Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Full Length Article

Soluble urokinase Plasminogen Activator Receptor (suPAR) levels are predictive of COVID-19 severity: an Italian experience

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ABSTRACT

Background: The soluble urokinase Plasminogen Activator Receptor (suPAR) has been identified as a reliable marker of COVID-19 severity, helping in personalizing COVID-19 therapy. This study aims to evaluate the correlation between suPAR levels and COVID-19 severity, in relation to the traditional inflammatory markers.
Methods: Sera from 71 COVID-19 patients were tested for suPAR levels using Chorus suPAR assay (Diesse Diagnostica Senese SpA, Italy). suPAR levels were compared with other inflammatory markers: IL-1β, IL-6, TNF-α, circulating calprotectin, neutrophil and lymphocyte counts, and Neutrophil/Lymphocytes Ratio (NLR). Respiratory failure, expressed as P/F ratio, and mortality rate were used as indicators of disease severity.
Results: A positive correlation of suPAR levels with IL-6 ($r = 0.479$, $p = 0.000$), TNF-α ($r = 0.348$, $p = 0.003$), circulating calprotectin ($r = 0.369$, $p = 0.002$), neutrophil counts ($r = 0.447$, $p = 0.001$), NLR ($r = 0.492$, $p = 0.001$) has been shown. Stratifying COVID-19 population by suPAR concentration above and below 6 ng/mL, we observed higher levels of circulating calprotectin (10.1 μg/mL, SD 7.9 versus 6.4 μg/mL, SD 7.5, $p < 0.001$), higher levels of P/F ratio (207.5 IQR 188.3 vs 312.0 IQR 127.8, $p = 0.013$) and higher mortality rate. Median levels of suPAR were increased in all COVID-19 patients requiring additional respiratory support (Nasal Cannula, Venturi Mask, BPAP and CPAP) (6.5 IQR = 4.9) compared to the group at room air (4.6 IQR = 4.2).
Conclusion: suPAR levels correlate with disease severity and survival rate of COVID-19 patients, representing a promising prognostic biomarker for the risk assessment of the disease.

1. Introduction

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused extensive morbidity and deaths, which has entailed an enormous burden on the healthcare system worldwide. SARS-CoV-2 can cause asymptomatic to severe coronavirus disease 2019 (COVID-19), primarily impacting the lungs, but also several other organs.

A large number of biomarkers have been evaluated to identify patients at risk of developing severe COVID-19, so that appropriate care interventions can be offered prophylactically or at least at an early stage of the disease [1–4].

Among these, the soluble urokinase Plasminogen Activator Receptor (suPAR), already known as a deterioration predictor for several infectious and inflammatory disorders, is proving to have an important role in COVID-19. It is generated by the proteolytic cleavage of the soluble form of the cell membrane-bound protein uPAR, which is expressed mainly on immune cells, endothelial cells, and smooth muscle cells. It is

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Table 1
Demographic, laboratory and clinical characteristics of study patients.

Patients, n	71
Age, years, mean (SD)	69.01 (18.21)
Male gender, n (%)	46 (64.8)
Comorbidity, n (%)	58 (81.7%)
Discharge, n (%)	
At home	13 (18.8)
Low care hospitals	47 (68.1)
Transferred to another ward	4 (5.8)
Dead, n (%)	5 (7.1)
Clinical course, n (%)	
Improved	18 (25.7)
Worsened	8 (11.4)
Stable	44 (62.9)
COVID-19 pneumonia, n (%)	51 (71.8)
Respiratory status, n (%)	
Room Air (RA)	20 (28.6)
Nasal Cannula/Venturi Mask	44 (62.9)
BiPAP-CPAP	6 (8.6)
PaO2/FiO2 (P/F) ratio at the time of blood collection mean (SD)	269.74(104.01)
CRP mg/dL, mean (SD)	6.43 (6.43)
Circulating calprotectin μg/mL, mean (SD)	8.30 (7.90)
IL-6 pg/mL, mean (SD)	12.74 (30.74)
IL-1β pg/mL, mean (SD)	11.09 (34.24)
TNF-α pg/mL, mean (SD)	6.63 (5.90)
Neutrophils % mean (SD)	75.07 (13.50)
Lymphocytes % mean (SD)	16.46 (10.55)
Neutrophils/Lymhocytes ratio mean (SD)	8.49 (8.30)

