

Letter to the Editor

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Elevated soluble urokinase plasminogen activator receptor (suPAR) in COVID-19 patients

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To the Editor,

Soluble urokinase-type plasminogen activator receptor (suPAR) is a soluble receptor derived from enzymatic cleavage of the membrane uPAR receptor at the surface of blood mononuclear and endothelial cells in response to a vast array of inflammatory and immunomodulatory stimuli, including viral infections [1]. Beside its consolidated role as a bioactive factor associated with various forms of endothelial dysfunction and sepsis [1], plasma levels of suPAR can predict the risk of developing both acute and chronic renal injury and failure [2, 3]. Recent evidence also suggests that this biomarker may have a role in a variety of thrombotic diseases. In a large population-based cohort study conducted by Engström et al. [4], including over 5,000 participants of the Malmö Diet and Cancer (MDC) study, high levels of suPAR were found to independently predict the risk of developing venous thromboembolism (hazard ratio, 1.7; 95% confidence interval [95% CI], 1.1–2.5 in the fully-adjusted model). In another study, not only were suPAR values found to be higher in patients with paroxysmal nocturnal hemoglobinuria (PNH) compared to healthy controls, but levels were also associated with the

risk of developing thrombotic events, and thrombosis-free survival was shorter in patients with suPAR values ≥ 2 ng/mL [5]. Since renal injury [6], and various forms of venous thrombosis [7, 8], are commonplace in patients with severe coronavirus disease 2019 (COVID-19), we aimed to review scientific studies which explored the concentration of suPAR in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with or without critical illness.

We carried out an electronic search in PubMed, Scopus and Web of Science, with the keywords “soluble urokinase plasminogen activator receptor” OR “suPAR” AND “coronavirus disease 2019” OR “COVID-19” OR “SARS-CoV-2” within all fields, and without language or date limits (i.e., up to May 10, 2021 and updated June 5, 2021). Two authors (G.L. and B.M.H.) reviewed title, abstract and full text (when available) of all documents that could be identified according to the predefined search criteria, choosing those which reported suPAR values in COVID-19 patients with or without critical disease and with cumulative sample size ≥ 50 . The reference list all initially identified articles was also scrutinized for detecting additional eligible studies. Mean and standard deviation (SD) of suPAR values were then included in a pooled analysis, with estimation of weighted mean difference (WMD) and 95% CI in patients with or without critical COVID-19 illness. When the mean value and/or the standard deviation (SD) were unavailable, these were approximated from the sample size, the median and the interquartile range (IQR), as for Hozo et al. [9], and/or from the graphical representation. A random effects model was also estimated for adjusting for the possible heterogeneity emerged among the different studies. Study heterogeneity was assessed with χ^2 test and I^2 statistic. The statistical analysis was performed using MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia), and the meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary File 1). The study was conducted in agreement with the declaration of Helsinki and within the terms of local legislation.

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Table 1: Summary of studies which have investigated the concentration of soluble urokinase plasminogen activator receptor (suPAR) in patients with or without severe coronavirus disease 2019 (COVID-19) illness.

Study	Study design and setting	Sample size	Critical illness	Endpoint	suPar values, ng/mL
Arnold et al. [10]	Prospective, UK	187 (Mean age, 59 ± 8 years; 460% females)	39/187 (20.9%)	ICU admission or death	7.66 ± 1.53 vs. 4.16 ± 0.86
Azam et al. [11]	Cross-sectional, multinational	352 (Mean age, 61 ± 26 years; 42.6% females)	91/352 (25.9%)	Acute kidney failure	7.66 ± 1.43 vs. 5.08 ± 0.94
Huang et al. [12]	Cross-sectional, China	78 (Demographic information unavailable)	21/78 (26.9%)	Critical illness (further specification unavailable)	6.68 ± 2.54 vs. 4.57 ± 2.35
Oulhaj et al. [13]	United Arab Emirates, prospective	403 (Mean age, 49 ± 12 years; 27.3% females)	25/403 (6.2%)	ARDS, ICU admission or death from any cause	5.51 ± 1.80 vs. 4.07 ± 1.62
Rovina et al. [14]	Cross-sectional, Greece	57 (Mean age, 64 ± 10 years; 40.1% females)	21/57 (36.8%)	Severe respiratory failure	7.54 ± 3.77 vs. 4.39 ± 2.17

