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Soluble urokinase plasminogen activator receptor (suPAR) as a prognostic marker in COVID-19 patients: a systematic review

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Abstract. – OBJECTIVE: The aim of this study was to perform a systematic review of the usefulness of suPAR as a prognostic marker in non-critical COVID-19 patients.

MATERIALS AND METHODS: We carried out a literature search in MEDLINE, Embase, and Web of Science using the following keywords: ("soluble urokinase receptor" OR "urokinase plasminogen activator receptor" OR "suPAR" OR "soluble uPAR" OR "soluble uPA receptor") AND ("COVID-19" OR "SARS-CoV-2"). We included observational studies (descriptive or analytic) that measured plasma suPAR on COVID-19 patients 18 years old or older, with non-critical disease at the beginning of the study.

RESULTS: After screening and eligibility assessment, a total of 16 articles were included in the review. Most studies that measured mean differences found that suPAR levels were higher in patients with worse outcomes. The studies that measured diagnostic accuracy concluded that suPAR was highly sensitive and moderately specific to predicting bad outcomes. Studies that performed a survival analysis found that patients with high suPAR levels were more at risk of bad outcomes. Most of the studies included in this review were performed before extensive vaccination and omicron wave.

CONCLUSIONS: COVID-19 patients with moderate initial disease and elevated suPAR levels are more at risk of poor outcomes. Larger prospective clinical trials are needed to confirm the results obtained in this review.

Key Words:
Soluble urokinase plasminogen activator receptor, Prognostic marker, COVID-19, Systematic review.

Abbreviations

suPAR: soluble urokinase plasminogen activator receptor; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; CPK: creatine phosphokinase; LDH: lactic dehydrogenase; CK-MB: creatinine-kinase myocardial band; BNP: brain natriuretic peptide.

Introduction

The coronavirus disease 2019 (COVID-19) clinical spectrum varies from a mild or moderate illness to pneumonia and systemic inflammation syndrome ("cytokine storm"), resulting in sepsis, respiratory distress, or multi-organ failure[1]. Besides other risk factors, such as older age, male sex, and pre-existing comorbidities, laboratory biomarkers can help identify COVID-19 patients at risk of severe disease or death in order to initiate early intensive treatment[2]. These biomarkers can express either systemic inflammation, such as white blood cell count[2], ferritin[2], albumin[3], C-reactive protein (PCR)[2-4] or procalcitonin[3,4], organ damage, like creatine phosphokinase (CPK)[2], lactic dehydrogenase (LDH)[2], troponin I, creatinine-kinase myocardial band (CK-MB) and brain natriuretic peptide (BNP); or hypercoagulation state, such as D-dimer[5].

Plasma levels of soluble urokinase plasminogen activator receptor (suPAR) express immune activation and systemic inflammation[6]. Elevated suPAR levels have already been associated[6] with worse outcomes and a higher mortality risk in many non-infectious conditions (kidney injury, diabetes, cancer, cardiovascular and rheumatic diseases, dementia, psychiatric disorders), as well as in a wide range of infectious diseases: pneumonia, meningitis, tuberculosis, malaria, type B and C hepatitis infection, human immunodeficiency virus infection, hantavirus and Crimea-Congo hemorrhagic fever. Therefore, suPAR plays an important role as a clinical, diagnostic, prognostic, and surveillance marker, and as such,

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it is one of the novel biomarkers studied as predictive markers in COVID-19[6].

The aim of our study was to perform a systematic review of the currently available evidence about the usefulness of suPAR as a prognostic marker in non-critical COVID-19 patients.

Materials and Methods

We carried out an updated literature search in MEDLINE, Embase, and Web of Science in April 2023, using the following keywords: ("soluble urokinase receptor" OR "urokinase plasminogen activator receptor" OR "suPAR" OR "soluble uPAR" OR "soluble uPA receptor") AND ("COVID-19" OR "SARS-CoV-2"), on all fields. We did not apply any publication date, status, or language filters. We removed all duplicates, and two authors (ELM and EdMB) made an initial assessment of all studies by screening titles and abstracts and classifying articles as relevant or irrelevant. Studies classified as relevant were retrieved, and the same authors (ELM and EdMB) assessed eligibility by reading the full text. Any differences were solved by consensus. The main researcher (ELM) extracted and summarized the data from each included study, presenting the results using an Excel spreadsheet. The last author (JMRR) reviewed the summarized data for quality control.

