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Running title: Supar in HD patients with Covid-19

Ioannis Griveas, Evaggelos Pratilas

PII: S1473-0502(22)00290-7
DOI: https://doi.org/10.1016/j.transci.2022.103590
Reference: TRASCI103590

To appear in: Transfusion and Apheresis Science

Please cite this article as: Ioannis Griveas and Evaggelos Pratilas, Soluble Urokinase Plasminogen Activator Receptor and its complicated role in hemodialysis (HD) patients with Covid-19 infection

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doi:https://doi.org/10.1016/j.transci.2022.103590

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Soluble Urokinase Plasminogen Activator Receptor and its complicated role in hemodialysis (HD) patients with Covid-19 infection

Ioannis Griveas¹,
Evaggelos Pratilas²

1. Medical Director, Consultant Nephrologist, Nephrology Department, Army Share Fund Hospital of Athens, Greece, 417 NIMTS
2. Resident in Nephrology, Nephrology Department, Army Share Fund Hospital of Athens, Greece, 417 NIMTS

Corresponding author

Ioannis Griveas

Address: 362 Kifisias Ave, 15233, Chalandri, Athens, Greece,

Telephone number: 00306932379323

Running title: Supar in HD patients with Covid-19

E-mail: giannisgriv@hotmail.com
Conflict of Interest: None

Source of funding: None

Abstract

Background: Soluble urokinase plasminogen receptor (suPAR) is a protein in the blood that has been described to reflect the severity status of systemic inflammation.

Aims and Objective: We investigated the association between admission suPAR levels and severity and outcome of HD patients with Covid-19 infection.

Materials and Method: In an observational study of adult HD patients hospitalized for Covid-19, we measured suPAR levels in plasma samples. The time table for those measurements were as follows: at the beginning of admission, after a hemoperfusion (HP) session for those patients that received them, and just before discharge.

Results: Of the 17 patients (7 were male), 13 patients received HP (mean age: 74 years old). The median suPAR level was 12.94 ng/ml. For those who undertook HP in HD unit the median suPAR level before the session was 12.95 ng/ml and 6.2 ng/ml at the end of each session (p<0.05). 3 patients had a suPAR level below 7 ng/ml. 2 of them survived without developing pleural effusions. 7 patients were discharged from the hospital with median suPAR level 12.08 ng/ml which did not differ significantly from the median suPAR level of the deceased ones (13.68 ng/ml).
Conclusion: Admission levels of suPAR in HD patients hospitalized for Covid-19 do not seem to be predictive for their clinical course in general. Chronic Kidney Disease and its relation to suPAR independently of patients’ inflammation status may be the key component for our notice. Despite that, in patients where low levels of suPAR combined with absence of pleural effusions the prognosis was excellent.

Keywords: hemodialysis, covid-19, supar

Introduction:
Soluble urokinase plasminogen receptor (suPAR) is a protein in the blood that has been described to reflect the severity status of systemic inflammation. It has also been connected with low grade inflammation\(^1\). Our research team suggested that plasma suPAR concentrations may be a promising inflammation biomarker for the HD population. We also noticed the existence of an independent association of suPAR with nutritional status, anemia, mineral bone disease, hospitalization and mortality in HD population\(^1\).

At the same time, an elevated level of suPAR has been independently associated with the incident of chronic kidney disease. In particular, it has been reported that in patients with Chronic Kidney Disease (CKD), suPAR correlated with reduced Glomerular Filtration Rate (GFR)\(^2\). It has been also demonstrated that suPAR provides prognostic data regarding cardiovascular events, and mortality rates in the general population in critical patients and in HD population\(^1,2,3,4\).
The Covid-19 outbreak has been connected with increased circulating levels of D-dimers, a fact that suggests endothelial activation\textsuperscript{5}. At the same time Covid-19 infection has been linked to several types of clinical presentation varying from low-degree fever or flu-like symptoms to severe respiratory failure\textsuperscript{6}. There are data from the literature that suggest suPAR may trace patients with Covid-19 infection who will need intense immediate therapeutic intervention early and also trace patients that are expected to have a milder clinical course\textsuperscript{6,7}.

Considering all the above parameters and having thought that HD population has a lot of specific features, we investigated the association between admission suPAR levels and severity and outcome of HD patients with Covid-19 infection.