an immune cell expressed GPI-linked receptor that is upregulated at sites of inflammation and tissue remodelling [5,6] and also forms part of the fibrinolysis cascade [7]. The uPAR interacts and cooperates with many ligands and receptors, primarily integrins, to facilitate intracellular signalling, cell migration, cell adhesion and tissue remodelling [8].The protein consists of three domains, D1-D3, connected with a linker region between D1 and D2-D3. Cleavage sites are in the linker region and the GPI anchor, and the three main suPAR isoforms are full-length suPAR I-III, suPAR I, and suPAR II-III. Interestingly, the cleavage of uPAR/suPAR in the linker region exposes an SRSRY sequence, which is involved in chemotaxis.

It is released during inflammation or immune activation [9] and it is not disease specific. Its circulating levels reflect severity and prognosticate outcome of renal failure [10] and high suPAR levels are associated with acute kidney injury in various clinical contexts [11]. In recent years, suPAR has been implicated to play a key role in attenuating the disease progression of rheumatoid arthritis [12], also in correlation with disease activity [13,14]. One of the most interesting application of the marker is in triaging patients to early predict clinical deterioration due to suspected bacterial infections [15]. A large Greek multicentre study showed that suPAR is a strong predictor of mortality including the sepsis marker among the parameters of the Acute Physiology and Chronic Health Evaluation (APACHE) II score [16].

Recently, suPAR has been shown to predict early respiratory failure [17,18], kidney injury [10], and clinical outcome in patients with SARS-CoV-2 infection. Huang et al. showed that active suPAR levels increase as the disease worsens [19]. A suPAR concentration is significantly elevated in patients with COVID-19, and stands out as a predictor of overall disease severity and outcome [20–23].

Patients with symptoms of COVID-19 and suPAR ≥6 ng/mL had high risk concerning the need for mechanical ventilation or mortality [24]. Levels of suPAR <4 ng/mL are usually found in the reference population composed of healthy subjects.

The suPAR guided Anakinra treatment for Validation of the risk and Early Management Of seveRE respiratory failure by COVID-19 (SAVE-MORE trial) has included suPAR (≥6 ng/mL) as inclusione criteria among traditional inflammatory biomarkers-for stratifying patients, showing how early identification of patients with risk of progression to severe disease is crucial for timely initiation of targeted interventions. This may prevent progression to severe respiratory failure and reduce mortality [25,26].

The aim of our study was to evaluate the clinical utility of measuring suPAR levels in an Italian setting of hospitalized COVID-19 patients for severity assessment and risk stratification, in relation to traditional markers.

2. Materials and methods

2.1. Study population

Serum samples from a total of 71 COVID-19 patients were collected from November 2021 to December 2021 (Delta was the predominant variant in that area) at the Internal Medicine of *S. Maria* Nuova Hospital and the Infectious Diseases Unit of *S. Maria* Annunziata Hospital (Florence, Italy). The main demographic, laboratory and clinical characteristics of the studied population are reported in Table 1.

Patients were tested for suPAR when admitted or a few days later (median 3 days, IQR = 3.73). Additionally, the sera were also tested for C reactive protein (CRP), interleukin 6 (IL-6), interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α), circulating calprotectin, neutrophil count, lymphocyte count, Neutrophil/Lymphocyte ratio (NLR).

The respiratory support required for COVID-19 patients was according to the following categories: Room Air (RA), Nasal Cannula (NC), oxygen mask Venturi Mask (VM), and Continuous/Bilevel Positive Airway Pressure (CPAP/BiPAP).

The current Berlin definition of acute respiratory distress syndrome (ARDS) using the PaO2/FiO2 (P/F) ratio was used to classify the severity of the respiratory status [27].

The clinical course and the severity of the disease were evaluated using the World Health Organization Clinical Progression Scale (WHO-CPS).

Informed consent was obtained from all subjects enrolled in the study. The study was in accordance with the Helsinki Declaration, as revised in 2013.

2.2. Laboratory examinations

suPAR levels were measured using Chorus suPAR assay (Diesse Diagnostica Senese SpA), performed on the Chorus Trio Instrument (Diesse Diagnostica Senese SpA), a fully automated instrument for the quantitative determination of suPAR in human serum and plasma (sodium citrate and lithium heparin). The novel test has been developed in collaboration with ViroGates company (Birkeroed, Denmark) by using suPARnostic reagents.

