

† Missing data due to homolysis n = 75 (mild 33, moderate 16, severe 10, very severe 16) missing data are omitted from the calculation of average.

‡ All patients who live in nursing homes receive home assistance and are included in the number.IQR = interquartile range; CRP = C-reactive protein; LDH = lactate dehydrogenase; ALAT = alanine aminotransferase; HgB = hemoglobin; suPAR = soluble urokinase plasminogen activator receptor; COPD = chronic obstructive lung disease; EWS = Early Warning Score; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 2. Treatment and Outcome in Relation to suPAR Levels

suPAR at admission ng/mL	< 2	2–3	3–4	4–5	> 5	*p* Value	Total
n	36	84	76	57	133		386
Length of stay (days) for those discharged at end of follow-up,* median (IQR)	0.36 (0.18–0.91)	0.29 (0.17–0.71)	0.59 (0.24–3.76)	1.26 (0.32–4.12)	2.98 (0.48–5.75)	< 0.001	0.62 (0.23–3.94)
Readmitted, n (%)	9 (25%)	6 (7.1%)	4 (5.3%)	7 (12.3%)	13 (9.8%)	0.0183	39 (10.1%)
Still hospitalized at end of follow-up, n (%)	2 (5.6%)	2 (2.4%)	3 (3.9%)	8 (14%)	42 (31.6%)	< 0.001	57 (14.8%)
Confirmed COVID-19 infection, n (%)†	2 (5.6%)	12 (14.3%)	17 (22.4%)	19 (33.3%)	49 (36.8%)	< 0.001	99 (25.6%)
Diagnosed with other infection, n (%)	6 (16.7%)	17 (20.2%)	19 (25%)	16 (28.1%)	38 (28.6%)	0.47	96 (24.9%)
Diagnosed with other infection and COVID-19, n (%)	1 (2.8%)	2 (2.4%)	3 (3.9%)	5 (8.8%)	16 (12%)	0.036	27 (7%)
Oxygen supplement on conventional mask or nose catheter, n (%)	5 (13.9%)	11 (13.1%)	19 (25%)	18 (31.6%)	67 (50.4%)	< 0.001	120 (31.1%)
High-flow oxygen supplement, n (%)	1 (2.8%)	3 (3.6%)	4 (5.3%)	9 (15.8%)	28 (21.1%)	< 0.001	45 (11.7%)
CPAP, n (%)	2 (5.6%)	2 (2.4%)	2 (2.6%)	4 (7%)	17 (12.8%)	0.0178	27 (7%)
NIV, n (%)	0 (0%)	2 (2.4%)	2 (2.6%)	0 (0%)	3 (2.3%)	0.681	7 (1.8%)
Mechanical ventilation, n (%)	0 (0%)	0 (0%)	0 (0%)	2 (3.5%)	10 (7.5%)	0.0049	12 (3.1%)
Antibiotics, n (%)	5 (13.9%)	13 (15.5%)	18 (23.7%)	27 (47.4%)	74 (55.6%)	< 0.001	137 (35.5%)
Transferred to ICU, n (%)	0 (0%)	0 (0%)	0 (0%)	2 (3.5%)	11 (8.3%)	0.00225	13 (3.4%)
Pressor drugs, n (%)	0 (0%)	0 (0%)	0 (0%)	1 (1.8%)	11 (8.3%)	0.00103	12 (3.1%)
Dialysis, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (3.8%)	0.047	5 (1.3%)
Acute organ failure, n (%)	0 (0%)	3 (3.6%)	4 (5.3%)	7 (12.3%)	29 (21.8%)	< 0.001	43 (11.1%)
Received palliative care, n (%)	0 (0%)	1 (1.2%)‡	1 (1.3%)	6 (10.5%)	20 (15%)	< 0.001	28 (7.3%)
Died at hospital, n (%)	0 (0%)	1 (1.2%)‡	0 (0%)	6 (10.5%)	20 (15%)	< 0.001	27 (7%)
Died at home, n (%)	0 (0%)	0 (0%)	1 (1.3%)	2 (3.5%)	5 (3.8%)	0.268	8 (2.1%)

Treatment during hospitalization and disease trajectory were assessed after 14 days. suPAR was measured at the first visit to the Emergency Department with COVID-19 symptoms.

* Calculated only for patients that are discharged prior to end of follow-up. Patients that were still hospitalized or died at hospital are not included in the number. Patients who died at home after discharge are included.

