*Article*

SCIENCE PROGRESS

Science Progress
2021, Vol. 104(S2) 1–13

DOI: 10.1177/00368504211026119
journals.sagepub.com/home/sci
SAGE

# Circulating furin, IL-6, and presepsin levels and disease severity in SARS-CoV-2–infected patients

**Abdurrahim Kocyigit[1], Ozgur Sogut[2], Ezgi Durmus[1], Ebru Kanimdan[1], Eray Metin Guler[1], Onur Kaplan[2], Vildan Betul Yenigun[1], Canan Eren[3], Zeynep Ozman[1] and Oznur Yasar[1]**

[1]Department of Medical Biochemistry, Bezmialem Vakif University, Istanbul, Turkey
[2]Department of Emergency Medicine, Health Science University, Haseki Training and Research Hospital, Istanbul, Turkey
[3]Marmara University Pendik Training and Research Hospital, Medical Microbiology and Blood Centre, Pendik, Istanbul

## Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a vast number of infections and deaths that deeply affect the world. When the virus encounters the host cell, it binds to angiotensin-converting enzyme 2, then the S protein of the virus is broken down by the transmembrane protease serine 2 with the help of furin, allowing the virus to enter the cell. The elevated inflammatory cytokines suggest that a cytokine storm, also known as cytokine release syndrome, may play a major role in the pathology of COVID-19. Therefore, the aim of this study is to investigate the relationship between circulating furin levels, disease severity, and inflammation in patients with SARS-CoV-2. A total of 52 SARS-CoV-2 patients and 36 healthy control participants were included in this study. SARS- CoV-2 patients were scored by the disease activity score. Serum furin, presepsin, and interleukin-6 (IL-6) levels were assessed using an enzyme-linked immunosorbent assay. The mean furin, presepsin, and IL-6 levels were significantly higher in the peripheral blood of SARS-CoV-2 compared to the controls ($p < 0.001$). There were close positive relationship between serum furin and IL-6, furin and presepsin, and furin and disease severity ($r = 0.793$, $p < 0001$; $r = 0.521$, $p < 0.001$; and $r = 0{,}533$, $p < 0.001$, respectively) in patients with

**Corresponding author:**
Abdurrahim Kocyigit, Department of Medical Biochemistry, Medical Faculty, Bezmialem Vakif University, Vatan Street, Fatih, Istanbul 34093, Turkey.
Email: abdurrahimkocyigit@yahoo.com

SARS-CoV-2. These results suggest that furin may contribute to the exacerbation of SARS-CoV-2 infection and increased inflammation, and could be used as a predictor of disease severity in COVID-19 patients.

**Keywords**
SARS-CoV-2, furin, IL-6, presepsin, inflammation, disease severity

## Introduction

The pandemic corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a serious public health problem.[1]

It is an enveloped, single-stranded, positive-sensitive RNA virus with a genome length of 29 kb, is thought to be transmitted from bats, although the primary source of transmission is not known. Since the mutations and genetic changes in SARS-CoV-2 continue to increase,[2] the virus has become difficult to control. There is still no definitive treatment for the disease, and its mortality and morbidity continue to increase.[3]

SARS-CoV-2 is composed of RNA-dependent RNA polymerase, spike glycoprotein (SP), envelope and membrane proteins, nucleocapsid phosphoproteins and a series of non-structural proteins.[4] Previous studies have shown that coronaviruses use different cell entry mechanisms in terms of membrane fusion activities[5] after SP proteins are bound to angiotensin-converting enzyme 2 (ACE2).[6] In fact, ACE2 is a functional receptor for coronavirus to enter host cells. When the virus binds to ACE2, the transmembrane protease-serine2 (TMPRSS2) cleaves the viral spike protein. Furin, another protease, hydrolyzes the spike fusion peptide so that the virus enters the host cell endosomally.[7,8] SARS-CoV-2 presents a complex pathology including inflammation, endothelial damage, thrombus formation, and acute respiratory failure.[9]

Furin is a member of the proprotein convertase subtilisin/Kexin family and is responsible for cleaving various precursor proteins in several physiological processes.[10]