The format is a monotest device containing all the reagents necessary to carry out the test, which is automatically processed by the instrument by reading a barcode and capable of processing 30 samples in about 75 min.

The Chorus suPAR test is an immunoenzymatic assay based on the ELISA sandwich method. suPAR present in the test sample is caught by specific monoclonal antibodies fixed on the solid phase and detected by a specific monoclonal antibody conjugated with peroxidase. Unbound components are eliminated by washing and bound enzymatic activity is evaluated colorimetrically by transformation of a chromogenic substrate. A colored product is formed in proportion to the amount of nanograms/ml (ng/mL). The analytical measuring range (AMR) of the assay extends from 1.5 to 20 ng/mL. Patients have also been evaluated for the following laboratory parameters: IL-6 (Human IL-6 Instant Enzyme-linked Immunosorbent assay; eBioscience, Bender MedSystem GmbH, Vienna, Austria); IL-1 β (Human IL-1 β Instant Enzyme-linked Immunosorbent assay; eBioscience, Bender MedSystem GmbH, Vienna, Austria); circulating calprotectin (QUANTA Flash® Circulating Calprotectin assay; Inova Diagnostics, San Diego, CA. USA); CRP (Unicel Coulter DxC 800 Synchron Central System; Beckman Coulter Inc., Brea, CA, USA); TNFα (Human TNF-alpha Quantikine Immunoassay; R&D

