**CURRENT OPINION**

# Soluble Urokinase Plasminogen Activator Receptor: A Biomarker for Predicting Complications and Critical Care Admission of COVID-19 Patients

Athanasios Chalkias[1] · Angeliki Mouzarou[2] · Evangelia Samara[3] · Theodoros Xanthos[4] · Eleni Ischaki[5] · Ioannis Pantazopoulos[6]

## Abstract

The novel coronavirus infection has spread worldwide, causing a wide spectrum of clinical manifestations. Most patients develop moderate clinical illness, but a substantial number will experience severe pneumonia, which may rapidly progress to acute respiratory distress syndrome and multiple organ failure. In this population, soluble urokinase plasminogen activator receptor (suPAR) could serve as a quick triage test and independent marker of clinical severity, hospital and intensive care unit admission, complications, and mortality.

✉ Athanasios Chalkias
thanoschalkias@yahoo.gr

1 Department of Anesthesiology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larisa, Greece

2 Department of Cardiology, General Hospital of Paphos, Paphos, Cyprus

3 Department of Anesthesiology, Tzaneio General Hospital, Piraeus, Greece

4 School of Medicine, European University Cyprus, Nicosia, Cyprus

5 First Department of Critical Care Medicine and Pulmonary Services, Evangelismos Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

6 Department of Emergency Medicine, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larisa, Greece

**Key Points**

Patients with COVID-19 may experience severe pneumonia, acute respiratory distress syndrome, and multiple organ failure.

A reliable prognostic biomarker would be invaluable today for the triage of COVID-19 patients.

Soluble urokinase plasminogen activator receptor (suPAR) could serve as a quick triage test and independent marker of clinical severity and outcome in this population.

## 1 Introduction

In late 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) was identified as the cause of an outbreak of acute respiratory illness in Wuhan, China. In February 2020, the World Health Organization designated the disease as coronavirus disease 2019 (COVID-19). So far, the infection has spread to include hundreds of thousands worldwide, with confirmed cases increasing despite the austere measures applied [1, 2].

The novel coronavirus causes a wide spectrum of clinical manifestations in humans, with a large fraction of patients developing a short period of moderate clinical illness [1–3]. Nevertheless, a small but substantial number of patients experience severe pneumonia, which may rapidly progress to acute respiratory distress syndrome (ARDS), sepsis and septic shock, and multiple organ failure [4]. The disease severity is influenced by many factors, such as the initial viral titers in the airways, the age, or the comorbid conditions of the infected individual [5].

The pathogenesis of COVID-19 disease is not completely understood. Virus may spread through the respiratory mucosa and infect other cells, inducing a cytokine storm in the body. A recent study demonstrated that patients with COVID-19 pneumonia who developed ARDS had significantly higher neutrophil count and more severe cytokine storm than those without ARDS [5], while several authors have reported a substantial decrease in the total number of lymphocytes, indicating the consumption of immune cells, which may be fatal in older patients or patients with comorbidities [6, 7]. In addition, although we know that coronaviruses are able to initiate myocardial injury, it is too early to fully characterize and quantify the cardiovascular impact of COVID-19. However, arrhythmias, hypotension, and coronary syndromes have been reported in patients diagnosed with COVID-19. Of note, by March 11, Italy had 12,462 confirmed cases and 827 deaths (6.6% mortality), with more than two out of three of them reporting diabetes or cardiovascular disease. At this time, the full breadth and kinetics of immune responses in COVID-19 patients remain largely unknown, but it seems that a common manifestation among severe cases is the high levels of proinflammatory cytokines [1]. Considering that this cytokine storm can initiate viral sepsis and inflammatory-induced complications which may lead to organ damage and death, a reliable prognostic biomarker would be invaluable today for the triage of COVID-19 patients.

## 2 Soluble Urokinase Plasminogen Activator Receptor

The soluble urokinase plasminogen activator receptor (suPAR) is the soluble form of the cell membrane-bound protein urokinase plasminogen activator receptor (uPAR). suPAR has a secondary structure of 17 anti-parallel β-sheets with three short α-helices. There are three homologous domains of suPAR, causing its distinct ligand binding properties. The GPI-anchor links uPAR to the cell membrane, making it available for uPA binding. Although there are three different suPAR forms (suPARI-III, suPARII-III, and suPARI), only suPARII-III is known to be a chemotactic agent for promoting the immune system. suPAR and its ligand are involved in numerous physiological and pathological pathways, including the plasminogen activating pathway, modulation of cell adhesion, and migration and proliferation through interactions with extracellular matrix proteins.