In addition to its key role in regulating blood coagulation, growth signal, and tumor progression,[11] furin plays a role in the pathogenesis of many viral infections, allowing the virus to enter the cell by breaking down viral envelope proteins.[12] It was demonstrated that the furin protease cleavage site in the spike glycoprotein (amino acids 682−689) is strikingly novel in SARS-CoV-2 and related to enhanced virulence.[13] The increase of furin activity while SP binds to ACE2 may increase the entry of SARS-CoV-2 into cells.[14] In particular, SARS-CoV-2 binds to ACE2 with higher affinity than other beta-coronaviruses and it has a furin cleavage site not found in other viruses of the same clade.[15] Increased affinity for the ACE2 receptor may also play a role in the higher pathogenicity of SARS-CoV-2.[16] Furin conceivably exerts its activity in the circulating area as well as intracellularly.[17] In this perspective, targeting furin may be a possible way to prevent or treat SARS-CoV-2 infection. However, studies to date have not yet investigated the usability of furin measurements in clinical practice in SARS-CoV-2 infection.

After SARS-CoV-2 enters the host cell through the aforementioned receptors and enzymes, they replicate using the cell's organelles and metabolic pathways. Cells undergo necrosis or apoptosis as a result of the stimulation of pro-inflammatory cytokines, activation of macrophages and Th1 cells in virus-infected cells.[1,18] A recent study showed that levels of IL-6, a pro-inflammatory cytokine, can be used as a good indicator to predict the poor prognosis of the disease and the need for mechanical ventilation.[19] Even an IL-6 level above 80 pg/mL has been shown to be sufficient to identify SARS-CoV-2 infected patients with a high risk of respiratory failure.[20] Serum SARS-CoV-2 nucleic acid, which is strongly associated with cytokine storm, has also been reported to be closely associated with extremely high serum levels of IL-6.[21]

It has been suggested that serial measurement of serum IL-6 levels may be an essential criterion in determining disease progression or when evaluated immediately after the diagnosis of COVID-19, can be used to predict the prognosis of the disease and impending respiratory failure.[22]

Presepsin, also known as soluble CD14 subtype, is a 13 kDA glycoprotein cleavage N-terminal fragment of CD14 released into the circulation after pro-inflammatory signal activation in cases of infection.[23] Studies have shown that apart from the diagnosis of sepsis, it can be used as an important marker in determining the severity of infectious diseases and the risk of death.[24] It has been reported that high serum presepsin levels can also be a biomarker for determining the severity of SARS-CoV-2 infection.[25,26]

Although there have been studies investigating the severity of SARS-CoV-2 infection and its relation with inflammation, furin, IL-6, and presepsin have been investigated separately, but no studies were found that investigated these biomarker levels and their relationship to each other and disease severity. Therefore, the aim of this study is to investigate serum furin, IL-6, and presepsin levels in patients with SARS-CoV-2 and healthy control participants, and analyze the correlations between these biomarkers and disease severity.

## Materials and methods

### *Study population*

Between June 2020 and July 2020, a total of 52 (27 female and 25 male) SARS-CoV-2 infected patients and 36 (20 female and 16 male) healthy control participants were selected for the study.SARS-CoV-2 patients were diagnosed according to real-time reverse transcription-polymerase chain reaction (RT-PCR) test criteria. Acute or chronic infectious disease, any clinically important disorder, and any drug with a known effect on immunological factors were identified as exclusion criteria for healthy control individuals.

The degree of illness in patients with SARS-CoV-2 was assessed by using the fifth edition of the Guidelines developed by the National Health Commission of China, which compiled national recommendations on the diagnosis and treatment of COVID-19 (26). According to this guidance, the disease severity was classified into three groups (mild, moderate, and severe) as follows:

(1) Mild type: The clinical symptoms (e.g. sore throat, fatigue, and myalgia) are mild, with no abnormal findings on chest X-ray or chest computed tomography (CT).
(2) Moderate type: Fever, cough, and other symptoms (e.g. dyspnea, fatigue, myalgia, and sore throat) are present with pneumonia on chest CT.
(3) Severe type: The inclusion criteria for the severe disease are as follows: respiratory distress, pneumonia on chest CT, respiratory rate $\geqslant 30$/min or room air oxygen saturation $\leq 93\%$ at rest or partial pressure of oxygen in arterial blood/FIO2 $\leq 300$ mmHg, in conjunction with moderate disease symptoms. The study was approved by the Medical Ethics Committee of Bezmialem Vakif University (Decision Number: 7/43) and informed consent was obtained from each patient.