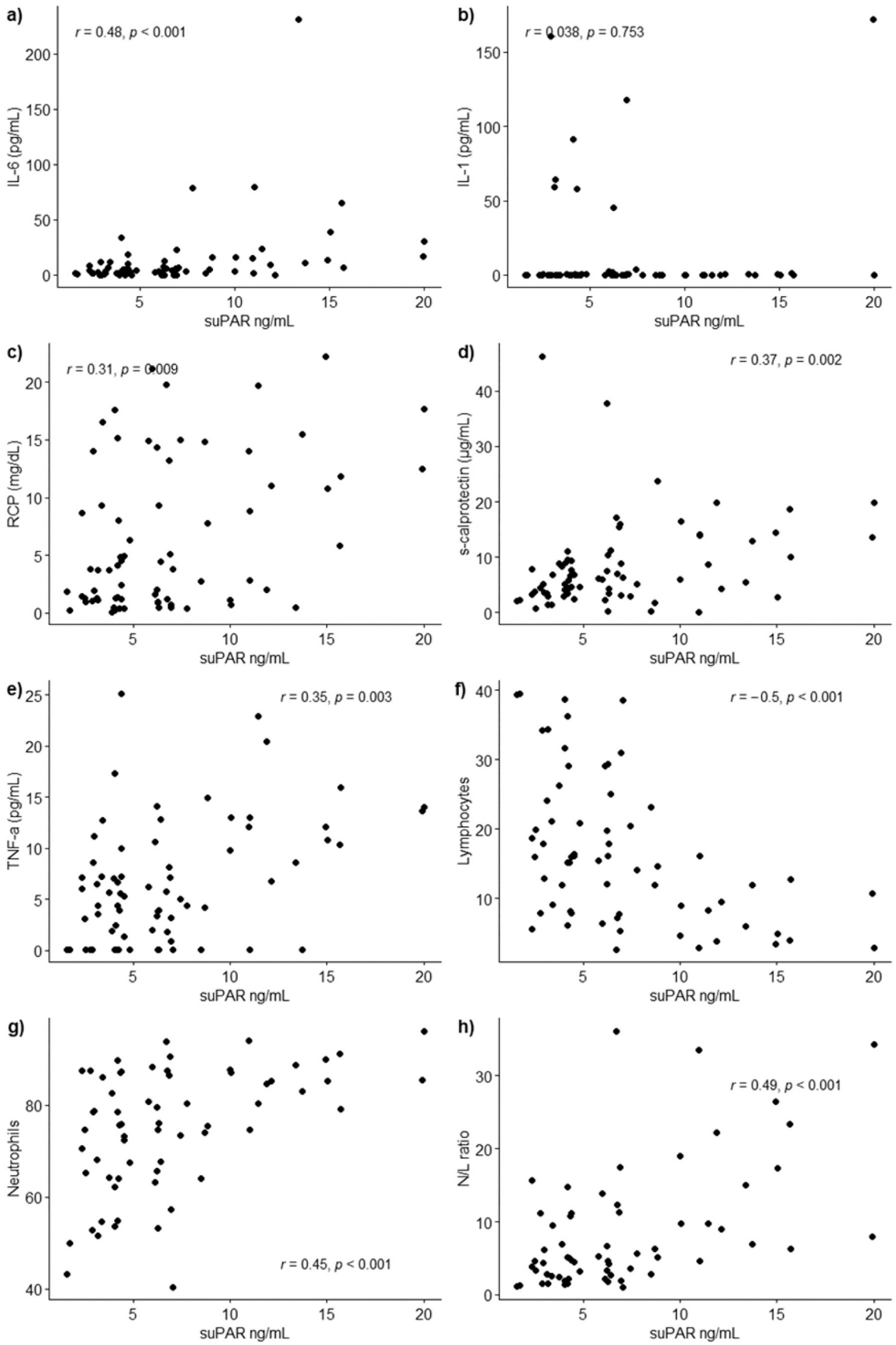


Fig. 1. suPAR levels compared to clinical laboratory parameters. Spearman's correlation coefficients were statistically significant with $p < 0.05$. *IL-1β, interleukin 1β; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha; CRP, C-Reactive Protein; s-calprotectin, serum-calprotectin; NLR, Neutrophils/Lymphocytes ratio.*