The predictive ability of suPAR has been reported to be equal to or better than other scoring systems, and thus, its addition to conventional triage algorithms may improve risk

stratification [8]. In a study of 42,452 acutely presenting patients, suPAR had the highest area under the curve of all investigated individual predictors, including C-reactive protein (CRP), while there was no significant difference in the predictive value between age groups [9]. In another study, including 17,312 acutely admitted medical patients, the addition of suPAR to National Early Warning Score significantly improved risk prediction of both low- and high-risk acute medical patients [10]. Interestingly, patients with low National Early Warning Score, but elevated suPAR had mortality risks comparable to that of patients with higher National Early Warning Score. Three other studies reported that suPAR is significantly associated with 28-day, 30-day, and 90-day mortality [11–13]. Of note, Nayak et al. confirmed the previous findings and also reported an association between suPAR and long-term readmission rates [14]. These cumulative data suggest that high suPAR level at admission is a marker of severe disease; suPAR is associated with increased risk of readmission, morbidity, and mortality and can facilitate discrimination between survivors and non-survivors [15–18]. It may therefore provide benefit for evaluation of COVID-19 patients to determine the requirement for a more intensive clinical assessment and care [19].

Inflammation and oxidative stress are central components of the pathogenesis of acute kidney injury, and emerging reports indicate that COVID-19 manifestations can include renal tubular injury and collapsing glomerulopathy [20–22]. The latter is an aggressive and distinct histological variant of focal segmental glomerulosclerosis characterized by segmental or global glomerular tuft collapse with hypertrophy and hyperplasia of the overlying podocytes [23]. Although the pathogenesis of collapsing glomerulopathy in COVID-19 patients is likely multifactorial, uPAR is required for the development of podocyte foot process effacement and proteinuria [24]. In addition, the recent identification of cellular sources of suPAR demonstrates its pathogenic role as a circulating mediator of kidney disease, indicating the devastating effects of inflammation and cytokine storm on the kidneys [25].

Hayek et al. identified an association between elevated plasma suPAR levels and the development of acute and chronic kidney disease. This association was observed in patients with normal baseline kidney function and was independent of conventional risk factors for kidney disease [26, 27]. Not surprisingly, the inclusion of the suPAR level in a prediction model significantly improved discrimination of future risk of chronic kidney disease, with the risk reclassification being greater than that with well-established biomarkers, such as high-sensitivity C-reactive protein (CRP). Considering that there has been little progress in the overall risk stratification, prevention, and treatment of acute kidney injury, these data suggest that suPAR meets critical requirements for a biomarker of acute and chronic kidney disease in patients with COVID-19.

What is most important is that suPAR increases with the severity of the infection or organ dysfunction, reflecting the body's immune response, and may have a strong prognostic value in COVID-19 patients, especially in those with systemic inflammatory response syndrome and sepsis/septic shock [28–32]. In patients with systemic inflammatory response syndrome, suPAR is a stronger marker of 2-day, 30-day, and 90-day mortality than CRP or interleukin-6 [28], while its levels do not correlate with the CRP in patients with sepsis [30–34]. Therefore, suPAR reflects general activation of the immune system rather than exerting inflammatory actions. This may be extremely important considering that the reported sensitivity for mortality and the negative predictive value of suPAR are > 80% and 94.5%, respectively [31]. Furthermore, suPAR may be able to assist in the discrimination between an excessive immune response and immunosuppression, facilitating early modulation of treatment strategy.

suPAR is an inflammatory biomarker that can be easily measured in plasma or serum. The available test allows a fast prognosis for patients, as the results can quickly be obtained on-site in the emergency room or other in-hospital settings, avoiding the need for samples to be passed through the clinical laboratory, or can even be obtained prior to hospitalization (time to result 20 min). Based on the aforementioned evidence, the suPAR could serve as a quick triage test and independent marker of clinical severity, 30-day readmission, complications, and mortality in this pandemic [10, 19, 35, 36]. We believe that the results of ongoing trials in Germany, the UK, Denmark, Greece, and the USA will be important for clinicians worldwide.

## 3 Conclusion

In conclusion, suPAR seems extremely promising as a COVID-19 prognostic marker and may assist in the early selection of patients who can stay at home or must be admitted to the hospital and/or intensive care unit. In this difficult outbreak, humanity must use all the available weapons, and suPAR may prove a powerful triage biomarker.

### Compliance with Ethical Standards

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