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Prediction value of soluble urokinase plasminogen activator receptor (suPAR) in COVID-19 patients – a systematic review and meta-analysis

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Abstract

Introduction and Objective. In COVID-19, the rapid prediction of the severity of a patient's condition using modern biomarkers can accelerate the implementation of appropriate therapy, and thus improve the patient's prognosis.

Materials and method. A meta-analysis was conducted of data available in the literature on the differences in baseline suPAR blood concentration between patients (1) who tested positive and negative for COVID-19, (2) who had severe and non-severe COVID-19, and (3) COVID-19 survivors and non-survivors.

Results. SuPAR levels in SARS-CoV-2 negative and positive patients varied and amounted to 3.61±1.59 ng/ml vs. 6.45±3.13 ng/ml, respectively (MD = -3.18; 95%CI: -4.71 to -1.66; p<0.001). suPAR levels among non-severe and severe COVID-19 patients were 5.7 ± 3.0 ng/ml and 7.3 ± 2.7 ng/ml (MD = -1.15; 95%CI: -1.97 to -0.33; p=0.006), respectively. Pooled analysis showed that suPAR levels between severe versus critical COVID-19 patients to be 5.59±1.54 ng/ml and 6.49±1.43 ng/ml, respectively (MD = -1.00; 95%CI: -1.31 to -0.70; p<0.001). The suPAR levels between ICU survivors versus non-survivors [10,16,26,29] amounted to 5.82±2.33 ng/ml and 8.43±4.66 ng/ml (MD = -3.59; 95%CI: -6.19 to -1.00; p=0.007). In the case of in-hospital mortality, the mean suPAR level among survivors to hospital discharge was 5.63±1.27 ng/ml, compared to 7.85±2.61 ng/ml for patients who did not survive (MD = -3.58; 95%CI: -5.42 to -1.74; p<0.001).

Conclusions. SuPAR levels are significantly elevated in severe COVID-19 illness and maybe useful in predicting mortality. Further studies are needed to determine cut-off points and clarify the association of suPAR levels with disease progression. This is of utmost importance given the ongoing pandemic and overburdened health care systems.

Key words

meta-analysis, predictor, marker, suPAR, COVID-19, SARS-CoV-2, soluble urokinase plasminogen activator receptor

INTRODUCTION AND OBJECTIVE

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected millions of people, caused many deaths and increasing morbidity worldwide [1, 2]. Even though it started more than two years ago and many risk factors have been described, the disease is still evolving [3]. Numerous biomarkers have been associated with severe cases of COVID-19, such as elevated inflammatory markers (C-reactive protein, procalcitonin, IL-6), neutrophil to lymphocytes ratio, or urea to creatinine ratio, but each has its limitations and cannot accurately predict disease progression [4–7]. Hence, there is a need for better biomarkers to identify patients who might be able to be discharged from hospital early from those who would require more intensive treatment. This distinction and early discharge could help optimize the resource utilization of the overwhelmed hospital systems during the pandemic.

The plasminogen activator (PA) system is an extracellular proteolytic enzyme system involved in various physiological processes. Urokinase-type plasminogen activator (uPA) is involved in the conversion of plasminogen to plasmin along with tissue-type plasminogen activator (tPA). Further, plasmin activates fibrinolysis, preventing clot formation [8].

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The urokinase-type plasminogen activator receptor (uPAR) is a plasma membrane receptor that is over-expressed in inflammation and in almost all human cancers [9]. The soluble form of uPAR (suPAR) is known as a prognostic factor of mortality in patients receiving treatment in an Intensive Care Unit (ICU; Fig. 1) [10]. Moreover, suPAR blood concentration was shown to predict mortality in Emergency Departments (ED) better than the triage ESI system (AUC 0.85, 95%CI: 0.80–0.89 vs. 0.71, 95% CI: 0.64–0.78, respectively, p<0.001) [11]. High suPAR levels (>6.15 ng/mL) at ICU admission correlated with ICU and 28-day mortality in critically ill septic patients [12]. Furthermore, suPAR was an independent predictor of mortality in patients with chronic heart failure (CHF) with an optimal cut-off for all-cause mortality of 4.4 ng/ml [13]. In addition, suPAR was associated with acute renal failure and had an odds ratio for acute kidney injury of 2.66 (95% CI: 1.77 to 3.99) [14].