† Including both cases confirmed prior to admission (n = 19) and during admission (n = 80).

‡ A case of a 93-year-old patient who died of natural causes/old age during follow-up.suPAR = soluble urokinase plasminogen activator receptor (ng/mL); IQR = interquartile range; NIV = noninvasive ventilation; CPAP = continuous positive air pressure; ICU = intensive care unit.

Table 3. Outcomes Stratified According to Disease Trajectory

	Mild Disease Trajectory	Moderate Disease Trajectory	Severe Disease Trajectory	Very Severe Disease Trajectory	*p*-Value	Total
n	171	79	63	73		386
Length of stay (days) for those discharged at end of follow-up,* median (IQR)	0.25 (0.17–0.42)	2.11 (1.25–3.73)	6.34 (5.47–7.88)	5.77 (4.11–8.02)	< 0.001	0.62 (0.23–3.94)
Readmitted, n (%)	0 (0%)†	22 (27.8%)	6 (9.5%)	11 (15.1%)		39 (10.1%)
Still hospitalized at end of follow up, n (%)	0 (0%)†	0 (0%)†	13 (20.6%)	44 (60.3%)		57 (14.8%)
Confirmed COVID-19 infection, n (%)	25 (14.6%)	19 (24.1%)	20 (31.7%)	35 (47.9%)	< 0.001	99 (25.6%)
Diagnosed with other infection after admission, n (%)	21 (12.3%)	30 (38%)	32 (50.8%)	40 (54.8%)	< 0.001	123 (31.9%)
Confirmed COVID-19 infection and diagnosed with other infection, n (%)	2 (1.2%)	3 (3.8%)	6 (9.5%)	16 (21.9%)	< 0.001	27 (7%)
Transferred to ICU, n (%)	0 (0%)†	0 (0%)†	0 (0%)†	13 (17.8%)		13 (3.4%)
Acute kidney failure, n (%)	0 (0%)†	0 (0%)†	0 (0%)†	6 (8.2%)		6 (1.6%)
Acute liver failure, n (%)	0 (0%)†	0 (0%)†	0 (0%)†	4 (5.5%)		4 (1%)
Acute lung failure, n (%)	0 (0%)†	0 (0%)†	0 (0%)†	37 (50.7%)		37 (9.6%)
Acute heart failure, n (%)	0 (0%)†	0 (0%)†	0 (0%)†	6 (8.2%)		6 (1.6%)
Received palliative care, n (%)	0 (0%)†	0 (0%)†	0 (0%)†	28 (38.4%)		28 (7.3%)
Died, n (%)	0 (0%)†	0 (0%)†	0 (0%)†	35 (47.9%)		35 (9.1%)
Died at home, n (%)	0 (0%)†	0 (0%)†	0 (0%)†	8 (11%)		8 (2.1%)
Died at hospital, n (%)	0 (0%)†	0 (0%)†	0 (0%)†	27 (37%)		27 (7%)

Outcomes and disease trajectories were assessed after 14 days.

* Calculated only for patients that are discharged prior to end of follow-up. Patients who were still hospitalized, or who died at the hospital, are not included in the number. Patients who died at home after discharge are included.

† Outcomes that, by definition, are not possible in the selected disease trajectory. See Materials and Methods section for details on definitions of disease trajectory groups.IQR = interquartile range; COVID-19 = Coronavirus disease 2019; ICU = intensive care unit.

Table 4. Treatment in Relation to Disease Trajectory

	Mild Disease Trajectory	Moderate Disease Trajectory	Severe Disease Trajectory	Very Severe Disease Trajectory	*p*-Value	Total
n	171	79	63	73		386
Oxygen supplement through conventional mask or nose cannula, n (%)	7 (4.1%)	23 (29.1%)	38 (60.3%)	52 (71.2%)	< 0.001	120 (31.1%)
High-flow oxygen supplement, n (%)	0 (0%)*	0 (0%)*	10 (15.9%)	35 (47.9%)		45 (11.7%)
CPAP, n (%)	0 (0%)*	0 (0%)*	6 (9.5%)	21 (28.8%)		27 (7%)
NIV, n (%)	0 (0%)*	0 (0%)*	0 (0%)*	7 (9.6%)		7 (1.8%)
Mechanical ventilation, n (%)	0 (0%)*	0 (0%)*	0 (0%)*	12 (16.4%)		12 (3.1%)
Pressor drugs, n (%)	0 (0%)*	0 (0%)*	0 (0%)*	12 (16.4%)		12 (3.1%)
Dialysis, n (%)	0 (0%)*	0 (0%)*	0 (0%)*	5 (6.8%)		5 (1.3%)
Antibiotics, n (%)	13 (7.6%)	32 (40.5%)	44 (69.8%)	48 (65.8%)	< 0.001	137 (35.5%)
ICU care, n (%)	0 (0%)*	0 (0%)*	0 (0%)*	13 (17.8%)	< 0.001	13 (3.4%)

Treatment during hospitalization and disease trajectory was assessed after 14 days.

