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## Presepsin as a Novel Biomarker in predicting In-hospital Mortality in Patients With COVID-19 Pneumonia

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### ABSTRACT

**Objectives:** Different biomarkers such as C-reactive protein (CRP), serum ferritin and D-dimer are used in prognostic assessment of patients with COVID-19 pneumonia. Presepsin (PSP) is a soluble CD14 subtype that has recently been proposed as a novel biomarker in patients with sepsis. The aim of the current study was to detect the relation of PSP to the outcome of COVID-19 as well as its relation to other inflammatory biomarkers.

**Methods:** This multicenter retrospective observational study was conducted in Saudi Arabia and Misr International Hospital, Egypt, from January 2021 to May 2021. Hospitalised patients who had positive throat swab of SARS-CoV-2 and radiological evidence of viral pneumonia (moderate and severe forms) were included in the study. Demographics and clinical features, as well as laboratory parameters, including serum ferritin, CRP, D-dimer and PSP, of enrolled patients were retrospectively collected. Pneumonia severity index (PSI) was used to evaluate the severity of pneumonia.

**Results:** A total of 202 hospitalised patients who were diagnosed with COVID-19 pneumonia and tested positive for SARS-CoV-2 RNA were enrolled in our study. Of 202 hospitalised patients, 67 (33.17%) required intensive care unit (ICU) admission. A total of 176 (87.1%) patients survived and were discharged, whereas 26 (12.9%) patients did not survive. PSP level was found to be significantly elevated in non-survivor versus survivor group (median [IQR] 978.5 [755.8–1400] vs 516.5 [343.3–720],  $P < 0.001$ ) as well as in ICU versus non-ICU patients (median [IQR] 800 [631–1200] and 446 [320–626], respectively) ( $P < 0.001$ ). Elevated levels were also found to be associated with increased length of hospital stay. Levels above 775 pg/mL were found to be associated with in-hospital mortality (specificity 80%, sensitivity 73%).

**Conclusion:** Elevated PSP levels indicated poor outcomes in hospitalised patients with COVID-19 pneumonia and were associated with in-hospital mortality.

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### Introduction

COVID-19 caused by SARS-CoV-2 is currently a challenging pandemic that has caused drastic impacts on health systems and economy worldwide. A severe form of pneumonia, potentially evolving

towards acute respiratory distress syndrome (ARDS) and occasionally associated with multiorgan failure, is the leading complication of the respiratory virus (Zaninotto et al., 2020).

Different inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and IL-6 have been reported to be significantly associated with the high risks of the development of severe COVID-19 (Zeng et al., 2020).

CD14 is a member of Toll-like receptor, which has the ability to identify several groups of ligands of both Gram-positive and Gram-negative pathogens, such as lipids, peptidoglycan and other surface patterns. CD14 plays an important role in the presentation

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of lipopolysaccharide of Gram-negative bacteria to Toll-like receptors and promotes the activation of immune response such as cytokines production by effector cells. CD14 has 2 forms: membrane-bound CD14 (mCD14) and soluble CD14 (sCD14). sCD14 is found in plasma and is produced by mCD14 fall-off or cell secretion. sCD14 is cleaved by proteases in plasma, and the N-terminal fragments of 13 kDa constitutes sCD14 subtype (sCD14-ST), which has been named presepsin (PSP) (Memar and Baghi, 2019).

PSP is reported to be a novel biomarker in sepsis. Several studies have shown that PSP is not only useful for the diagnosis of sepsis but could also be predictive of the severity and mortality of the disease. Recently, it was also reported that elevated PSP could be a biomarker in the prognostic assessment of patients with COVID-19 (Zeng et al., 2020).

The aim of the current study was to detect the relation of PSP to the outcome of COVID-19 as well as its relation to other inflammatory biomarkers.

## Patients and methods

This multicenter retrospective observational study was conducted in Saudi Arabia and Misr International Hospital, Egypt, from January 2021 to May 2021. The study was approved by the ethical committee of both hospitals as well as the institutional review board of the Ministry of Health, Cairo, Egypt (No: 3-2021/19).