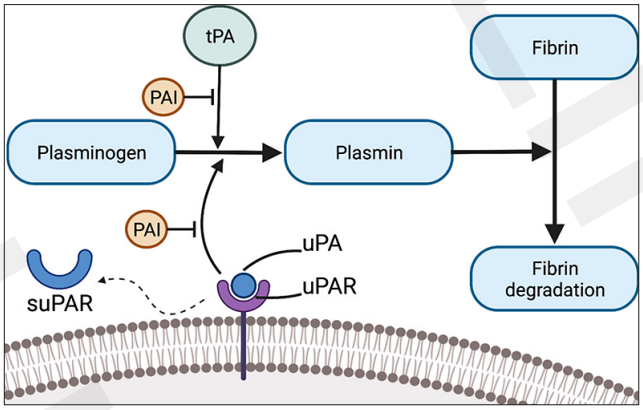

Figure 1. Simplified diagram of the pathophysiological role of the plasminogen activator system. uPA, when combined with the uPAR receptor, and tPA can independently activate the conversion of plasminogen to plasmin. Plasmin subsequently activates the process of fibrinolysis. The soluble form of uPAR (suPAR) is derived through the activity of phospholipases

During the pandemic, the predictive ability of suPAR as a biomarker of illness severity and mortality gained attention. SuPAR levels at admission in patients who survived hospitalization for COVID-19 were lower than in those who died (5.8 ng/mL vs. 8.2 ng/mL, respectively, p<0.001) [15]. SuPAR levels also differed based on disease outcomes: severe cases had significantly higher suPAR levels than mild cases (3.87 ng/mL vs. 2.84 ng/mL, respectively; p=0.01), whereas patients with mild COVID-19 had elevated suPAR levels compared to healthy subjects (2.84 ng/mL vs. 1.68 ng/mL, respectively; p=0.02) [16]. Moreover, baseline suPAR levels were associated with the length of hospitalization of patients with COVID-19 (rho = 0.35; p=0.006) [17]. However, some studies have reported conflicting results, hence there is a need for a meta-analysis to determine the predictive ability of suPAR in COVID-19 [18].

A meta-analysis of data was conducted in the available literature on the differences in baseline suPAR blood concentration between patients (i) who tested positive and negative for COVID-19, (ii) who had severe and non-severe COVID-19, and (iii) COVID-19 survivors and non-survivors.

MATERIALS AND METHODS

This study was carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement, and registered in the PROSPERO international prospective register of systematic reviews (No. CRD42022349500). All analyses were based on previously published studies; thus, ethical approval or patient consent was not necessary for this meta-analysis.

Search strategy. Excerpta Medica data BASE (EMBASE), PubMed/MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to 28 November 2022. The search strategy included the Medical Subject Headings terms and/or text words by two reversers independently (M.P. and L.S.). The literature was searched using the following keywords: 'SuPAR', 'soluble urokinase plasminogen activator receptor' and 'SARS-CoV-2' and 'COVID-19'. The studies were restricted to humans and studies published in English, but not restricted by date, or publication status. All studies were carefully screened and exported to Endnote vX7 (Clarivate Analytics, Bloomington (MN), USA). The reference lists of selected articles were also searched manually to identify additional eligible studies.

Eligibility criteria. The inclusion criteria were studies that reported suPAR levels in COVID-19 positive and negative patients, COVID-19 severe and non-severe, and COVID-19 survivors and non-survivors. The following categories of research were excluded from this analysis: (1) publications with no comparator group; (2) papers with a paediatric population; (3) conference or poster papers, reviews or meta-analyses, case reports; (4) articles with no original data; and (5) works published in a language other than English. Review articles, meta-analyses, editorials, letters to editor, animal studies, conference papers or duplicated publications were also excluded.

Data extraction. The following information was independently extracted from the included studies by two investigators (L.S. and M.P.) and jointly verified for accuracy: author, year of publication, country of study and COVID-19 severity data (i.e. number of patients, suPAR levels), etc. Authors were contacted when information was unclear. Data from included studies were recorded using a Microsoft Excel (Microsoft Corporation, Redmond (WA), USA) specific pre-defined report form.

Risk of bias. The methodology of each study was assessed independently by the two reviewers (L.S. and M.P.). Disagreements were referred to a third reviewer (J.S.) to obtain a resolution. The Newcastle-Ottawa scale was used to assess cohort and case-control study quality by group selection (0–4 points), comparability (0–2 points), and exposure/outcome reliability 0–3 points) [19]. The studies were categorized as good quality if they scored ≥ 7 points, fair quality if they scored 5–6 points, and poor quality if they scored < 5 points.