* Outcomes that by definition are not possible in the selected disease trajectory. See Materials and Methods section for details on definitions of disease trajectory groups.CPAP = continuous positive air pressure; NIV = noninvasive ventilation; ICU = intensive care unit.

severe disease trajectory and 97% for either severe or very severe disease trajectories (Table 5). Any combination of NEWS, CRP, and duration of symptoms including suPAR was superior to the corresponding combination without suPAR (Table 5).

Discussion

In summary, we found that suPAR levels were strongly associated with patient trajectories within 14 days, with low suPAR levels identifying patients with a mild disease trajectory.

Our results suggest that suPAR can aid emergency physicians in their decision on whether a patient presenting with COVID-19 symptoms should be admitted or discharged, without having the result of a SARS-CoV-2 test ready in hand. Based on our results, we can generate the following hypothesis: if suPAR is used as a single parameter, the results suggest that a suPAR level < 2.0 ng/mL could be a possible cut-off for early discharge of patients with COVID-19 symptoms. Specificity for suPAR < 2 ng/mL was above 90% in both patients with mild disease trajectory and patients with either mild or moderate disease trajectories (Figures 1 and 2, Table 5). Further, suPAR < 2 provides a high NPV for severe and very severe disease trajectories (Table 5). An even better prediction can be achieved if suPAR is combined with other parameters. A suPAR level < 3 ng/mL could be a possible cut-off for early discharge if suPAR is combined with CRP $\leq$ 10 and NEWS ≤ 4. Specificity for this combination was 93% for patients with mild disease trajectory and 99% for patients with either mild or moderate disease trajectory. Further, the combination of suPAR < 3 ng/mL, CRP $\leq$ 10, and NEWS ≤ 4 provides very high NPV for moderate, severe, and very severe disease trajectories (Table 5).

Our study included patients with COVID-19 symptoms regardless of SARS-CoV-2 test status, thus, disease trajectories cover both COVID-19 and non-COVID-19 complications in the patient group. Clinicians are therefore not forced to wait for SARS-CoV-2 testing to use the above stratifications and can also avoid admitting patients for observation waiting for progression or regression of symptoms. The severity of COVID-19 can increase dramatically during the first days after infection. A similar increase in the suPAR response is possible but has not yet been fully examined. To adjust for patients presenting early after infection, duration of symptoms was included in our analysis. But this addition did not change results compared with combinations including only suPAR, NEWS, and CRP. It is likely that a wait-and-see approach will be suitable for patients with short duration of symp-

Table 5. Specificity and NPV for Combinations of suPAR, NEWS, Length of Symptoms, and CRP

Cut-off	No. of Patients with Mild Disease Trajectory	No. of Patients with Moderate Disease Trajectory	No. of Patients with Severe Disease Trajectory	No. of Patients with Very Severe Disease Trajectory	Specificity for Cut-Off for Patients with Mild Disease Trajectory	Specificity for Cut-Off for Patients with Mild or Moderate Disease Trajectory	NPV for Moderate, Severe, or Very Severe Disease Trajectory	NPV for Severe or Very Severe Disease Trajectory	NPV for Very Severe Disease Trajectory
suPAR $<$ 2.0	22	9	5	0	0.93	0.96	0.61	0.86	1.00
suPAR $<$ 3.0	82	22	9	7	0.82	0.88	0.68	0.87	0.94
CRP $\leq$ 10	116	29	15	11	0.74	0.81	0.68	0.85	0.94
NEWS $\leq$ 4	166	68	35	36	0.35	0.48	0.54	0.77	0.88
Duration of symptoms $>$ 5 days	90	34	23	26	0.60	0.62	0.52	0.72	0.85
suPAR $<$ 3.0 + CRP $\leq$ 10	63	13	4	1	0.92	0.96	0.78	0.94	0.99
suPAR $<$ 3.0 + NEWS $\leq$ 4	80	21	4	5	0.86	0.93	0.73	0.92	0.95
suPAR $<$ 3.0 + Length of symptoms $>$ 5	47	12	3	3	0.92	0.96	0.72	0.91	0.95
suPAR $<$ 3.0 + CRP $\leq$ 10 + NEWS $<=$ 4	61	12	2	0	0.93	0.99	0.81	0.97	1.00
suPAR $<$ 3.0 + CRP $\leq$ 10 + Length of symptoms $>$ 5	38	7	3	0	0.95	0.98	0.79	0.94	1.00
suPAR $<$ 3.0 + NEWS $\leq$ 4 + Length of symptoms $>$ 5 days	45	11	2	2	0.93	0.97	0.75	0.93	0.97
suPAR $<$ 3.0 + CRP $\leq$ 10 + NEWS $\leq$ 4 + Length of symptoms $>$ 5 days	36	6	2	0	0.96	0.99	0.82	0.95	1.00