### *Sample*

Blood samples were taken from the antecubital veins of the patient and control groups and centrifuged at $2500 \times g$ for 10 min. Serum samples were separated and stored at $-80$°C until biochemical analyses. Furin, presepsin, and IL-6 levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA) kits (Human Furin ELISA kit: Bioassay Technology Laboratory, Cat.No E2321Hu, China; Human IL6 ELISA kit: Hangzhou Sunlong Biotech Co., Ltd, Cat.No 20171201, China; Human presepsin (PSPN) ELISA kit: Hangzhou Sunlong Biotech Co., Ltd, Cat.No CK-E91662, China). The assays were carried out by making single measurements from the samples, following the manufacturer's instructions for analysis of a 96-well plate. Results are presented in ng/L.

## Statistical methods

All data are expressed as the Mean $\pm$ SD. The difference in biomarker levels between the SARS-CoV-2 patient group and the healthy control group was tested using Student's *t*-test. One-Way ANOVA tests were used to compare serum furin, IL-6, and presepsin levels among moderate, severe, and mild patient groups. A multivariate logistic regression was used to estimate the effect of serum furin, IL-6, and presepsin levels on disease severity. All statistical tests were calculated using SPSS 27.0 for Windows (IBM, Chicago, Ill). *p* value of less than 0.05 was considered statistically significant.

## Results

### *Demographic data of control and patient groups*

This study included 52 SARS-CoV-2 patients and 36 healthy control participants. The median ages of the SARS-CoV-2 patients and healthy control participants were $52.72 \pm 18.88$ (range, 27–91 years) years and $48.55 \pm 18.19$ (range, 18–84 years) years, respectively. Age and sex did not significantly differ between

**Table 1.** Demographic and clinical characteristics of SARS-CoV-2–infected patient groups classified according to the disease severity (mild, moderate, and severe).

| | Mild ($n = 15$) | Moderate ($n = 18$) | Severe ($n = 19$) |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | Mean ± SD |
| Age, years | 50.86 ± 9.81 | 51.38 ± 11.99 | 55.78 ± 11.23 |
| Sex, *n* (%) | | | |
| Male | 7 (46.7) | 7 (39.9) | 10 (52.6) |
| Female | 8 (53.3) | 11 (61.1) | 9 (47.4) |
| Comorbidity, *n* (%) | | | |
| Hypertension | 2 (13.3) | 8 (44.4) | 10 (52.6) |
| Diabetes mellitus | 2 (13.3) | 5 (27.8) | 9 (47.4) |
| Cardiovascular disease | 1 (6.7) | 4 (16.7) | 4 (21) |
| Cerebrovascular disease | 0 (0) | 2 (11.1) | 1 (0) |
| Chronic pulmonary disease | 1 (6.7) | 3 (16.7) | 3 (15.8) |
| Malignancy | 0 (0) | 0 (0) | 3 (15.8) |
| Other | 3 (20) | 0 (0) | 2 (10.5) |
| Symptoms at admission, *n* (%) | | | |
| Fever | 11 (73.3) | 13 (72.2) | 16 (84.2) |
| Cough | 8 (53.3) | 11 (61.1) | 15 (78.9) |
| Dyspnea | 3 (20) | 7 (38.9) | 19 (100) |
| Fatigue | 9 (60) | 14 (77.8) | 15 (78.9) |
| Myalgia | 7 (46.7) | 8 (44.4) | 13 (68.4) |
| Sore throat | 6 (40) | 7 (38.9) | 10 (52.6) |

patients and healthy controls ($p > 0.05$). The demographic and clinical characteristics of the patients who were divided into mild, moderate and severe groups according to the severity of the disease are shown in Table 1. As seen from the table, 15 of the patients were mild, 18 were moderate and 19 were seriously ill. No significant difference was also found between the patient groups in terms of age and gender ($p > 0.05$).

## *Serum furin and IL-6 and presepsin levels in SARS-CoV-2–infected patients and controls*

The serum furin, IL-6, and presepsin levels were investigated together in SARS-CoV-2 infected patients and healthy controls. The obtained results showed that serum furin levels were 2.5 fold, IL-6 levels were 3.5 fold, and presepsin levels were 5 fold higher in patients with SARS-CoV-2 comparing to the control patients (all comparisons, $p < 0.001$; Table 2).