We included observational studies (descriptive or analytic) that matched our PICO (population, intervention, control, and outcomes) question, in which our "P" stood for COVID-19-positive patients 18 years old or older, with non-critical disease at the beginning of the study; the "I" was represented by plasma suPAR concentrations; the "O" stood for any clinical or analytical bad outcome. We excluded experimental studies with animal models, clinical trials, narrative reviews, systematic reviews, meta-analyses, and studies including COVID-19 negative controls.

We registered the study in the International Prospective Register of Systematic Reviews (PROSPERO) in October 2021 (CRD42021288071). We carried out the review following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[7].

Results

A total of 252 results were initially identified through the online research, 124 after removing duplicates. After screening and eligibility assessment, a total of 16 articles[8-23] were included in the review, one including patients from two different cohorts[8], which are presented separately. The search and study inclusion flowchart is shown in Figure 1, and the summarized characteristics from the included articles are shown in Table I.

The studies include patients from Europe, Asia and America, and 4 of them[10,11,17,21] are multicentre studies carried out in more than one country, and one[20] exclusively included patients of African descent. The inclusion criteria for all studies that detailed it in their methods included a positive molecular test for COVID-19, such as a RT-PCR test; some studies[9,13,21,22] also mentioned radiological inclusion criteria. Two studies[22,23] include patients with severe disease at the time of recruitment, defined by the presence of systemic inflammatory response syndrome[22] or acute respiratory distress syndrome[23]. On the other hand, 3 studies[12,15,19] excluded COVID-19 patients with a need for oxygen therapy, mechanical ventilation, or ICU admission at the time of recruitment.

The studies' setting was mainly the hospital ward (87.5%), with only two studies[8,20] taking place in the Emergency Department. The included studies collected the blood sample for the measure at different times, mostly on admission (6 out of 16 studies, 37.5%)[8,9,11,15,16,20], but also within 24 (3 out of 16, 18.75%)[19,21,22] or 48 (2 out of 16, 12.5%)[10,17] hours of admission, whereas some studies acquired the blood sample on the day of the enrolment[12,23]. We could not find the sample timing in two studies[13,18]. The follow-up time, when mentioned, ranged from 14[8,12,22] to 90 days[8].

The most frequently measured outcomes of interest in the included studies were death (68.8%)[8,9,11-16,19,20,23], need for oxygen or ventilation support (56.3%)[8,10-12,14,19-22] and intensive care admission (25%)[8,9,19,20]. Some studies included other specific outcomes, such as acute kidney injury[10] and deep venous thromboembolism[16,17].

The statistical methods of the included studies are varied, and some analyzed studies perform more than one analysis. Mean suPAR level comparison between patients with and without the outcome of interest was used in 12 of the 16 studies (75%)[10-20,22]. From these, 11[10-12,14-20,22] concluded that suPAR levels were higher in those patients with worse outcomes, while the remaining study[13] found no significant differences in suPAR levels between patients with good and poor outcomes. Nine studies[8-11,17,18,20,22,23] (56.6%) performed an analysis of suPAR as a diagnostic test, either by

Table I. Summary of the included studies: setting, population characteristics, outcomes, and analysis.

Author, year	Country	N	COVID-19 diagnostic criteria	Inclusion/ Exclusion criteria	Setting	suPAR cutoff	Sample timing	Time of follow-up	Death	Need for invasive ventilation / ARDS /oxygen requirement	ICU admission	Other outcomes	Mean suPAR comparison	S,Sp, PPV, NPV	ROC curve	Survival analysis
Altintas et al[8] (Hvidovre)	Denmark	72	Symptoms + RT-PCR confirmation	Exclusion: Not eligible for invasive ventilation	ED	4 ng/ml & 6 ng/ml	On admission at ED (within 2h)	14 days	Yes	Yes	No	Organ failure, discharged <24h/ still admitted, oxygen, NIV, CPAP, VV-ECMO, vasopressor drugs	No	Yes	No	No
Altintas et al[8] (Mikkeli)	Finland	100	Symptoms + RT-PCR confirmation	Exclusion: Not eligible for invasive ventilation	ED	4 ng/ml & 6 ng/ml	As part of standard admission blood sample	20-90 days	Yes	Yes	Yes	Organ failure, discharged <24h/still admitted, oxygen, NIV, CPAP, VV-ECMO, vasopressor drugs	No	Yes	No	No
Arnold et al[9]	UK	150	Positive RT- PCR test or compatible clinic-radiological syndrome	Exclusion: Inability to consent	H	5.2 ng/ml & 6 ng/ml	First admission result/Day of COVID diagnosis result	28 days	Yes	No	Yes	BiPAP or CPAP outside ICU	No	Yes	Yes	No
Azam et al[10]	US, Denmark, Greece, Germany	352	Positive RT-PCR test	Exclusion: Not primarily admitted for COVID-19	H	4.6 ng/ml & 6.86 ng/ml	Within 48 hours of admission	N/A	No	Yes	No	AKI	Yes	No	Yes	Yes
Chalkias et al[11]	Greece, US, Spain	767	Positive RT-PCR test	Exclusion: Not admitted in hospital, incomplete data	H	NU	On admission	30th day post-discharge or death	Yes (WHO-CPS)	Yes (WHO-CPS)	No	WHO COVID-19 CPS	Yes	No	Yes	No
Chandna et al[12]	India	426	Clinical suspicion + Positive RT-PCR test	Inclusion: moderate disease Exclusion: oxygen requirement at baseline, no systemic manifestations, previous confirmed COVID-19, vaccinated, unable to consent	H	NU	Day of enrollment	14 days	Yes	Yes	No	Need for oxygen requirements: SPO_2<94%, respiratory rate >30, SpO_2/ FiO_2<400	Yes	No	No	No