(*continued on next page*)

Table 5. (*continued*)

Cut-off	No. of Patients with Mild Disease Trajectory	No. of Patients with Moderate Disease Trajectory	No. of Patients with Severe Disease Trajectory	No. of Patients with Very Severe Disease Trajectory	Specificity for Cut-Off for Patients with Mild Disease Trajectory	Specificity for Cut-Off for Patients with Mild or Moderate Disease Trajectory	NPV for Moderate, Severe, or Very Severe Disease Trajectory	NPV for Severe or Very Severe Disease Trajectory	NPV for Very Severe Disease Trajectory
CRP $\leq$ 10 + NEWS $\leq$ 4	114	25	9	5	0.82	0.90	0.75	0.91	0.97
CRP $\leq$ 10 + Length of symptoms $>$ 5	67	16	8	4	0.87	0.91	0.71	0.87	0.96
NEWS $\leq$ 4 + Length of symptoms $>$ 5 days	88	31	14	10	0.74	0.82	0.62	0.83	0.93
CRP $\leq$ 10 + NEWS $\leq$ 4 + Length of symptoms $>$ 5 days	65	15	5	1	0.90	0.96	0.76	0.93	0.99

The closer the specificity is to 1.0, the higher is the probability of values below cut-off in the given disease trajectory group. Very severe disease trajectory was defined as, One or more of: acute organ failure, admission to intensive care unit (ICU), palliative care, or death. Severe disease trajectory was defined as, No indication of very severe disease trajectory and one or more of: hospitalization more than 5 days, ongoing hospitalization at end of follow-up, CPAP, NIV, or high flow oxygen. Moderate disease trajectory was defined as, No indication of very severe or severe disease trajectory and hospitalization for more than 24 h or readmission. Mild disease trajectory was defined as, No indication of very severe, severe, or moderate disease trajectory, i.e., hospitalization $<$ 24 h, without readmission, high-flow oxygen, CPAP, NIV, acute organ failure, admission to ICU, palliative care, or death. The closer NPV is to 1.0, the higher the probability of avoiding the given disease trajectories.

suPAR = soluble urokinase plasminogen activator receptor; CRP = C-reactive protein; NEWS = National Early Warning Score; NPV = negative predictive value.