When the severity of the disease was classified as mild, moderate and severe patient groups, serum furin, IL-6, and presepsin levels were found to increase significantly in a manner proportional to the degree of disease severity (all comparisons, $p < 0.001$; Table 3). As seen from the table, while IL-6 levels were found to be significantly higher in all patient groups compared to the control group, the

**Table 2.** Serum furin, IL-6, and presepsin levels of SARS-CoV-2–infected patients and healthy controls.

| Biochemical markers | Control group ($n = 36$) | Patients group ($n = 52$) | $p$ |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Furin (ng/L) | 20.17 ± 8.41 | 49.77 ± 49.82 | <0.001 |
| IL-6 (ng/L) | 40.76 ± 16.57 | 137.35 ± 116.06 | <0.001 |
| Presepsin (ng/L) | 0.49 ± 0.22 | 2.32 ± 0.73 | <0.001 |

**Table 3.** Serum furin, IL-6, and presepsin levels of control, and SARS-CoV-2–infected patient groups classified according to the disease severity (mild, moderate, and severe).

| Biochemical markers | Control ($n = 36$) | Mild ($n = 15$) | Moderate ($n = 18$) | Severe ($n = 19$) | $p$ |
|---|---|---|---|---|---|
| | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | |
| Furin (g/L) | 20.2 ± 8.4 | 20.1 ± 10.3 | 34.5 ± 25.8[b] | 87.6 ± 61.7[c] | <0.001 |
| IL-6 (ng/L) | 40.8 ± 16.6 | 79.8 ± 45.0[a] | 104.5 ± 90.6[b] | 213.9 ± 137.2[c] | <0.001 |
| Presepsin (ng/L) | 0.49 ± 0.2 | 0.59 ± 0.4 | 1.2 ± 1.1[b] | 3.5 ± 3.3[c] | <0.001 |

Significant differences between groups are indicated by $p < 0.001$. A significant differences between control and mild groups are indicated by "[a]" mild and moderate groups are indicated by "[b]", and mild and severe groups are indicated by "[c]".

**Table 4.** Correlations between serum furin, IL-6, and presepsin levels and disease severity in patients with SARS-CoV-2.

| | IL-6 | Presepsin | Disease severity |
|---|---|---|---|
| Furin | $r = 0.793$<br>$p < 0.001$ | $r = 0.521$<br>$p < 0.001$ | $r = 0.564$<br>$p < 0.001$ |
| IL-6 | | $r = 0.514$<br>$p < 0.001$ | $r = 0.482$<br>$p < 0.001$ |
| Presepsin | | | $r = 0.493$<br>$p < 0.001$ |

furin and presepsin levels of the mild patient group were not found to be significantly different than the control group.

There were significant correlation between furin, Il-6, presepsin, and disease severity in SARS-CoV-2 infected patients (Table 4).

The highest correlation was found between furin and Il-6 levels (Figure 1).

Multivariate regression analysis was performed to estimate the degree of disease using the variables of furin, IL-6, and presepsin. The results of logistic regression analysis demonstrated that a significant regression model, $F\ (3.48) = 9.5$, $p < 0.001$, and 33% of the variance in the dependent variable ($R^2$ adjusted = 0.33)