Statistical analysis. All statistical work including analyses and graphical illustrations was conducted using STATA (version 17.0, StataCorp LLC, College Station (TX), USA) and the Review Manager software version 5.4 (Nordic Cochrane

Centre, Cochrane Collaboration, Copenhagen, Sweden). For continuous measures (procedure time), the mean differences (MD) with 95% confidence intervals (CIs) were calculated When the continuous outcome was reported in a study as median, range, and interquartile range, means and standard deviations we estimated using the formula described by Hozo et al. [20]. $P < 0.05$ was considered indicative of statistically significant difference. Heterogeneity was estimated with use of the I^2 statistic, and quantified as low (0%–25%), moderate (26%–50%), substantial (51%–75%), or considerable (76%–100%) [21]. $I^2 > 50\%$ was considered as the apparent heterogeneity between the studies and the random-effects model (Der Simonian and Laird method) was adopted. For the analyses with $I^2 < 50\%$, the fixed-effect model (Mantel–Haenszel model) was used. For evaluation of publication bias among the studies, a visual inspection of the generated funnel plot was employed. Asymmetry, which is an indication for publication bias, was evaluated visually and with the Egger test.

RESULTS

Basic data of the included literature. A preliminary search of the literature was conducted, and 159 studies obtained. After excluding duplicate studies, 128 studies remained. 27 were selected for full text review, as displayed in the flow-chart in Figure 2. Finally, 15 studies were included in this meta-analysis [10, 15–17, 22–31].

Of the 14 studies, four were from Greece [26, 27, 29, 30], two from Turkey [18, 23], two from Denmark [22, 28], two from Italy [16, 31], and one in each of the following countries: Sweden [17], China [24], India [25],and Australia [10], and one was an international study [15]. One study was published in 2020 [24], ten in 2021 [10, 16–18, 22, 23, 26–28, 30] and four in 2022 [15, 25, 29, 31]. All included studies had sample sizes ranging from 31 – 767 patients. Baseline characteristics of the study population are presented in Table 1.

The risk of bias for the included studies was assessed using the Newcastle-Ottawa scale and was ≥7 for each study (Tab. 1).

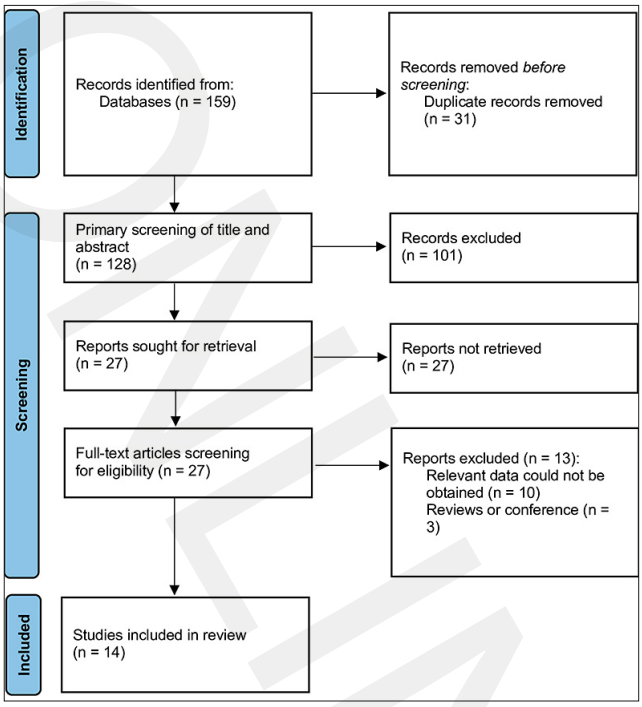

Figure 2. PRISMA flow diagram of the study selection process

Meta-analysis results. Five studies [16–18, 22, 30] reported suPAR levels in SARS-CoV-2 negative and positive patients with mean level of 3.61±1.59 ng/ml, and 6.45±3.13 ng/ml (MD = -3.18; 95%CI: -4.71 to -1.66; p<0.001), respectively (Fig. 3).

Five studies reported suPAR levels among non-severe and severe COVID-19 patients [16, 18, 24, 27, 28]. Pooled analysis showed that suPAR levels among non-severe and severe group were 5.7 ± 3.0 ng/ml and 7.3 ± 2.7 ng/ml (MD = -1.15; 95%CI: -1.97 to -0.33; p=0.006), respectively (Figure 4).

Additionally, pooled analysis showed that suPAR levels between severe versus critical COVID-19 patients [24, 28] to be 5.59±1.54 ng/ml and 6.49±1.43 ng/ml, respectively (MD = -1.00; 95%CI: -1.31 to -0.70; p<0.001).