Hospitalised patients who had positive throat swab of SARS-CoV-2 and radiological evidence of viral pneumonia (moderate and severe forms) were included in the study.

Demographics and clinical features, as well as laboratory parameters of enrolled patients, were retrospectively collected. Creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine transaminase (ALT) and albumin were measured using Dimension EXL 200 (Siemens Healthcare Diagnostics Inc., Newark, NJ, USA). Lactate dehydrogenase (LDH), ferritin, CRP and D-dimer were measured using Cobas C311 analyser (Roche Diagnostics, GmbH, Mannheim, Germany). Haematological parameters (white blood cell [WBC], haematocrit, neutrophil, lymphocyte and platelets) were measured using Sysmex XS-500i (Sysmex corporation, Kobe, Japan). PSP levels were measured in lithium-heparin plasma samples using a chemiluminescent enzyme immunoassay using PATH-FAST (Chemical Medience Corporation, Tokyo, Japan). Neutrophil-lymphocyte ratio was calculated by dividing the absolute neutrophil count by the lymphocyte count.

To evaluate the severity of COVID-19 pneumonia, pneumonia severity index (PSI) was calculated. PSI uses 20 clinical variables to predict the patient's outcome. The patients are then categorised into 5 severity classes with increasing likelihood of death within 30 days. Classes I–III are low-risk groups with cumulative mortality rate <1%, whereas classes IV and V are intermediate- and high-risk groups with mortality rates ranging from 9% to 30% (Fine et al., 1997).

## Statistical Analysis

The data were collected and tabulated for statistical analysis using Minitab 17.1.0.0 for windows (Minitab Inc., 2013, Pennsylvania, USA). Continuous data were presented as mean and SD and categorical data as number and percentage (%); the normality of data was examined using Shapiro-Wilk test. Association with mortality was determined by chi-square test, independent *t*-test or Mann-Whitney test. Comparison between length of hospital stay in patients with elevated PSP level and length of hospital stay in patients with low PSP level was done by independent *t*-test.

Multivariate logistic regression analysis was performed to test for the preferential effect Diabetes Mellitus (DM) on the relation

**Table 1**

Laboratory data of the studied group.

Variables	Median (IQR)
Presepsin pg/mL	540 (116–14631)
LDH U/L	337 (144–5917)
Ferritin ng/ml	456.5 (5.3–9370)
CRP mg/L	24 (0.1–407)
ESR mm/hr	40 (1.7–150)
D-Dimer mg/L	0.685 (0.07–29.3)
CPK U/L	120 (19–3242)
AST U/L	45 (11–984)
ALT U/L	45 (5–414)
Albumin g/dL	3.8 (2.2–5.1)
TLC × 10 <sup>3</sup> /UL	6.3 (1.2–28.9)
Neutrophil count × 10 <sup>3</sup> /uL	4.4 (0.7–27)
Lymphocyte count × 10 <sup>3</sup> /uL	1 (0.2–3.3)
Platelet count × 10 <sup>3</sup> /uL	213 (50–693)
Haematocrit	39.8 (19–61.4)
NLR	4.2 (0.9–90)

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; TLC, total leucocytic count.

between PSP level and survivorship. A 2-sided P value less than 0.05 was considered statistically significant. Regression was done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Pearson correlation was used to find the linear relationship between continuous data. The prognostic utility of PSP and other inflammatory markers was determined using receiver operating characteristic curve (ROC curve); area under the curve (AUC) above 0.6 was considered acceptable for test capability. P was considered significant if the value was <0.05.

## Results

A total of 202 hospitalised patients who were diagnosed with COVID-19 pneumonia and tested positive for SARS-CoV-2 RNA were enrolled in our study.

There were 159 (78.71%) males and 43 (21.29%) females. Mean age of the patients was 48.63±12.3 years. Their mean length of hospital stay was 13.69±6.38. Seventy-two (35.64%) patients had diabetes.