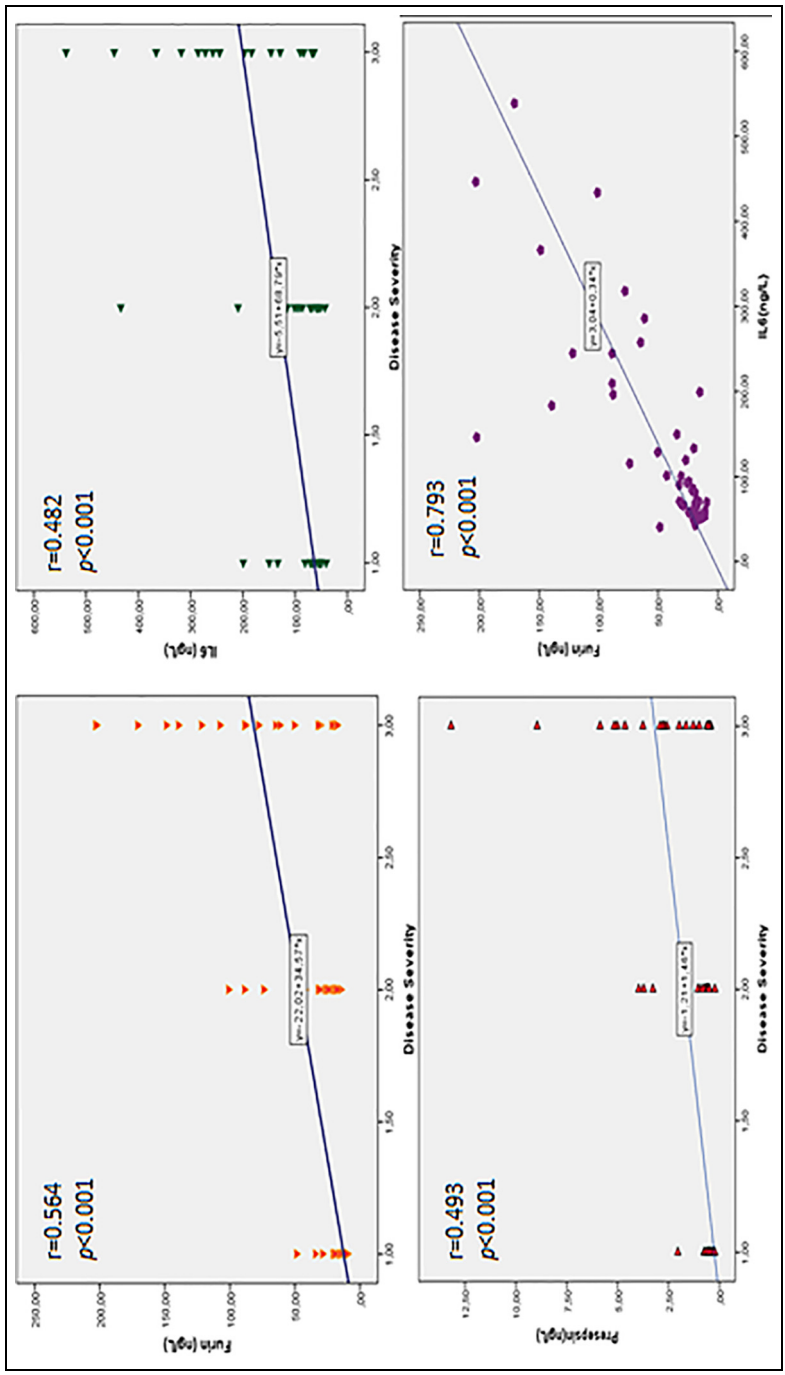


**Figure 1.** Correlations between circulating furin, IL-6, presepsin, and disease severity in patients with COVID-19.

**Table 5.** Multivariate regression analysis of disease severity and serum furin, Il-6, and presepsin levels.

| Variable | Non-std. coefficient | | Std. coefficient | $R$ | $R^2$ | $t$ | $p$ |
|---|---|---|---|---|---|---|---|
| | $B$ | Std. error | Beta | | | | |
| Constant | 1.56 | 0.14 | | 0.33 | 0.33 | 10.8 | $<0.001$ |
| Furin | 0.07 | 0.003 | 0.41 | 0.29 | 0.09 | 2.12 | $<0.05$ |
| IL-6 | 0.00 | 0.001 | 0.02 | 0.02 | 0.002 | 0.11 | $>0.05$ |
| Presepsin | 0.09 | 0.046 | 0.27 | 0.28 | 0.058 | 1.98 | $>0.05$ |

were explained by the independent variables. According to the analysis, furin predicted disease severity positively and significantly, $\beta = 0.407$, $t$ (48) = 2.12, $p < 0{,}05$, $pr^2 = 0{,}09$. However, IL-6 and presepsin levels were insufficient to predict the severity of the disease ($\beta = 0.02$, $t = 0{,}11$, $p > 0.05$, $pr^2 = 0.0002$ and $\beta = 0.27$, $t = 1.98$, $p > 0.05$, $pr^2 = 0.08$, respectively) (Table 5).

## Discussion

SARS-CoV-2 is a major public health problem that caused a pandemic worldwide, and a specific drug used in the treatment of SARS-CoV-2 has not yet to be developed. Biomarkers such as oxygen saturation, pro-inflammatory cytokines, furin, and presepsin levels are used to evaluate the severity of the disease, the degree of inflammation, and the effectiveness of treatment.