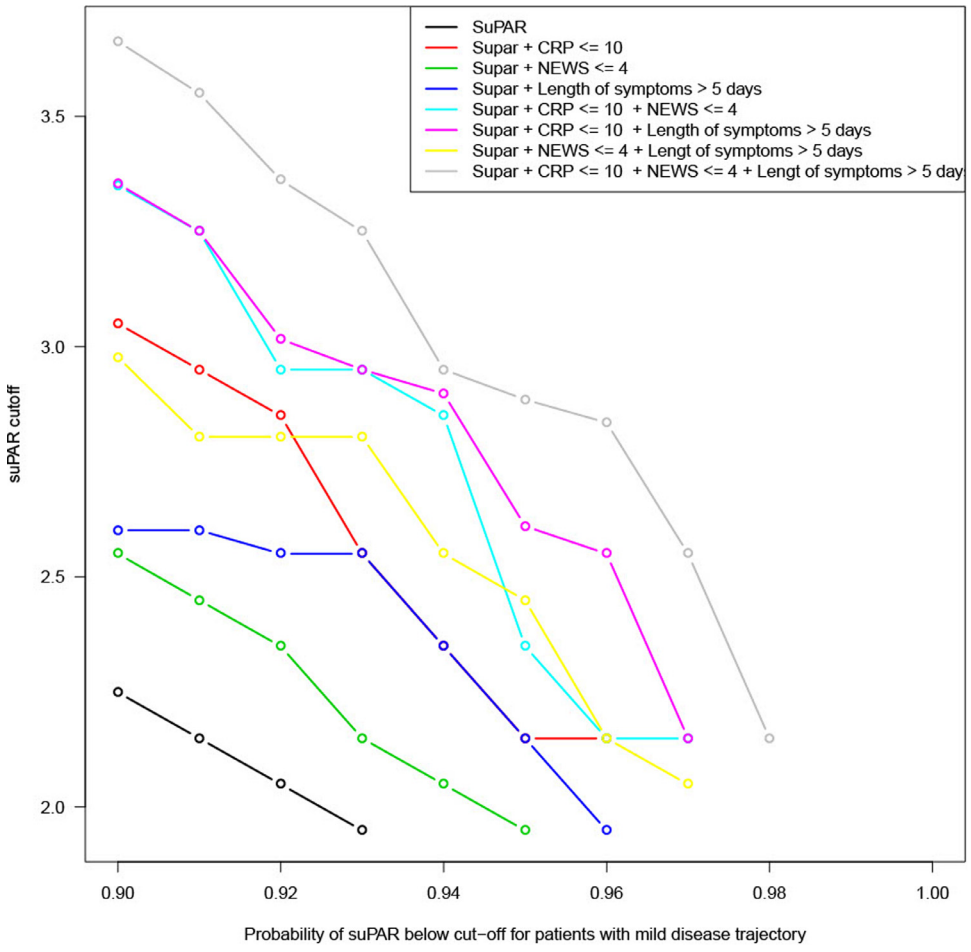

Figure 1. Relationship between suPAR and specificity for a mild disease trajectory. The closer the specificity is to 1.0, the higher is the probability of a mild disease trajectory. The length of symptoms means duration from patients experienced first symptoms until first contact to the emergency department. Mild disease trajectory was defined as: Hospitalization < 24 h, without readmission, high-flow oxygen, continuous positive air pressure, noninvasive ventilation, acute organ failure, admission to intensive care treatment, palliative care, or death.
suPAR = soluble urokinase plasminogen activator receptor (ng/mL); NEWS = National Early Warning Score; CRP = C-reactive protein.

toms but with low suPAR, low NEWS, and low CRP. Patients could most likely be sent home for self-isolation and only be referred to hospital examination if symptoms progress. It should, however, be noted that the combination of any three out of four of: suPAR < 3 ng/mL, NEWS ≤ 4, CRP < 10, and duration of symptoms > 5 days provides close to the same high specificity and NPV as a combination of all variables (Figures 1 and 2, Table 5).

As with all decisions to admit or discharge, the full clinical picture and health history of the patient should be considered. Our results are related to patients with COVID-19 symptoms; if the patients show symptoms or are diagnosed with other diseases, these should be considered and treated. It should also be noted that the aim of the study was to provide tools for a safe and early discharge before SARS-CoV-2 status is known. Discharged patients should self-isolate until results of SARS-CoV-2 testing is available and comply with local health authorities' recommendations for further testing or isolation.

Findings in Relation to Existing Knowledge

Our study is in agreement with studies conducted prior to the COVID-19 pandemic, where elevated suPAR was found to be a strong marker of disease severity, readmission, and mortality in patients admitted to the ED (6,7,26). A recent position paper on suPAR in the ED suggests 4 ng/mL as a cut-off level for safe discharge (27). However, this recommendation was based on a single study conducted prior to the SARS-CoV-2 pandemic, focusing primarily on mortality (26). Our results suggest a lower cut-off value for safe discharge in pa-