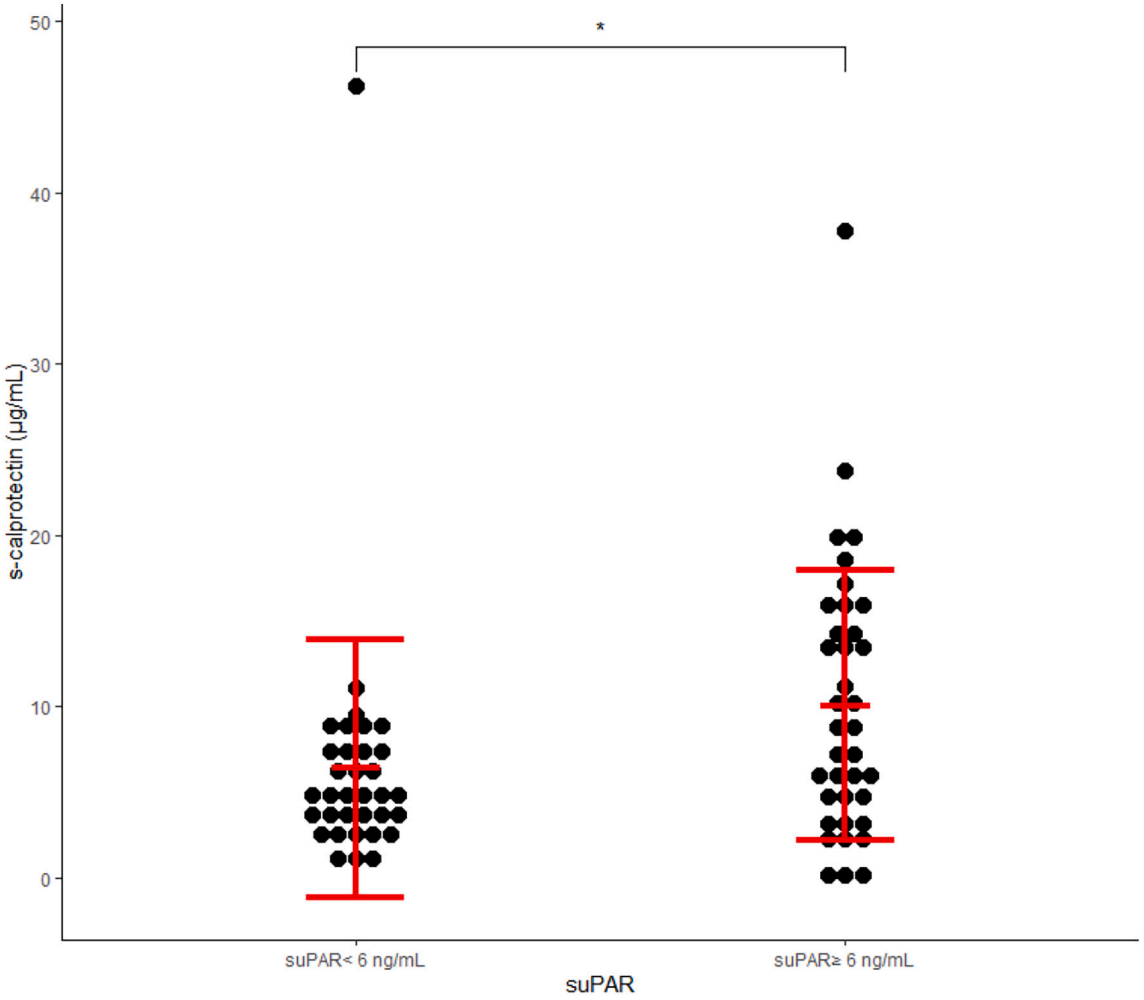


Fig. 2. Comparison of s-calprotectin between groups with suPAR levels above and below the cutoff value of 6 ng/mL (Mann Whitney *U* test; $p < 0.05$).

Systems Inc., Minneapolis, MN, USA). Moreover, all samples were processed for hemochromocytometric exam through Sysmex DI-60 system (Sysmex, Kobe, Japan).

2.3. Statistics

A previous descriptive analysis was carried out, absolute frequencies and percentages were calculated for qualitative variables, mean and standard deviation (SD) or median and interquartile range for quantitative ones. The association between qualitative variables and suPAR was evaluated by chi-squared test; instead, the difference of quantitative variables between the two groups was determined by *t*-test or Mann-Whitney test, according to the normality distribution, evaluated by Kolmogorov-Smirnov test. The correlation between suPAR and the other laboratory parameters were evaluated with the Spearman correlation coefficient.

The Kaplan-Meier curves were carried out to compare survival between the group with suPAR ≥6 ng/mL and < 6 ng/mL which were compared by log-rank test.

Each statistical test was two-tailed and was considered significant for *p*-values <0.05. Statistical analyses were carried out by R software version 4.0.0.

3. Results

We assessed potential correlation of suPAR with IL-1β, IL-6, TNF-α, circulating calprotectin, neutrophil and lymphocyte counts, and NLR, demonstrating a positive correlation with IL-6 ($r = 0.48$, $p = 0.000$), TNF-α ($r = 0.35$, $p = 0.003$), circulating calprotectin ($r = 0.37$, $p = 0.002$), neutrophil count ($r = 0.45$, $p = 0.001$), NLR ($r = 0.49$, p = 0.001). There was no correlation with IL-1β and a negative correlation with lymphocyte count ($r = -0.5$, p = 0.001) (Fig. 1).

Comparing the mean value of the circulating calprotectin between the two groups below and above 6 ng/mL of suPAR concentration, 6.4 µg/mL, SD 7.5 and 10.1 µg/mL, SD 7.9, respectively, the difference was statistically significant ($p < 0.001$) (Fig. 2). Analyzing the two aforementioned groups according the P/F ratio, the box-whisker plot showed that the median measurement of P/F ratio was lower in the group with suPAR <6 ng/mL (207.5 IQR 188.3 vs 312.0 IQR 127.8, $p = 0.013$) (Fig. 3). Moreover, median levels of suPAR were increased in all COVID-19 patients requiring additional respiratory support (Nasal Cannula, Venturi Mask, BPAP and CPAP) (6.5 IQR = 4.9) compared to group at room air (4.6 IQR = 4.2).

Fig. 4 depicts the Kaplan-Meier curve stratified by suPAR concentration below and above 6 ng/mL. Across all patients, the group with a