Considering the severity of the disease, patients were stratified into groups according to the PSI. A total of 57 (28.2%) patients had PSI score ≥91 (risk class IV and V) and were considered to have severe COVID-19 pneumonia (high-risk groups), whereas the rest of the patients (71.8%) had PSI <90 (risk class I, II, III) and were considered to be patients with mild COVID-19 pneumonia (low-risk groups).

Of 202 hospitalised patients, 67 (33.17%) required ICU admission. A total of 176 (87.1%) patients survived and were discharged, and 26 (12.9%) patients did not survive.

The factors associated with COVID-19 mortality are summarised in Table 2, older age, diabetes and hypertension were significantly associated with mortality (P=0.01, P<0.001 and P=0.05, respectively). Moreover, PSI score (P<0.001), LDH level, ferritin level, CRP level, ESR, D-dimer level, total leucocytic count (TLC), neutrophil count and neutrophil to lymphocyte ratio (NLR) (P<0.001) were significantly higher in patients who did not survive, whereas lymphocyte count was significantly lower in them (Table 2).

The mean and median level of PSP was 707.4 pg/mL and 545 pg/mL, respectively, and ranged from 116 to 14681 pg/mL, with

**Table 2**  
Epidemiological, inflammatory markers and length of hospital stay comparison between survivor and nonsurvivor groups.

Factors	Survival (n=176)	Nonsurvival (n=26)	P value
Age(years) <sup>a</sup>	54.038±9.035	47.835±12.552	0.01 <sup>b</sup>
Sex:Female, N (%)Male, N (%)	39 (22.16%)137 (77.84%)	4 (15.38%)22 (84.62%)	0.48 <sup>c</sup>
Diabetic, N (%)	55 (31.25%)	17 (65.38%)	0.001 <sup>c</sup>
HTN, N (%)	45 (25.57%)	14 (53.85%)	0.005
IHD, N (%)	10 (5.68%)	2 (7.69%)	0.69
Hypothyroidism, N (%)	7 (3.98%)	1 (3.85%)	0.97
ICU admission (yes), N (%)	41 (23.3%)	26 (100%)	< 0.001 <sup>e</sup>
PSI risk class, N (%)IIIIIIIVV	76 (43.18%)46 (26.14%)20 (11.36%)30 (17.05%)4 (2.27%)	1 (3.85%)02 (7.69%)18 (69.23%)5 (19.23%)	< 0.001 <sup>e</sup>
Presepsin pg/mL <sup>d</sup>	516.5 (343.3–720)	978.5 (755.8–1400)	< 0.001 <sup>e</sup>
LDH U/L <sup>d</sup>	318.5 (244.5–412)	532 (425.25–665.2)	< 0.001 <sup>e</sup>
Ferritin ng/mL <sup>d</sup>	413.5 (175.8–901.5)	1289 (669.7–1765.7)	< 0.001 <sup>e</sup>
CRP mg/L <sup>d</sup>	24 (10.3–48)	48 (12.7–179.3)	< 0.001 <sup>e</sup>
ESR mm/hour <sup>d</sup>	35 (20–57)	59.5 (40–87.8)	< 0.001 <sup>e</sup>
D-dimer mg/L <sup>d</sup>	0.6 (0.4–1.1)	1.8 (0.9–6.4)	< 0.001 <sup>e</sup>
TLC × 10 <sup>3</sup> /UL <sup>d</sup>	6.1 (4.5–8.3)	10.55 (6.7–12.8)	< 0.001 <sup>e</sup>
Neutrophil × 10 <sup>3</sup> /UL <sup>d</sup>	4.15 (2.6–6.2)	8.5 (5.5–12.1)	< 0.001 <sup>e</sup>
Lymphocyte × 10 <sup>3</sup> /UL <sup>d</sup>	1.1 (0.7–1.7)	0.7 (0.4–1)	< 0.001 <sup>e</sup>
NLR <sup>d</sup>	3.7 (1.8–6.5)	14.8 (5.4–21.3)	< 0.001 <sup>e</sup>
LOS <sup>d</sup>	12 (9–17)	18.5 (8–22.3)	0.08

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HTN, Hypertension; ICU, intensive care unit; IHD, ischemic heart disease; LDH, lactate dehydrogenase; LOS, length of hospital stay; NLR, Neutrophil to lymphocyte ratio; PSI, pneumonia severity index; TLC, total leucocytic count .