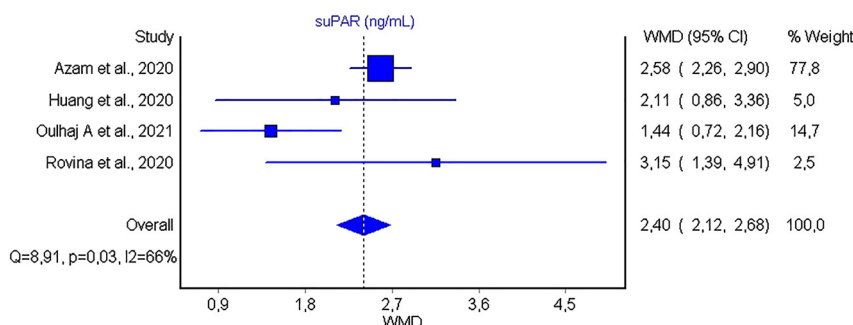
ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

After elimination of duplicates among the three scientific repositories, a total number of 57 documents could be initially identified with our electronic search, 52 of which were excluded because they were review articles ($n=27$), did not specifically deal with COVID-19 illness ($n=12$), were commentaries or other editorial material ($n=7$), or did not show suPAR value differentiated between patients with or without severe COVID-19 illness ($n=6$). One study ought to be excluded since suPAR concentration was compared between COVID-19 patients with moderate or severe illness, but not between those with or without severe disease. No disagreement emerged between the two reviewers. Therefore, five studies could be included in our final pooled analysis, totalling 1,077 COVID-19 patients, 197 (18.3%) with various forms of critical illness [10–14]. The main characteristics of these studies as summarized in Table 1. Notably, the clinical endpoints reflecting severe/critical COVID-19 illness were different, represented by acute kidney failure ($n=1$), acute respiratory distress syndrome or intensive care unit (ICU) admission or death from any cause ($n=2$), and severe respiratory failure ($n=1$), whilst no specific definition of critical disease was available in the remaining study.

The pooled analysis of these five studies is shown in Figure 1, which demonstrates a positive difference of suPAR values in each study in patients with critical COVID-19

compared to those without. The WMD of suPAR values in patients with critical illness vs. those without was 2.44 (95% CI, 2.17–2.72) ng/mL (heterogeneity, $I^2=64\%$) (Figure 1), and 2.40 (95% CI, 1.72–3.08) ng/mL using the random effects model, respectively. Overall, suPAR values were found to be increased by 55% (95% CI, 35–75%) in COVID-19 patients with various forms of critical illness compared to those without. In the study of Kerget et al. [15], excluded from our analysis since suPAR concentration was compared between patients with severe or moderate COVID-19 illness and controls, COVID-19 cases displayed 4.2–6.5 folds higher values than asymptomatic healthcare workers.

Taken together, the results of our analysis suggest that the measurement of suPAR in COVID-19 patients may represent a valuable tool for improving risk stratification accuracy, helping to predict the risk of developing severe consequences of SARS-CoV-2 infection, especially acute kidney injury (AKI), along with micro- and macrothrombosis. Some plausible mechanisms may support this conclusion. First, increased suPAR concentration has been associated with enhanced extra-mitochondrial enzymatic oxidation and oxidative stress in renal cells [2, 3], which may act in synergy with the direct kidney cell injury caused by SARS-CoV-2 and indirect injury

**Figure 1:** Weighted mean difference (WMD) and 95% confidence interval (95% CI) of soluble urokinase plasminogen activator receptor (suPAR) levels in patients with or without severe coronavirus disease 2019 (COVID-19) illness.

triggered by microthrombi in the renal vasculature, thus augmenting the risk of developing AKI [16]. It has also been suggested that enhanced suPAR release in the bloodstream may contribute to reduce plasmin generation by competitive inhibition of urokinase-type plasminogen activator (uPA) at cell surface [17]. This would ultimately promote the development of a hypofibrinolytic condition, a characteristic component of the hypercoagulable state that is common in patients with severe COVID-19 [7, 8], and would finally converge to synergically exacerbate the severity of thrombosis.