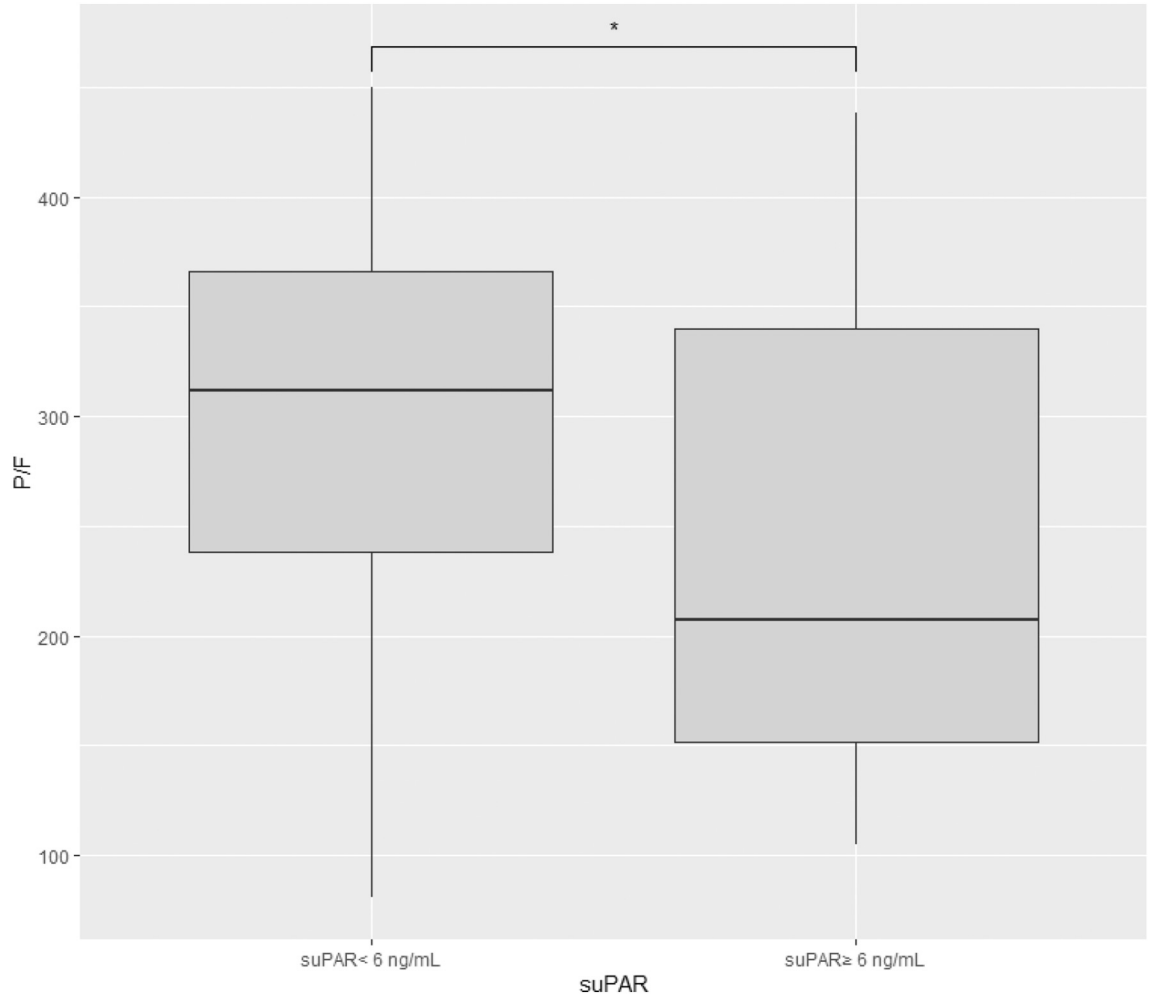


Fig. 3. Respiratory failure expressed as P/F ratio and suPAR levels of COVID-19 patients at admission.

suPAR concentration < 6 ng/mL showed a better survival probability, statistically significant ($p \leq 0.025$), than the group of patients with a suPAR concentration ≥ 6 ng/mL. This is further confirmed comparing the median of survived (4.82 ng/mL, IQR 3.92–7.03) and non survived (11.03 ng/mL, IQR 10.94–13.73) groups with a statistically significant difference ($p = 0.015$) by a Mann-Whitney test.