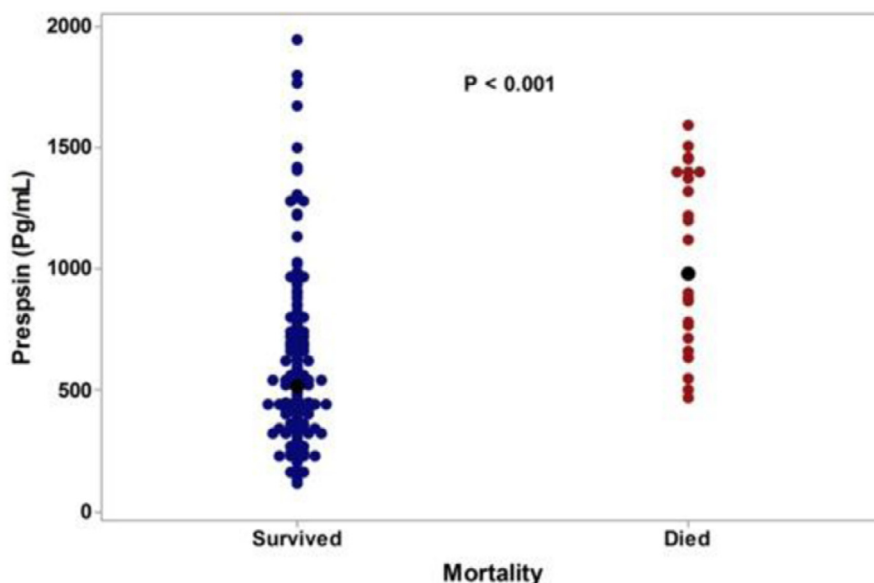
<sup>a</sup> Data are represented as mean and SD

<sup>b</sup> Independent t-test

<sup>c</sup> chi square test, P considered significant if <0.05

<sup>d</sup> Data are represented as median and IQR and categorical data as number (N) and percentage (%)

<sup>e</sup> Mann-Whitney test.



**Fig. 1.** Presepsin level in survivor versus nonsurvivor group.

significant higher elevation in the nonsurvivor group; median (IQR) was 978.5 (755.7–1400) ( $P < 0.001$ ) (Table 1 and 2; Fig. 1). To adjust for the effect of DM as a confounder, we performed a multivariate logistic regression. The analysis showed that PSP was still a significant predictor of mortality (odds ratio [OR]=0.997, 95% CI=0.996–0.999,  $P < 0.005$ )

Further comparison was done between PSP levels in patients who required ICU admission and PSP levels in patients who did not; this revealed a statistically significant increase in PSP level in patients admitted to the ICU, with median (IQR) being 800 (631–1200) and 446 (320–626) in ICU and non-ICU patients, respectively ( $P < 0.001$ ) (Fig. 2).

The performances of PSP level, NLR, ferritin level, CRP level and PSI score in predicting in-hospital mortality from COVID-19 pneumonia sepsis were evaluated using ROC curves (Fig. 3). The levels of PSP as well as PSI score and NLR showed good performance in predicting the prognosis of COVID-19 pneumonia (AUC = 0.84, 0.87, and 0.83, respectively) (Table 3)

PSP showed linear positive correlation with PSI and biomarkers of inflammation, including NLR, D-dimer, ferritin, CRP and ESR, and negative correlation with lymphocytic count (Table 4) (Fig. 5a–5g)

Patients were divided into 2 groups according to the proposed cut-off value of PSP (775 pg/mL). Patients with PSP levels greater than 775 pg/mL (148 patients) had a significant increase