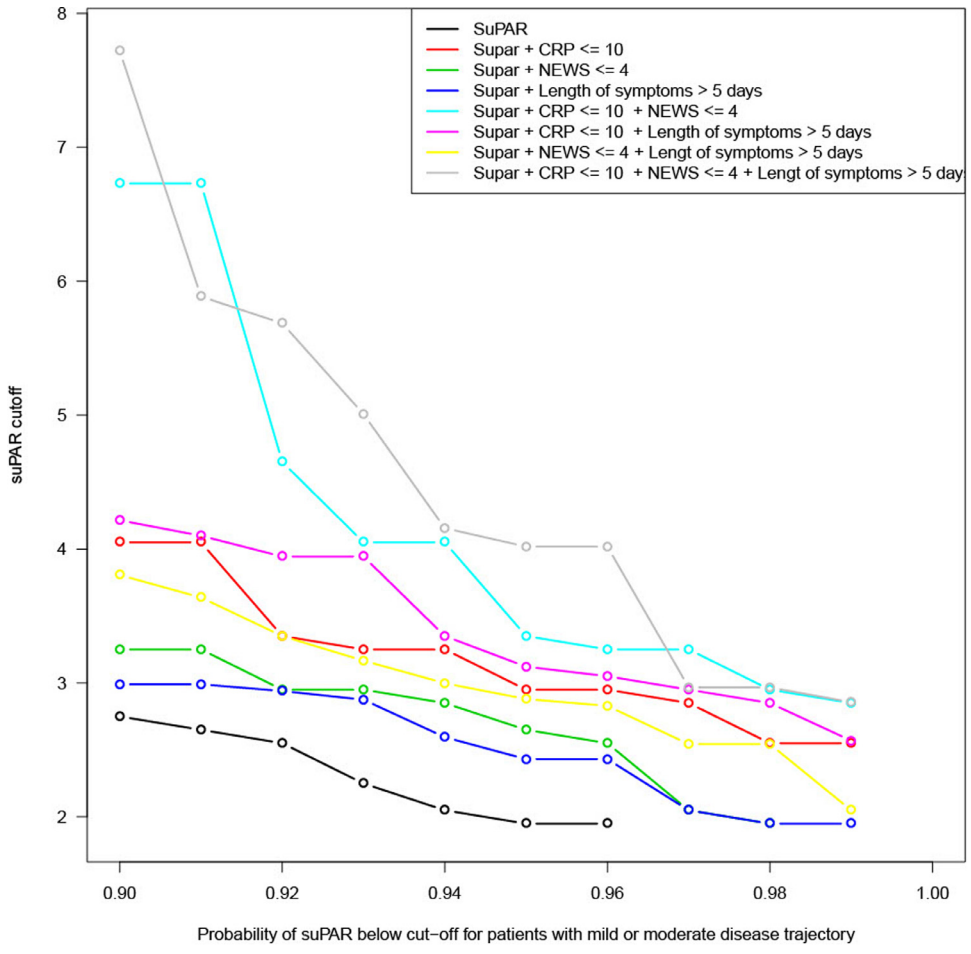

Figure 2. Relationship between suPAR and specificity for a mild or moderate disease trajectory. The closer the specificity is to 1.0, the higher is the probability of a mild or moderate disease trajectory. The association between suPAR levels, other variables, and specificity for a mild disease trajectory, was calculated with logistic regression model and receiver operating characteristics. Mild disease trajectory was defined as: Hospitalization < 24 h, without readmission, high-flow oxygen, continuous positive air pressure, noninvasive ventilation, acute organ failure, admission to intensive care treatment, palliative care, or death. Moderate disease trajectory was defined as: Hospitalization < 5 days, without high-flow oxygen, continuous positive air pressure, noninvasive ventilation, acute organ failure, admission to the intensive care unit, palliative care, or death.
suPAR = soluble urokinase plasminogen activator receptor (ng/mL); NEWS = National Early Warning Score; CRP = C-reactive protein.

tients with COVID-19 symptoms. Few studies have been conducted on suPAR in COVID-19 patients. Elevated suPAR levels have been shown associated with risk of intubation and mechanical ventilation, as well as risk of acute kidney failure in confirmed COVID-19 patients (21,22). A recent UK study found NEWS to be a good predictor of ICU admission and mortality in confirmed COVID-19 patients (28). This is an interesting result for in-hospital distribution of patients, however, ICU and mortality are too-narrow endpoints for ED discharge, and we have therefore also included readmissions, duration of hospitalization, and specific treatments in our analysis.