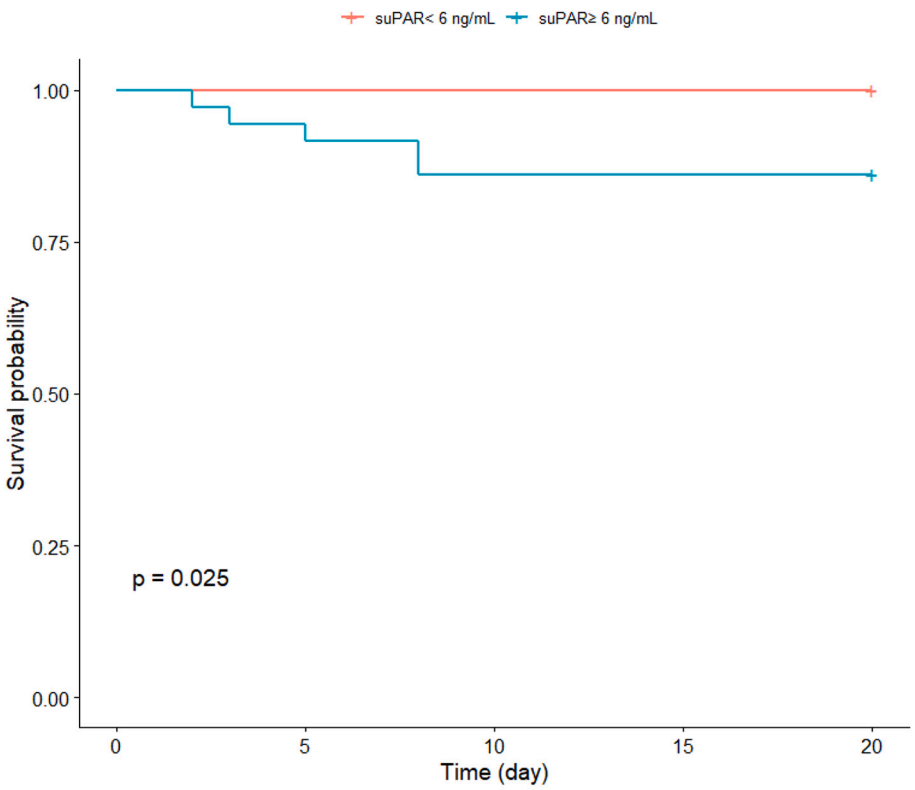
Moreover, stratifying groups according to the clinical course by WHO-CPS, suPAR levels showed a difference between the median value of the worsened (12.38, IQR 9.71, 15.11) and stable patients' groups (4.46, IQR 3.15, 6.89), statistically significant ($p < 0.05$) compared to the improved patients' group (6.50, IQR 4.27–8.30). Similarly, the differences were statistically significant also for the other clinical laboratory parameters studied (Table 2).

4. Discussion

SARS-CoV-2 may induce a heterogeneous clinical presentation ranging from asymptomatic to life-threatening infection [28,29]. Respiratory signs are the most common features in patients affected by the symptomatic disease and severe infections, and manifest as pneumonia and progressive respiratory failure up to acute respiratory distress syndrome (ARDS) and multi-organ dysfunction, typically complicated by deep vein thrombosis and pulmonary embolism [30]. Accordingly, several scoring systems such as the modified Early Warning Score (mEWS) [31], revised National Early Warning Score (NEWS) [32], APACHE score, Sequential Organ Failure Assessment (SOFA) score, and quick SOFA (qSOFA) score have been used for triage decision-making but without reaching high sensitivity and specificity. Moreover different Intensive Care Unit (ICU) models and therapeutic strategies have been proposed over this period to optimize ICU management of COVID-19 patients [33–36] and for the same purpose several biomarkers have been assessed to predict worse outcomes and treatment responses at an early stage of the disease [37–41].

A suPAR concentration ≥ 6 ng/mL has been identified as predictor of severe consequences of SARS-CoV-2 infection or death in patients hospitalized with COVID-19 pneumonia [22–26, 42–44]. In particular, suPAR showed good performance in predicting the need for invasive ventilation and ICU admission.

In line with the aforementioned studies, our data showed that suPAR levels ≥6 ng/mL in patients hospitalized for COVID-19 are predictive of clinical worsening, poor prognosis and mortality, adding significant prognostic information to the well-established prognostic indicators [45], such as raised NLR [46,47]. In our study suPAR correlated with all studied markers, except IL-1β. We would have expected high levels of IL1β as patients with high levels of suPAR are candidates for the anti-IL1 therapy. Although a role for IL-1 β in inflammation is well known [48,49], several studies both in animal models and humans demonstrated that circulating levels of this cytokine are frequently not elevated or slightly increased [50–53]. Conversely, elevated IL-6 levels are consistently found throughout the studies. This is due to the fact that



	survived	dead	p-value
n.	65	5	
suPAR ng/mL (median [IQR])	4.82 [3.92, 7.03]	11.03 [10.94, 13.73]	0.015

Fig. 4. Kaplan-Meier survival analysis: comparison between groups with suPAR levels above and below the cutoff value of 6 ng/mL in predicting mortality.