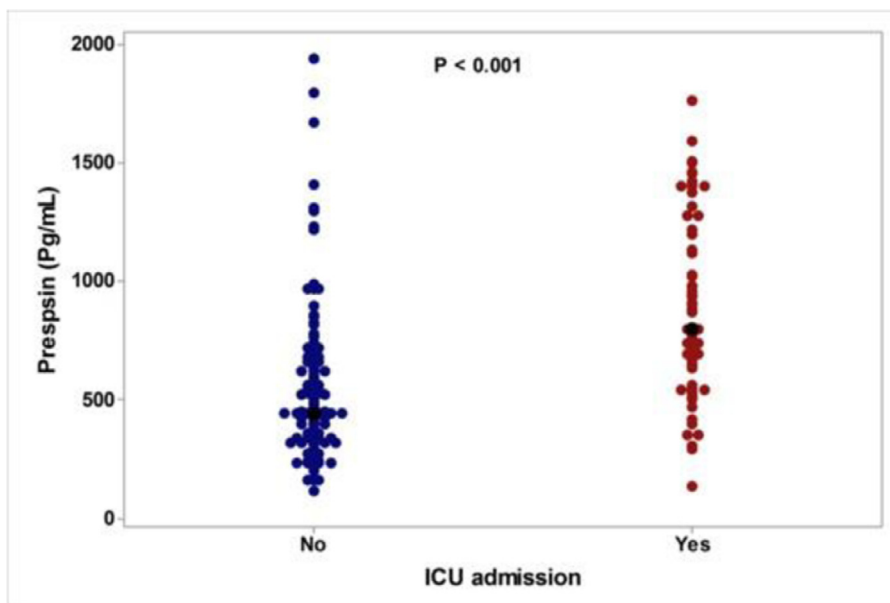


Fig. 2. Prepsin level in patients who required ICU admission versus patients who did not. ICU, intensive care unit.

Table 3  
Diagnostic utility of prepsin and other inflammatory markers.

Marker	Cut-off level	Sensitivity	95% CI	Specificity	95% CI	PPV	NPV
Prepsin pg/mL	>775	0.73	0.5221–0.8843	0.80	0.7344–0.8574	0.45	0.93
PSI score	>3.5	0.81	0.7407–0.8624	0.88	0.6985–0.9755	0.61	0.95
NLR	>4.55	0.88	0.6985–0.9755	0.61	0.5317–0.6805	0.33	0.96
Ferritin ng/mL	>507.5	0.81	0.6065–0.9345	0.59	0.5144–0.6643	0.30	0.93
CRP	>23.5	0.73	0.5221–0.8843	0.48	0.4071–0.5594	0.24	0.89

Abbreviations: CRP, C-reactive protein; NLR, Neutrophil to lymphocyte ratio; NPV, negative predictive value; PPV, positive predictive value; PSI, pneumonia severity index.

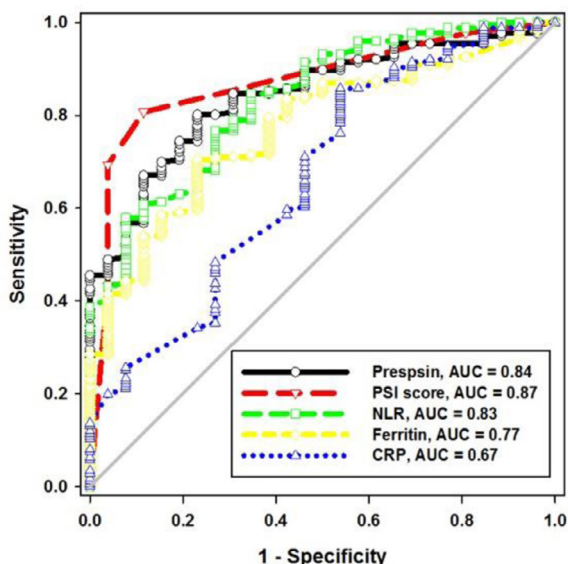


Fig. 3. ROC curves of the prepsin levels, PSI score, Ferritin levels, CRP levels and NLR in predicting patients' in-hospital mortality. AUC, area under the curve; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PSI, pneumonia severity index; ROC, receiver operating characteristic.

in length of hospital versus patients with PSP level less than 775 pg/mL (54 patients) (mean±SD 17.02±6.78 vs 12.48±5.8,  $P < 0.001$ ) (Fig. 4).