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References

- Huang Q, Xiong H, Yan P, Shuai T, Liu J, Zhu L, et al. The diagnostic and prognostic value of suPAR in patients with sepsis: a systematic review and meta-analysis. *Shock* 2020;53:416–25.
- Faubel S. SuPAR: a potential predictive biomarker for acute kidney injury. *Nat Rev Nephrol* 2020;16:375–6.
- Saleem MA. What is the role of soluble urokinase-type plasminogen activator in renal disease? *Nephron* 2018;139:334–41.
- Engström G, Zöller B, Svensson PJ, Melander O, Persson M. Soluble urokinase plasminogen activator receptor and incidence of venous thromboembolism. *Thromb Haemostasis* 2016;115:657–62.
- Sloand EM, Pfannes L, Scheinberg P, More K, Wu CO, Horne M, et al. Increased soluble urokinase plasminogen activator receptor (suPAR) is associated with thrombosis and inhibition of plasmin generation in paroxysmal nocturnal hemoglobinuria (PNH) patients. *Exp Hematol* 2008;36:1616–24.
- Menon T, Sharma R, Kataria S, Sardar S, Adhikari R, Tousif S, et al. The association of acute kidney injury with disease severity and mortality in COVID-19: a systematic review and meta-analysis. *Cureus* 2021;13:e13894.
- Lippi G, Sanchis-Gomar F, Favaloro EJ, Lavie CJ, Henry BM. Coronavirus disease 2019-associated coagulopathy. *Mayo Clin Proc* 2021;96:203–17.
- Vadasz Z, Brenner B, Toubi E. Immune-mediated coagulopathy in COVID-19 infection. *Semin Thromb Hemost* 2020;46:838–40.
- Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
- Arnold DT, Attwood M, Barratt S, Morley A, Elvers KT, McKernon J, et al. Predicting outcomes of COVID-19 from admission biomarkers: a prospective UK cohort study. *Emerg Med J* 2021. <https://doi.org/10.1136/emered-2020-210380> [Epub ahead of print].
- Azam TU, Shadid HR, Blakely P, O'Hayer P, Berlin H, Pan M, et al. Soluble urokinase receptor (SuPAR) in COVID-19-related AKI. *J Am Soc Nephrol* 2020;31:2725–35.
- Huang M, Li L, Shen J, Wang Y, Wang R, Yuan C, et al. Plasma levels of the active form of suPAR are associated with COVID-19 severity. *Crit Care* 2020;24:704.
- Oulhaj A, Alsuwaidi AR, Suliman A, Gasmelseed H, Khan S, Alawi S, et al. Admission levels of soluble urokinase plasminogen activator receptor (suPAR) associate with development of severe complications in hospitalised COVID-19 patients: a prospective cohort study. *Int J Infect Dis* 2021;107:188–94.
- Rovina N, Akinosoglou K, Eugen-Olsen J, Hayek S, Reiser J, Giamarellos-Bourboulis EJ. Soluble urokinase plasminogen activator receptor (suPAR) as an early predictor of severe respiratory failure in patients with COVID-19 pneumonia. *Crit Care* 2020;24:187.
- Kerget B, Kerget F, Aksakal A, Aşkın S, Uçar EY, Sağlam L. Evaluation of the relationship between KIM-1 and suPAR levels and clinical severity in COVID-19 patients: a different perspective on suPAR. *J Med Virol* 2021. <https://doi.org/10.1002/jmv.27099> [Epub ahead of print].
- Braun F, Lütgehetmann M, Pfefferle S, Wong MN, Carsten A, Lindenmeyer MT, et al. SARS-CoV-2 renal tropism associates with acute kidney injury. *Lancet* 2020;396:597–8.
- Lin H, Xu L, Yu S, Hong W, Huang M, Xu P. Therapeutics targeting the fibrinolytic system. *Exp Mol Med* 2020;52:367–79.

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