Table I. ***(continued).*** Summary of the included studies: setting, population characteristics, outcomes, and analysis.

Author, year	Country	N	COVID-19 diagnostic criteria	Inclusion/ Exclusion criteria	Setting	suPAR cutoff	Sample timing	Time of follow-up	Death	Need for invasive ventilation / ARDS / oxygen requirement	ICU admission	Other outcomes	Mean suPAR comparison	S,Sp, PPV, NPV	ROC curve	Survival analysis
Genc et al[13]	Turkey	36	Clinical suspicion + compatible CT findings & positive RT-PCR	Exclusion: Malignancy, bacterial &/ or fungal co-infection	H	NU	N/A	N/A (recruitment: 2 months)	Yes	No	No	No	Yes (median)	No	No	No
Infantino et al[14]	Italy	71	N/A	N/A	H	6 ng/ml	Median: within 3 days from admission (IQR 3'73)	N/A (recruitment: 1 month)	Yes (WHO-CPS)	Yes	No	WHO COVID-19 CPS, respiratory support requirement, ARDS, concentrations of tumor necrosis factor-alpha, calprotectin, neutrophils, lymphocytes, Neutrophil/Lymphocyte ratio	Yes	No	No	Yes
Kakar et al[15]	India	31	Positive RT-PCR test	Exclusion: required mechanical ventilation at the beginning of the study	H	NU	Day 1, day 3 & day 5 since admission	45 days	Yes	No	No	No	Yes	No	No	No
Luo et al[16]	US	109	N/A	Inclusion: COVID-19 patients with serum sample stored on admission	H	NU	On admission	N/A (recruitment: 4 months)	Yes	No	No	Thromboembolic complications (pulmonary embolism, deep venous thrombosis)	Yes (Odds ratio per quartile)	No	No	No
Luo et al[17]	US, Denmark, Greece, Germany	1,960	Positive RT-PCR test	Exclusion: Not primarily admitted for COVID-19	H	Tertiles: 4.12, 4.54, 6.70 & 10.1 ng/ml	Within 48 hours of admission	Until discharge or death	No	No	No	Thromboembolic complications (pulmonary embolism, deep venous thrombosis)	Yes	Yes	No	Yes

Table continued

Table I. ***(continued).*** Summary of the included studies: setting, population characteristics, outcomes, and analysis.

Author, year	Country	N	COVID-19 diagnostic criteria	Inclusion/ Exclusion criteria	Setting	suPAR cutoff	Sample timing	Time of follow-up	Death	Need for invasive ventilation/ARDS/ oxygen requirement	ICU admission	Other outcomes	Mean suPAR comparison	S,Sp, PPV, NPV	ROC curve	Survival analysis
Nekrasova et al[18]	Russia	151	Positive RT-PCR test	N/A	H	6 ng/ml	N/A	N/A (recruitment: 3 months)	No	No	No	Lung involvement measured by CT scan	Yes	Yes	Yes	No
Oulhaj et al[19]	UAE	403	Positive RT-PCR test	Exclusion: pregnancy, endpoint already present at recruitment	H	3.91 ng/ml	Within 24 hours of admission	Until occurrence of endpoint	Yes	Yes	Yes	No	Yes	No	No	Yes
Padelli et al[20]	France (Martinique)	64	Positive RT-PCR test	Exclusion: inability to consent, pregnancy, uncertain African descent, in-hospital COVID-19, incomplete data	ED	NU	On admission	N/A	Yes	Yes	Yes	Composite outcome: ICU admission requiring ventilation/death	Yes	Yes	Yes	Yes
Renieris et al[21]	Italy, Greece	40	Positive molecular test + lower respiratory tract infection (X-Ray, CT)	Exclusion: HIV infection, neutropenia	H	NU	Within 24 hours of admission	Hospital stay	No	Yes	No	Concentrations of calprotectin	No	No	No	No
Rovina et al[22]	Greece	57	Community pneumonia + Molecular documentation of COVID-19	Inclusion: infection + at least 2 points in SIRS score	H	6 ng/ml	Within 24 hours of admission	14 days	No	Yes	No	Need for MV or CPAP as a combined outcome	Yes	Yes	Yes	Yes
Sarif et al[23]	India	93	Positive RT-PCR test	Inclusion: COVID-19 patients with mild symptoms & ARDS	H	1.996 pg/ml	Day of enrollment	Survival: 30 days	Yes	No	No	Disease remission (time till discharge)	No	No	Yes	Yes