Table 4  
Correlation between prepsin and clinical and laboratory markers of inflammation.

Factors	Prepsin	
	R	P
PSI score <sup>a</sup>	0.29	<0.001
Lymphocytes <sup>a</sup>	-0.20	0.004
NLR <sup>a</sup>	0.46	<0.001
D-dimer <sup>a</sup>	0.24	0.001
Ferritin <sup>a</sup>	0.22	0.001
CRP <sup>a</sup>	0.23	0.001
ESR <sup>a</sup>	0.27	<0.001

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NLR, neutrophil to lymphocyte ratio; PSI, pneumonia severity index.

<sup>a</sup>: Person correlation, the sign before "r" denoting the direction of relationship,  $P < 0.05$  considered significant.

### Discussion

PSP is a soluble CD14 subtype that has recently been proposed as a novel biomarker in patients with sepsis. Several studies have proved its role in risk stratifying patients with sepsis and its ability to differentiate between patients with sepsis and those progressing to septic shock (Ajete et al., 2020). It has been reported to be involved in the early stages of the septic process. When monocytes are activated by an infectious agent, the sCD14 subtype (PSP) is released into the plasma. Subsequently, PSP levels continue to increase in the early stages of sepsis (Koh et al., 2021). In other words, it has been proposed that the elevation of PSP results

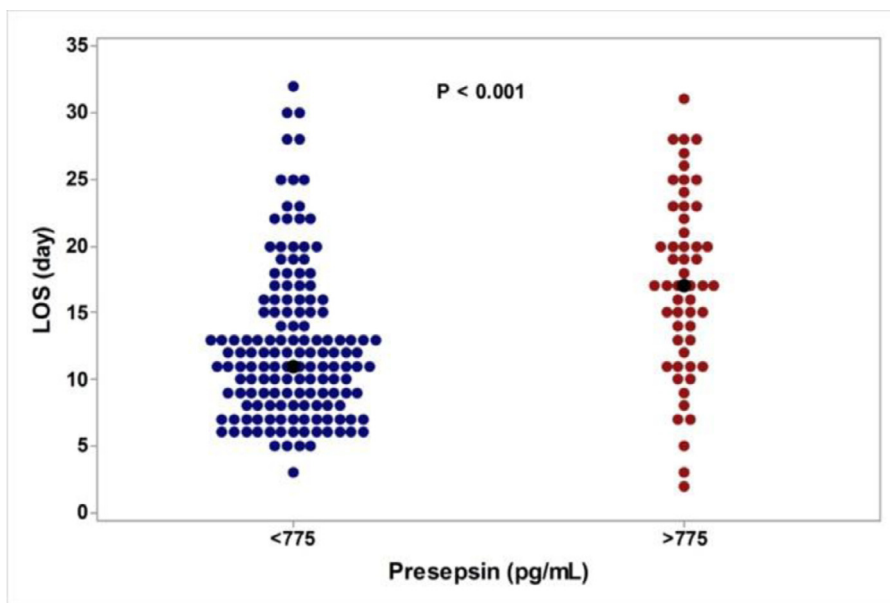


Fig. 4. Relationship between presepsin values and hospital stay. LOS, length of hospital stay.