Perspectives

During a pandemic, testing is not always available, can have long latency, and may produce false negative results. Further, EDs are burdened by a large patient intake, creating ED overcrowding. SuPAR could enhance the clinical response and ensure a better distribution of resources by identifying patients that can be early discharged without risk of complications. Our results are particularly relevant because suPAR was measured with a POC test that provided results in < 30 min, including time for collection and preparation of blood samples. The POC test could easily be implemented in the primary sector or temporary outpatient clinics and possibly aid in the decision on whom to refer for hospital examination. Further studies are needed to test the predictive value

of suPAR in such settings. The role of suPAR has been investigated in many other viral diseases and has correlated well to disease severity (11–16). It is therefore likely that suPAR can be a biomarker for triage in future pandemics with other viral diseases or mutant derivatives of SARS-CoV-2. Another interesting perspective relates to drugs like Remdesivir and dexamethasone in the treatment of COVID-19 (29). If treatment is not available for all COVID-19 patients, or if patients experience side effects, suPAR could help identify patients that are most likely to have mild disease trajectories without specific treatment. Furthermore, there is still uncertainty about the indication of Remdesivir in COVID-19 infection (30). suPAR can identify patients that are likely to have mild disease trajectories without specific treatment. If trials evaluating Remdesivir or other drugs control for this subgroup, greater accuracy can be achieved.

Limitations

As a single-center study, we cover a relatively small (n = 386) and homogeneous patient sample, primarily of white ethnicity. Further studies are needed to test suPAR's ability in larger and more diverse samples. The suggested cut-off values will thus require verification in prospective cohort studies or intervention studies. Our study has included only patients with COVID-19 symptoms referred to the ED, and we have therefore not been able to test hypotheses of suPAR's predictive value outside the ED setting. Further studies testing the value of suPAR in the primary sector will be of high relevance. In our study, we intended to examine suPAR's predictive ability at a very early stage, enabling physicians to apply the results regardless of SARS-CoV-2 test result. We have therefore included patients with COVID-19 symptoms, rather than confirmed SARS-CoV-2. It is possible that the result would have been different if the study population were restricted to including only patients with confirmed SARS-CoV-2. Physicians had access to routine admission blood samples and chest x-ray study when examining the patients. The isolated effect of suPAR can therefore not be examined in our study design. Our results suggest that suPAR in some patients possibly can replace broad admission blood samples and chest x-ray study by identifying patients with a high chance of exhibiting a mild disease trajectory with the combination of a few simple parameters. Further studies are needed to test this hypothesis. An economic cost–benefit evaluation of suPAR in the ED is beyond the scope of this study. However, the cost of test equipment and sample preparation should be viewed against the cost of admitting patients for observation. NEWS was updated in 2019 to NEWS-2 (31). This update has not been incorporated at our hospital, but the only difference is a slight adjustment in pO_2 scale specific for patients with hypercapnic respiratory failure, while scoring of the remaining patients remain the same (31). It is highly unlikely that this adjustment would have resulted in different scores in the mild and moderate disease trajectory groups, and our result can therefore unproblematically be compared with studies using NEWS-2.

Conclusion

In conclusion, suPAR is a potential biomarker for triage of patients with COVID-19 symptoms in the ED. Our results suggest a cut-off value for discharge for suPAR at < 2.0 ng/mL if suPAR is used as a single parameter, and <3.0 ng/mL if combined with NEWS < 4, and CRP < 10 mg/L. Triage by suPAR can be used even before SARS-CoV-2 status is known.

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JEO is a co-founder, shareholder, and CSO of ViroGates. JEO and OA are named inventors on patents on suPAR. The patents are owned by Copenhagen University Hospital Hvidovre, Denmark and licensed to ViroGates A/S.

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ARTICLE SUMMARY

1. Why is this topic important?

Severe acute respiratory syndrome coronavirus 2 (The Covid-19 pandemic) places extraordinary stress on the health care system, and especially on hospital bed capacity. Better risk stratification, with early discharge of patients with a predicted mild disease trajectory, could ease this burden.

2. What does this study attempt to show?

First, to evaluate whether point-of-care (POC) measures of blood-level soluble urokinase plasminogen activator receptor (suPAR) in patients presenting to the emergency department with symptoms of Coronavirus disease 2019 (COVID-19), can identify patients that can be safely discharged. Second, to estimate cut-off values of suPAR for safe discharge of patients with COVID-19 symptoms.

3. What are the key findings?

suPAR is a potential biomarker for safe, early discharge of patients with COVID 19 symptoms in the ED. suPAR can be used even before SARS-CoV-2 status is known.

4. How is patient care impacted?

In the COVID-19 pandemic, hospital resources must be used for the critically ill patients. Rapid POC measurement of suPAR can identify a group of patients with COVID-19 symptoms, who are at very low risk for severe disease trajectory. If this group is early discharged, resources can be directed to those most in need.