Furin has been found to be a key process in the entry of the virus into the host cell and an enzyme for which has an important role in promoting virulence.[27] However, the relationship between furin levels and the degree of inflammatory markers is still not clear. Therefore, we wanted to find out whether there is a difference between furin and inflammatory markers comparing the non-covid patients with SARS-CoV-2 infected patients and whether there is a relationship between furin and inflammatory markers in these patients. In this study, we found that serum furin, IL-6 and presepsin levels were significantly higher in patients with SARS-CoV-2 infection compared to healthy subjects, and there was a positive close correlations between these biomarkers and disease severity.

In the present study, the mean level of furin was significantly increased in moderate and severe cases compared to the mild group and control group. Furin was also found to be a significant biomarker in predicting the severity of the disease. Furin is known to play an important role in the pathogenesis of coronavirus and other viral infections including HIV, increasing the functionality of the virus by breaking down serum proteins, including blood clotting factors, cell surface receptors, hormones, growth factors, and receptors.[11,12] Circulating and intracellular furin increases the binding of the virus to ACE2 not only by exposing the viral binding site in the S1 domain, but also by exposing the effusion site in the S2 domain in viral SP.[28] This can create a feed-forward cycle of furin-facilitated coronavirus replication leading to myocarditis, destroyed lung tissue, and fatal multi-

organ failure, which may be responsible for the cytokine storm caused by excessive immunological activity in some patients.[29] It has also been reported that cellular and serum furin levels increase in diabetes, hypercholesterolemia and obesity, and that the elevated risk of COVID-19 complications and mortality in such diseases may be associated with high furin levels.[30] Therefore, our findings and literature data suggest that furin may be a predictive factor in determining disease severity in patients with SARS-CoV-2 infection.

Significant increases in furin, IL-6, and presepsin levels and strong positive correlations between furin and these biomarkers in these patients support previous findings.

In this regard, targeting furin for prevention or treatment of SARS-CoV-2 infection and inflammation may be a possible option. Indeed, with this approach, furin Inhibitor I, Furin Convertase Inhibitor (Chloromethylketone or peptidyl-chloromethyl ketones) has been used for the treatment of HIV infection.[31] Furin inhibitors can also be used in the treatment of SARS-CoV-2. It has been demonstrated that furin expression increased in the cartilage of patients with osteoarthritis, and treatment of mouse models of arthritis with furin inhibitors decreased inflammation and arthritis.[32] Furin inhibition also reduced viral infections in in vitro models.[33] However, since furin-like enzymes are involved in a large number of cellular processes, systemic inhibition that may cause some toxicity should be avoided. Thus, oral administration of such small molecule inhibitors or other more potent orally active ones might be tested to evaluate their antiviral effects against SARS-CoV-2 to avoid possible systemic side effects of furin inhibitors.

It has been found that patients most severely affected by SARS-CoV-2 exhibit elevated levels of serum pro-inflammatory cytokines due to cytokine storm induction.[34] The majority of severe cases of SARS-CoV-2 with respiratory distress syndrome have been associated with hyperactivation of the immune system and excessive IL-6 production.[1] Consistent with previous studies, we corroborate that circulating IL-6 levels were significantly higher in these patients, and unlike other investigators, we found a strong positive correlation between plasma furin and IL-6 levels. Although the exact cause is not known, furin levels were found to be higher in diabetic, elderly, smokers, and male SARS-CoV-2 patients.[35] However, contrary to our findings, no correlation was found between furin and IL-6 levels in patients with rheumatoid arthritis.[35] Although inflammation occurs in both diseases, etiological reasons are different. Therefore, the reasons that trigger inflammation may be different.

Presepsin is an N-terminal fragment of the 13-kDa glycoprotein of CD14 that is released into circulation after pro-inflammatory signal activation in conjunction with contact with infectious agents.[23] It is a new biomarker for diagnosing sepsis, but its prognostic value in other inflammatory diseases is unknown. As a matter of fact, presepsin has also been investigated in SARS-CoV-2 patients, and it has been reported that it can help identify patients who will have a more severe course and stay in the hospital for a longer period at an early stage of infection.[25,36] In the present study, we found that presepsin levels were significantly higher in patients with

SARS-CoV-2, and there was a significant correlation between presepsin and disease severity. However, when evaluated together with furin and IL6, we found that presepsin was not significant to predict the severity of the disease.