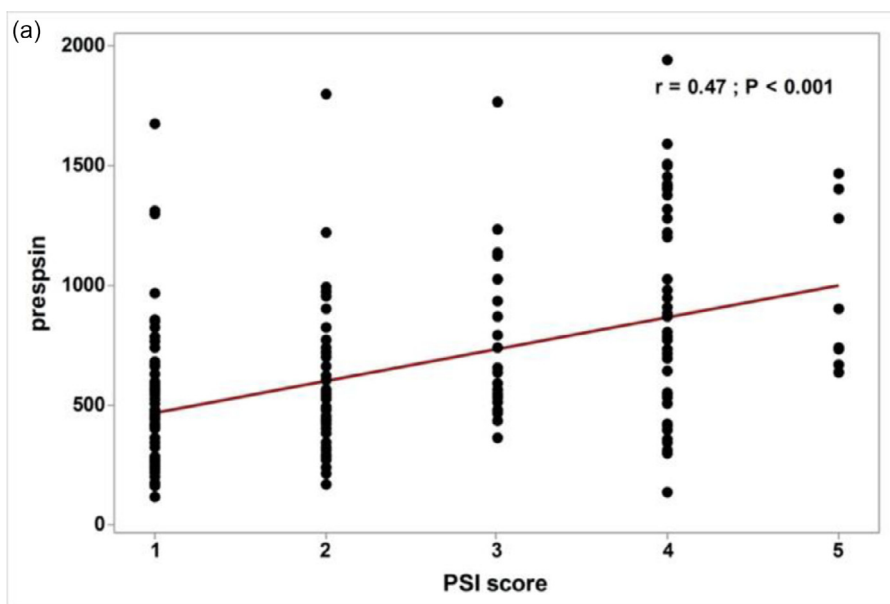


Fig. 5. a: Correlation between Presepsin and PSI score. PSI, pneumonia severity index. b: Correlation between presepsin and neutrophil-lymphocyte ratio. NLR, neutrophil to lymphocyte ratio. c: Correlation between presepsin and D-dimer. d: Correlation between presepsin and ferritin levels. e: Correlation between presepsin and CRP level. f: Correlation between presepsin and ESR levels. g: Correlation between presepsin and lymphocyte count.

from a dose-response mechanism of the host-pathogen interaction, which occurs in the initial phase of the pathogen recognition and remains elevated during several days depending on disease severity (Zaninotto et al., 2020).

Investigating the role of PSP in patients with COVID-19 is still an area of limited research and needs to be further investigated and understood. In the current study, we retrospectively studied the serum levels of PSP in patients with COVID-19 pneumonia to determine its relation to the outcome of COVID-19 as well as its relation to other inflammatory biomarkers.

In agreement with our findings, Zaninotto et al found PSP level to be significantly elevated in hospitalised patients with COVID-19

who died versus patients who survived; PSP was also found to be significantly elevated in patients who required ICU admission versus patients admitted in the regular ward (Zaninotto et al., 2020). In the current study, increased PSP levels were associated with increase in length of hospital stay (Fig. 4). This was in accordance with Zaninotto et al who found significant increase in hospital stay in patients with COVID-19 and high PSP levels (Zaninotto et al., 2020).

In a case series done by Fukada et al who investigated PSP, CRP, PCT and Krebs von den Lungen-6 (KL-6) levels in hospitalised patients with COVID-19, PSP and CRP levels were found to be higher on admission in the moderate-to-severe group than in those in the