**Material and Methods:**

In an observational study of adults HD patients hospitalized for Covid-19 infection, we measured suPAR levels in plasma samples. In some of our patients we used resin-directed hemoadsorption cartridges (HA-330 and HA-130) manufactured by the Jafron Biomedical Company, China. This group of patients received hemoperfusion (HP) for 1-2 sessions in hemodialysis unit (HD) and 5 sessions in Intensive Care Unit (ICU). The time table for those measurements were as follows: at the beginning of admission, before and after hemoperfusion (HP) session for those patients that received them, and just before discharge. suPAR was measured by an enzyme immunoassay in duplicate (suPARnostic\textsuperscript{™}, ViroGates, Lyngby, Denmark).
Results:

Of the 17 patients (7 were male), 13 patients received HP (mean age: 74 years old), 12 patients in HD unit and one patient in ICU. 9/17 patients were diabetic. 12/17 officially had a cardiovascular background.

The median suPAR level for all of our study group at admission was 12.94 ng/ml. For those who undertook HP in the HD unit the median suPAR level before the session was 12.95 ng/ml and 6.2 ng/ml at the end of each session (p<0.05). suPAR levels at the end of session in the dialysate fluid (waste) was 5.9 ng/ml.

One patient in ICU received 5 sessions of HP at the same time with CRRT with 3 sessions during three consecutive days and one session after a week and then the fifth one after 3 days. In this case, median suPAR levels started from 15 ng/ml before each HP session, ended at 5.7 ng/ml at the end of the HP session and rose again to 15 ng/ml before the next session.

3 patients had suPAR levels below 7 ng/ml. Two of them survived without developing pleural effusions or pulmonary infiltrates.

7 patients were discharged from the hospital with a median suPAR level of 12.08 ng/ml which did not differ significantly from the median suPAR level of the deceased (13.68 ng/ml).

Discussion:
The Covid-19 pandemic and its unpredictable clinical course in many cases opened the discussion regarding early prognostic markers. Endothelial activation seems to have a crucial role in Covid-19 infection. Urokinase plasminogen activator receptor (uPAR) that is bound on the endothelium may be cleaved early during the disease course leading to an increase of its soluble counterpart, namely suPAR. On this basis, suPAR proposed as an early predictor of the risk of severe respiratory failure in Covid-19 patients, which could give physicians an early tool to trace patients that could benefit from intensified management.

The Covid-19 infection by itself and Chronic Kidney Disease are entities which need closer insight regarding suPAR usefulness. suPAR, has been suggested to mirror the degree of immunoactivation and can be measured from blood, urine, saliva, or cerebrospinal fluid. In critically ill patients, several independent investigations have reported elevated suPAR in conditions of systemic inflammatory response syndrome (SIRS), bacteriemia, sepsis, and septic shock, in which high circulating suPAR levels indicated an unfavorable prognosis. However, this ‘dogma’ had been based on various studies investigating circulating suPAR levels in different disease etiologies, including sepsis, cardiovascular disorders, and cancer. At the same time, elevated suPAR has been linked with an incident CKD and as a promoting pathogenic factor for renal scarring in focal segmental glomerulosclerosis.

Our patients had CKD under HD, a cardiovascular disease background and diabetes as a major primary cause of their renal disease. Along with Covid-19 infection, they...
have many of contributing factors that may affect suPAR levels. This is the reason, from our point of view, that suPAR levels have not the same prognostic value in our study for Covid-19 patients has been mentioned previously. It has been pointed out that with HP sessions, suPAR levels decreased significantly. Due to the suPAR molecular weight (45-55kd), it can be removed with the hemoadsorption cartridges that have been used. Another proof of that is the detection of suPAR in the dialysate waste products. Thereby, our findings support the view that suPAR could be used as a biomarker of clinical course of patients with Covid-19 and CKD. The tendency of increasing suPAR levels before the next HP promotes the view of frequent and intense HP sessions in order to control inflammatory markers such as suPAR. How the decreased levels of suPAR correlate with improvement of Covid-19 infection is an issue open for further investigation.

Despite our previous comments, it has to be pointed out that we had 3 patients with suPAR levels below 7 ng/ml and 2 of them survived without developing pleural effusions or pulmonary infiltrates. It seems that low levels of suPAR in patients who are asymptomatic without pulmonary involvement have a favorable prognostic value.

**Conclusion:**

In conclusion, admission of suPAR levels in HD patients hospitalized for Covid-19 do not seem to be predictive for their clinical course in general. A Chronic Kidney Disease background and its relation to suPAR levels, independently of the patients’
inflammation status, may be the key component for our notice. Additionally, other comorbidities of our patients and lack of strong evidence regarding the importance of suPAR level measurement and systemic inflammation provoke the need for further investigation. Despite that, in patients where low levels of suPAR combined with the absence of pleural effusions the prognosis was excellent. Future clinical studies may therefore consider suPAR not only as an epiphenomenon but also as a potential therapeutic target in inflammatory disorders especially in combination with HP sessions.

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