## Conclusion

In summary, furin, IL-6, and presepsin are thought to play an important role in the exacerbation of SARS-CoV-2, and an elevated serum furin levels in infected individuals is thought to predict poor outcomes in COVID-19 patients. Furthermore, the present study suggests that furin can be used as a predictor of disease severity in patients with COVID-19, and inhibition of furin, may be one of the potential treatment options in combating SARS-CoV-2 infection and preventing inflammation. However, randomized, controlled studies with more cases are needed to validate the use of furin for clinical decision-making in disease severity.

### Acknowledgements

This study was carried out at the Medical Biochemistry Research Laboratory, Faculty of Medicine, Bezmialem Vakif University (Istanbul, Turkey), in collaboration with the University of Health Sciences Turkey Hamidiye Faculty of Medicine, Haseki Training and Research Hospital (Istanbul, Turkey), Department of Emergency Medicine, University of Health Sciences Turkey, Hamidiye School of Medicine, Department of Medical Biochemistry, and Marmara University Pendik Training and Research Hospital, Medical Microbiology (Istanbul, Turkey).

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

We did not receive any funding from any institution for this study. We carried out this study with our personal budget.

### ORCID iDs

Abdurrahim Kocyigit https://orcid.org/0000-0003-2335-412X
Ozgur Sogut https://orcid.org/0000-0003-3365-3713
Vildan Betul Yenigun https://orcid.org/ 0000-0002-8021-8629

### Supplemental material

Supplemental material for this article is available online.

## References


1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
2. Vankadari N. Overwhelming mutations or SNPs of SARS-CoV-2: a point of caution. *Gene* 2020; 752: 144792.
3. Zhang J, Zhou L, Yang Y, et al. Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics. *Lancet Respir Med* 2020; 8: e11–e12.
4. Mousavizadeh L and Ghasemi S. Genotype and phenotype of COVID-19: their roles in pathogenesis. *J Microbiol Immunol Infect*. 2021; 54(2): 159–163.
5. White JM and Whittaker GR. Fusion of enveloped viruses in endosomes. *Traffic* 2016; 17: 593–614.
6. Simmons G, Zmora P, Gierer S, et al. Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research. *Antiviral Res* 2013; 100: 605–614.
7. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; 181(2): 271–280.
8. Walls AC, Park Y-J, Tortorici MA, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell* 2020; 181(2): 281–292.
9. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020; 323: 1574–1581.
10. Jaaks P and Bernasconi M. The proprotein convertase furin in tumour progression. *Int J Cancer* 2017; 141: 654–663.
11. Thomas G. Furin at the cutting edge: from protein traffic to embryogenesis and disease. *Nat Rev Mol Cell Biol* 2002; 3: 753–766.
12. Hallenberger S, Bosch V, Angliker H, et al. Inhibition of furin-mediated cleavage activation of HIV-1 glycoprotein gpl60. *Nature* 1992; 360: 358–361.
13. Hasan A, Paray BA, Hussain A, et al. A review on the cleavage priming of the spike protein on coronavirus by angiotensin-converting enzyme-2 and furin. *J Biomol Struct Dyn* 2021; 39(8): 3025–3033.
14. Vidricaire G, Denault J-B and Leduc R. Characterization of a secreted form of human furin endoprotease. *Biochem Biophys Res Commun* 1993; 195: 1011–1018.
15. Naveja JJ, Madariaga-Mazón A, Flores-Murrieta F, et al. Union is strength: antiviral and anti-inflammatory drugs for COVID-19. *Drug Discov Today* 2021; 26(1): 229–239.
16. Li G, He X, Zhang L, et al. Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19. *J Autoimmun* 2020; 112: 102463.
17. Ichiki T and Burnett JC Jr. Post-transcriptional modification of pro-BNP in heart failure: is glycosylation and circulating furin key for cardiovascular homeostasis? *Eur Heart J* 2014; 35(43): 3001–3003.
18. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8(5): 475–481.
19. Gong J, Dong H, Xia Q, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. *medRxiv* 2020. DOI: 10.1101/2020.02.25.20025643.