ARDS: Adult Respiratory Distress Syndrome; ICU: Intensive Care Unit; S: Sensitivity; Sp: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; ROC: Receiver Operator Characteristics; RT-PCR: Reverse Transcription Polymerase Chain Reaction; ED: Emergency Department; NIV: Non Invasive Ventilation; CPAP: Continuous Positive Airway Pressure; VV-ECMO: Venous Extracorporeal Membrane Oxygenation; UK: United Kingdom; H: Hospitalized patients; BiPAP: Bilevel Positive Airway Pressure; US: United States; N/A: Not Available; AKI: Acute Kidney Injury; NU: Non Used; WHO-CPS: World Health Organization Clinical Progression Scale; SpO_2: Oxygen Saturation; FiO_2: Fraction of Inspired Oxygen; IQR: Interquartile Range; CT: Computed Tomography; UAE: United Arab Emirates; HIV: Human Immunodeficiency Virus; MV: Mechanical Ventilation; SIRS: Systemic Inflammatory Response Syndrome.

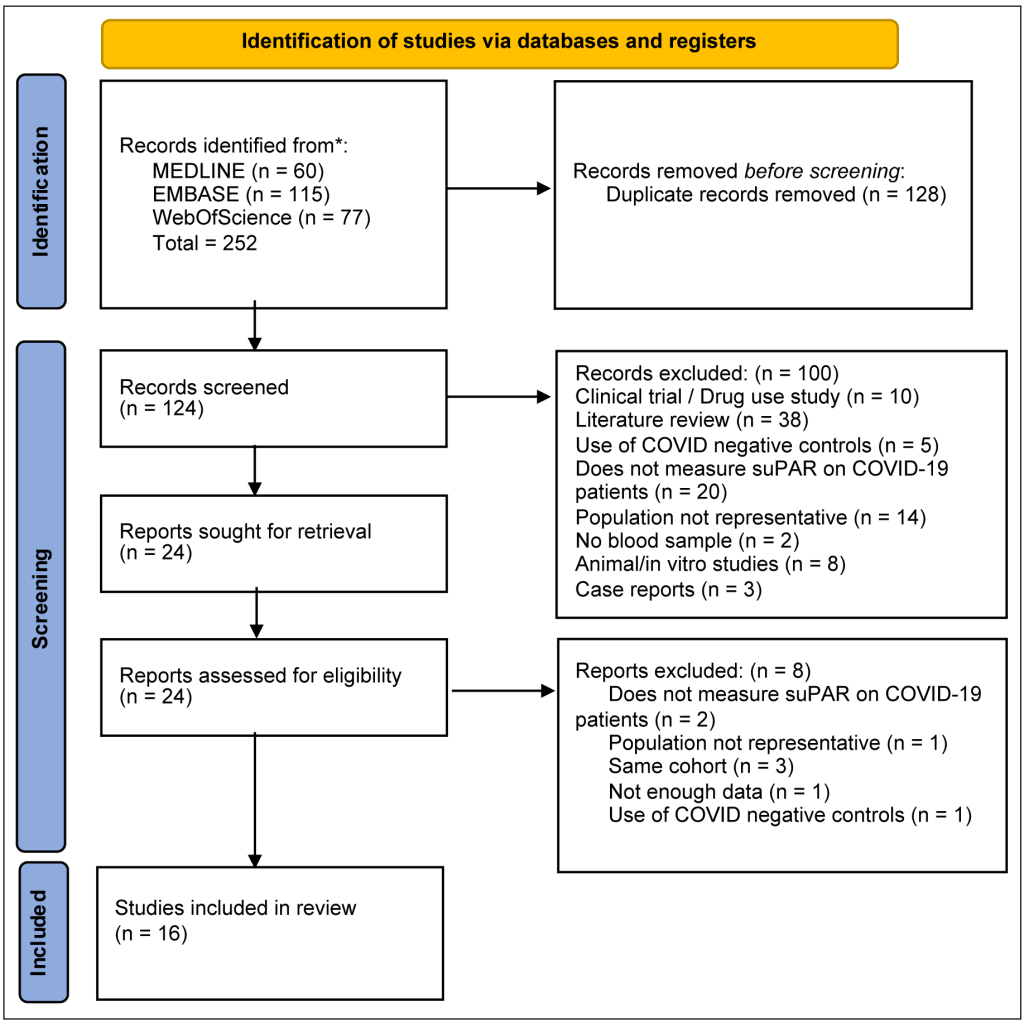

Figure 1. PRISMA flow diagram.