Table 1. Characteristics of included trials

Study	Country	Study design	No of patients	Age	Sex, male	NOS scale
Altintas et al. 2021 [22]	Denmark	Observational cohort study	386	64 (46-77)	165 (42.7%)	8
Chalkias et al. 2022 [15]	International	multicentre, prospective, observational study	767	64 (53-73)	440 (57.4%)	9
Enocsso et al. 2021 [17]	Sweden	prospective, observational cohort study	60	47.5 (23-91)	40 (66.7%)	7
Genc et al. 2021 [23]	Turkey	Retrospective cohort study	36	72 (47-88)	21 (58.3%)	7
Huang et al. 2020 [24]	China	Retrospective cohort study	117	NS	NS	7
Infantino et al. 2022	Italy	Retrospective cohort study	70	NS	NS	8
Kakar et al. 2022 [25]	India	Prospective comparative study	31	61.84 ± 2.17	20 (64.5%)	8
Kerget et al. 2021 [18]	Turkey	Retrospective cohort study	102	56.1 ± 14.9	59 (57.8%)	8
Keskinidou et al. 2021 [26]	Greece	Observational, single-center study	37	63.6 ± 10.9	30 (81.1%)	8
Kyriazopoulou et al. 2021 [27]	Greece	Prospective, observational cohort study	260	NS	NS	7
Napolitano et al. 2021 [16]	Italy	Single-center cohort study	28	57.6 ± 14.6	16 (571.%)	8
Reisinger et al. 2021 [10]	Austria	Prospective, observational cohort study	237	65 (55-74)	142 (59.9%)	7
Stauning et al. 2021 [28]	Denmark	Observational cohort study	386	64 (46-77)	165 (42.7%)	8
Vassiliou et al. 2022 [29]	Greece	Cbservational study	95	NS	NS	7
Velissaris et al. 2021 [30]	Greece	Prospective, observational cohort study	41	61.63 ± 16.77	29 (70.7%)	8

NOS - Newcastle-Ottawa Scale; NS - not specified

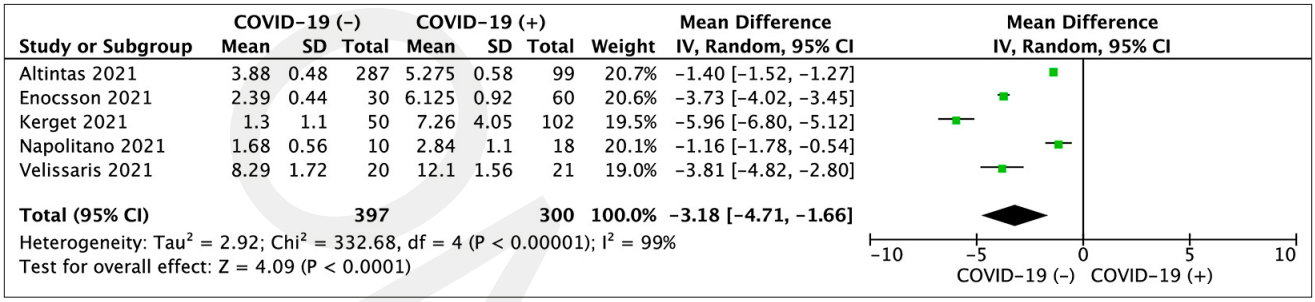

Figure 3. Forest plot of suPAR levels among COVID-19 negative and positive patients. The centre of each square represents the mean differences for individual trials; the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

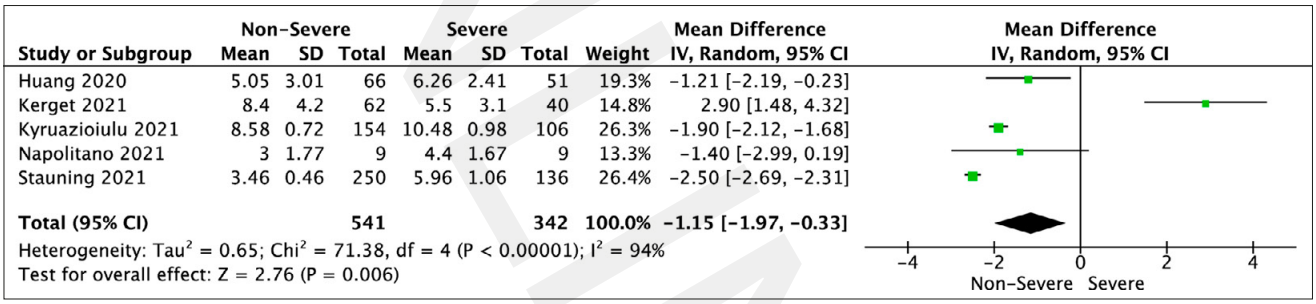

Figure 4. Forest plot of suPAR levels among non-severe vs. severe COVID-19 patients. The centre of each square represents the mean differences for individual trials; the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

Lastly, the suPAR levels between ICU survivors versus non-survivors [10, 16, 26, 29] amounted to 5.82±2.33 ng/ml and 8.43±4.66 ng/ml (MD = -3.59; 95%CI: -6.19 to -1.00; p=0.007). On the other hand, in the case of in-hospital mortality, the mean suPAR level among survivors to hospital discharge [15, 23, 25, 29, 31] was 5.63±1.27 ng/ml, compared to 7.85±2.61 for patients who did not survive (MD = -3.58; 95%CI: -5.42 to -1.74; p<0.001).