Table 2
Comparison of clinical laboratory parameters (including suPAR levels) using the clinical status assessed with the WHO-CPS score.

	Improved	Worsened	Stable	p
MARKER (median [IQR])				
suPAR (ng/mL)	6.50 [4.27, 8.30]	12.38 [9.71, 15.11]	4.46 [3.15, 6.89]	0.005
RCP (mg/dL)	1.26 [0.80, 4.54]	14.75 [8.22, 18.54]	3.78 [1.22, 10.81]	0.001
IL-6 (pg/mL)	4.35 [2.80, 14.60]	14.25 [8.85, 39.27]	3.05 [0.58, 6.50]	0.010
IL-1 (pg/mL)	0.10 [0.10, 0.10]	0.20 [0.10, 0.70]	0.10 [0.10, 0.50]	0.081
Neutrophil %	77.75 [72.98, 86.85]	90.00 [85.70, 92.65]	75.20 [64.52, 85.05]	0.010
Lymphocite %	14.35 [8.95, 16.10]	3.90 [3.10, 9.15]	16.05 [8.60, 24.77]	0.019
N/L ratio	5.44 [4.54, 9.71]	23.41 [10.39, 30.02]	4.65 [2.62, 9.51]	0.016

TNF-α and IL-1 are early regulators of the immune response, actively involved in promoting the release of downstream proinflammatory molecules, particularly IL-6 which in turn inhibits the release of TNF-α and IL-1 β [54]. Accordingly, serum concentrations of TNF-α and IL-1 β reach a peak very early (60–90 min) during an inflammatory process, and then rapidly diminished. At this point, IL-6 levels markedly increase and remain stably elevated until sepsis recovers.

The main limitation of our study is that almost all COVID-19 patients had comorbidities which could affect suPAR levels, especially cardiovascular and kidney diseases. Nevertheless, Enocsson et al. showed that suPAR functioned as an independent predictor of COVID-19 disease severity. Another limitation is the lack of longitudinal samples to investigate the response to treatment. However, the strength of our study is that it is a so called "real-life" Italian setting of COVID-19 patients, hospitalized for severity and risk stratification, also in relation to traditional markers. Up to now, the use of suPAR has been partial in this scenario due to its low familiarity to clinicians or its limited access. Therefore, future studies are needed to include suPAR among clinical and laboratory risk stratification tools in prognostic models for personalized treatment.

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Data availability statement

The data are available upon request to the corresponding author.

CRediT authorship contribution statement

Maria Infantino: Data curation, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision, Conceptualization. **Lorenza Morena:** Investigation, Writing – original draft, Writing – review & editing. **Massimo Antonio Di Pietro:** Investigation, Writing – review & editing. **Benedetta Romanin:** Investigation, Writing – original draft. **Barbara Cimolato:** Writing – review & editing. **Beatrice Anna Luisa Rocca:** Writing – original draft. **Silvia Tunnera:** Writing – original draft. **Giulia Modi:** Writing – original draft. **Marta Tilli:** Writing – original draft. **Valentina Grossi:** Writing – original draft. **Barbara Lari:** Writing – original draft. **Helena Cerutti:** Data curation, Formal analysis. **Giulia Tesi:** Data curation, Formal analysis. **Valentina Anrò:** Data curation, Formal analysis. **Alessandra Cartocci:** Data curation, Methodology, Formal analysis. **Maurizio Benucci:** Writing – original draft, Conceptualization. **Francesca Veneziani:** Writing – original draft, Conceptualization. **Patrizia Casprini:** Writing – original draft, Conceptualization. **Mariangela Manfredi:** Data curation, Methodology, Writing – original draft, Supervision, Conceptualization.

Declaration of Competing Interest

Helena Cerutti, Giulia Tesi, Valentina Anrò are employees of Diesse Diagnostica Senese SpA (Siena, Italy). The other authors have no conflict of interests.

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