20. Herold T, Jurinovic V, Arnreich C, et al. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. *medRxiv* 2020. DOI: 10.1101/2020.04.01.20047381.
21. Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clin Infect Dis* 2020; 71(8): 1937–1942.
22. Ulhaq ZS and Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. *Med Mal Infect* 2020; 50(4): 382–383.
23. Wright SD, Ramos RA, Tobias PS, et al. CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. *Science* 1990; 249: 1431–1433.
24. Masson S, Caironi P, Spanuth E, et al. Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: data from the Albumin Italian Outcome Sepsis trial. *Crit Care* 2014; 18(1): R6.
25. Zaninotto M, Mion MM, Cosma C, et al. Presepsin in risk stratification of SARS-CoV-2 patients. *Clin Chim Acta* 2020; 507: 161–163.
26. Favaloro EJ and Lippi G. Recommendations for minimal laboratory testing panels in patients with COVID-19: potential for prognostic monitoring. *Semin Thromb Hemost* 2020; 46: 379–382.
27. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: a multicenter study of clinical features. *Am J Respir Crit Care Med* 2020; 201: 1380–1388.
28. Abassi Z, Skorecki K, Hamo-Giladi DB, et al. Letter to the editor: angiotensin-converting enzyme 2: an ally or a Trojan horse? Implications to SARS-CoV-2-related cardiovascular complications. *Am J Physiol Heart Circ Physiol* 2020; 318.5: H1080–H1083.
29. Abassi ZA, Skorecki K, Heyman SN, et al. Covid-19 infection and mortality: a physiologist's perspective enlightening clinical features and plausible interventional strategies. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 2020; 318: L1020–L1022.
30. AbdelMassih AF, Ye J, Kamel A, et al. A multicenter consensus: a role of furin in the endothelial tropism in obese patients with COVID-19 infection. *Obes Med* 2020; 19: 100281.
31. Van Lam van T, Ivanova T, Hardes K, et al. Design, synthesis, and characterization of macrocyclic inhibitors of the proprotein convertase furin. *ChemMedChem* 2019; 14: 673–685.
32. Lin H, Ah Kioon MD, Lalou C, et al. Protective role of systemic furin in immune response–induced arthritis. *Arthritis Rheum* 2012; 64: 2878–2886.
33. Ozden S, Lucas-Hourani M, Ceccaldi P-E, et al. Inhibition of Chikungunya virus infection in cultured human muscle cells by furin inhibitors impairment of the maturation of the E2 surface glycoprotein. *J Biol Chem* 2008; 283: 21899–21908.
34. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; 130(5): 2620–2629.
35. Cao R, Zhang Y, Du J, et al. Increased FURIN expression in rheumatoid arthritis patients and its anti-inflammatory effect. *J Clin Lab Anal* 2020; 34(12): e23530.
36. Yang HS, Hur M, Yi A, et al. Prognostic value of presepsin in adult patients with sepsis: systematic review and meta-analysis. *PLoS One* 2018; 13: e0191486.

## Author biographies

Professor Abdurrahim Kocyigit is a professor of medical biochemistry at Department of Medical Biochemistry, Bezmialem Vakif University, Istanbul, Turkey.

Professor Ozgur Sogut is emergency medicine doctor at Department of Emergency Medicine, Health Science University, Haseki Training and Research Hospital, Istanbul, Turkey.

Ms. Ezgi Durmus is a medical biochemistry research assistant at Department of Medical Biochemistry, Bezmialem Vakif University, Istanbul, Turkey.

Ms. Ebru Kanimdan is a medical biochemistry research assistant at Department of Medical Biochemistry, Bezmialem Vakif University, Istanbul, Turkey.

Dr. Eray Metin Guler is an assistant professor of medical biochemistry at Department of Medical Biochemistry, Health Science University, Istanbul, Turkey.

Dr. Onur Kaplan is emergency medicine doctor at Department of Emergency Medicine, Health Science University, Haseki Training and Research Hospital, Istanbul, Turkey.

Dr. Vildan Betul Yenigun is an assistant professor of medical biochemistry at Department of Medical Biochemistry, Bezmialem Vakif University, Istanbul, Turkey.

Dr. Canan Eren is a microbiologist and blood bank specialist at Marmara University Pendik Training and Research Hospital, Medical Microbiology and Blood Centre, Pendik, Istanbul.

Ms. Zeynep Ozman is a medical biochemistry research assistant at Department of Medical Biochemistry, Bezmialem Vakif University, Istanbul, Turkey.

Dr. Oznur Yasar is a medical biochemistry research assistant at Department of Medical Biochemistry, Bezmialem Vakif University, Istanbul, Turkey.