DISCUSSION

The presented meta-analysis demonstrates that patients who tested positive for SARS-CoV-2 had significantly higher serum suPAR levels than those who tested negative. Moreover, there was significant difference in the serum suPAR concentration between patients with severe and non-severe disease. However, both critically ill patients and ICU non-survivors had significantly higher suPAR levels, when compared to severe cases and non-survivors, respectively. There were also statistically significantly higher suPAR levels in patients who died compared to patients who survived to hospital discharge.

All studies included in the current meta-analysis showed increased suPAR levels in SARS-CoV-2 positive patients compared to negative ones [16–18, 22, 30]. Thus, it can be concluded that SARS-CoV-2 infection causes a significant increase in serum suPAR level, although the underlying mechanism is not fully understood. However, a cut-off point to determine SARS-CoV-2 infection has not been established. Since, the polymerase chain reaction (PCR) test is highly accurate and widely used to establish the diagnosis [31], the ability to predict disease progression would be more helpful.

The presented meta-analysis shows that there are discrepancies and high heterogeneity in the data on the association between suPAR levels and COVID-19 severity. Studies have shown that the initial suPAR level can be an indicator of further disease progression. Receiver operating curve (ROC) analysis indicated a suPAR level of 6ng/ml, which significantly increased the risk of developing severe respiratory failure [32]. This cu-off point was used in a double-blind randomized clinical trial evaluating the efficacy of Anakinra (a recombinant IL-1 receptor antagonist that blocks both IL-1α and IL-1β) in patients with high risk of impending severe respiratory failure (those with serum suPAR level >6ng/ml). Compared to standard care, Anakinra administration was associated with better 28-day survival and shorter hospital stay [33]. On the other hand, a study by Kerget et. al, demonstrated that patients with moderate COVID-19 had higher suPAR levels than patients with severe COVID-19 (8.4±4.2 vs. 5.5±3.1, respectively; p=0.001) [18]. The presented meta-analysis shows that mean suPAR levels were higher in patients with a non-severe course than in patients with a severe course, but the difference was not statistically significant. Of note, in the presented meta-analysis there was also a significant difference between serum suPAR levels in patients with a severe and critical course of COVID-19.

The above data indicate existing inaccuracies in determining disease severity and the need for further research to clearly define the usefulness of suPAR in predicting disease course.

Regarding the association of suPAR levels with COVID-19 mortality, the presented meta-analysis showed significantly increased suPAR levels in ICU non-survivors, when compared to survivors (p= 0.007). Likewise, there were higher suPAR levels in patients who did not survive hospitalization, compared to survivors, taking into account general in-hospital mortality, not only in the ICU. In this case, however, statistical significance was at the margin (p=0.05). These results are consistent with previous knowledge of suPAR's ability to predict poor prognosis in various diseases. Increased levels of suPAR were associated with higher mortality in patients with sepsis, chronic obstructive pulmonary disease,

renal or liver failure, or after myocardial infarction [34–38]. However, there is no unified cut-off point that indicates a poor prognosis in patients. Further research is needed to determine the cut-off point that would be most sensitive in identifying patients with higher mortality. This would allow individualized and intensified care for such patients, leading to a reduction in mortality.

Limitation of the study. The main limitation of the meta-analysis is the limited number of studies evaluating the association of suPAR levels with the course of COVID-19 and related mortality. Additionally, there is always the possibility of publication bias, due to higher acceptance rate or significant and positive results [39, 40]. Finally, the differentiation between the various illness severity of COVID-19 is not entirely clear, possibly causing discrepancies in results between severe and non-severe disease.

CONCLUSIONS

SuPAR levels are significantly elevated in severe COVID-19 illness and maybe useful in predicting mortality. Further studies are needed to determine cut-off points and clarify the association of suPAR levels with disease progression. This is of utmost importance given the ongoing pandemic and overburdened health care systems.

Data availability statement. The data that support the findings of this study are available from the corresponding author [L.S.] upon reasonable request.

Acknowledgments
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