calculating sensitivity, specificity, and predictive values, building a ROC curve, or both. The cutoff suPAR value used to calculate diagnostic accuracy varies between studies, the most common being 6 ng/ml. Regardless of the different thresholds, all studies found that suPAR is a biomarker with high sensitivity and moderate specificity to predict bad outcomes. Lastly, the seven studies[10,14,17,19,20,22,23] (43.8%) that performed a survival analysis found that patients with higher suPAR levels are more at risk for the outcome of interest.

Discussion

The results from our review suggest that high suPAR levels are associated with worse outcomes in people with initial moderate disease. Moreover, we provide detailed information on the setting, patients, analysis, and results of each reviewed article, which can be helpful to better understand the available evidence on suPAR and COVID-19. Previous systematic reviews and meta-analyses have identified suPAR as a sensitive and specific biomarker for diagnosis and prognosis in bacterial infections[24] and sepsis[25], the latter being a time-dependent entity in which an early identification and risk stratification reduces mortality[25]. The usefulness of suPAR in these scenarios is consistent with what we found in our COVID-centred review.

This is not the first review of suPAR in COVID-19. Lippi et al[26] performed a literature search and pooled analysis of mean differences in suPAR blood concentration up until June 2021. They found five studies; from these, four[9,10,19,22] are also included in our review. In their pooled analysis, they found that suPAR values were 55% higher in patients with critical COVID-19 disease compared to patients with non-critical disease,

suggesting that suPAR may help stratify the risk of severe illness in COVID-19 patients[26].

More recently, Matuszewski et al[27] carried out a systematic review up until November 2022, including 14 studies, and a suPAR mean difference meta-analysis. Their results showed that mean suPAR levels were higher in critically ill COVID-19 patients, compared with patients with non-severe disease, as well as in patients who died of COVID-19 compared with survivors. We include in our review 5[8,11,13-15] out of the 14 studies found in the review from Matuszewski et al[27].

Strengths and Limitations

In our study, we performed an updated literature search and included more studies with different methodological approaches, and the results we obtained are also consistent with the conclusions that Lippi et al[26] and Matuszewski et al[27] found in their respective studies. Therefore, our study provides more backing evidence to the hypothesis that suPAR can predict bad outcomes and help stratify risk in COVID-19 patients.

However, our study has some limitations. First, we were not restrictive on outcomes or statistical analysis in order to provide a wide scope of the currently available literature on suPAR levels and COVID-19. However, this meant that the included studies had heterogeneous definitions of outcomes, methodological approaches, and even suPAR thresholds, which hindered comparisons between studies, as found by other reviews[27]. Seeing the disparity of methods and outcomes, we decided not to do a meta-analysis, which is a limitation of our study. Moreover, the sample size of the primary studies is relatively small, with half of the cohorts including less than 100 patients[8,13-15,20-23].

Another issue to consider when interpreting the results is represented by the differences between the scope and population in the included studies and the current clinical context of COVID-19. Most of the published studies were carried out before vaccines reached the general population (second trimester of 2021) and before Omicron became the dominant variant, and one cohort[12] excluded vaccinated patients. It would be interesting to research whether these two events have an influence on the role of suPAR as a prognostic marker in COVID-19 infection.

Conclusions

The findings of this review suggest that COVID-19 patients with moderate initial disease and elevated suPAR levels have more risk of poor outcomes. The available literature, however, differs greatly in populations and outcomes, as well as in the statistical methods used.

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Authors' Contributions
Ester Lobato-Martínez contributed to the acquisition, analysis and interpretation of data, as well as the article drafting. Jose-Manuel Ramos-Rincon, Eva de-Miguel Balsa and Rosario Sanchez-Martinez contributed to the conception and design of the study, supervision, validation and final approval of the final version. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Conflict of Interest
The authors state no conflict of interest.

Data Availability
All data generated or analyzed during this study are included in this published article and its supplementary material.

Ethics Approval
Not applicable.

Informed Consent
Not applicable.

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