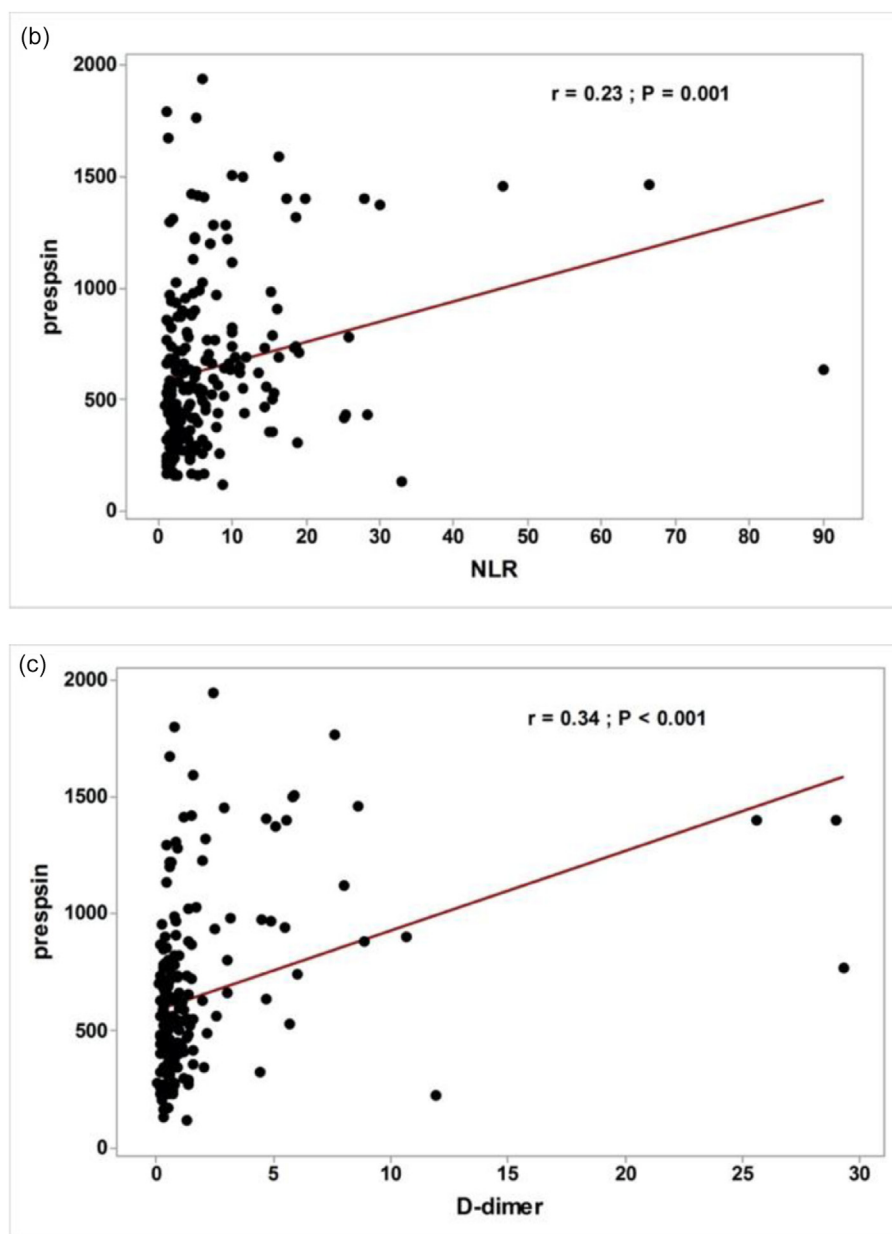


Fig. 5. Continued

mild group. In addition, serial PSP measurements showed an increase in PSP levels in patients showing progression of the disease and requiring invasive mechanical ventilation. In contrast, patients with severe conditions who showed improvement in their COVID-19 pneumonia had concomitantly decreasing PSP level. Fukada et al found PSP levels to be increased before KL-6 levels in patients presenting with moderate disease progressing to severe, showing its potential as a good predictor of severity in moderate-to-severe cases of COVID-19 (Fukada et al., 2020)

Elevated proinflammatory cytokines or chemokines described as cytokine storm has been well established in the pathogenesis of SARS-CoV-2. In our study, PSP showed significant positive correlation with PSI score as well as inflammatory markers (NLR, D-dimer, ferritin, CRP, ESR). However, PSP was superior to NLR, ferritin and CRP in predicting in-hospital mortality due to COVID-19 pneumonia (AUC = 0.84, 0.83, 0.77 and 0.67, respectively) (Table 3 and Fig 3).

ARDS develops in 42% of patients presenting with COVID-19 pneumonia and 61%–81% of those requiring intensive care (Wu et al., 2020). ARDS is characterised by the release of proinflammatory cytokines and recruitment of neutrophil into the lungs. This results in release of toxic mediators that damage the capillary endothelium and alveolar epithelium (Piantadosi and Schwartz, 2004). Postmortem pathological examination of lung tissues obtained from patients dying secondary to severe COVID-19 pneumonia had shown typical pathological features of ARDS in the form of diffuse alveolar damage in the lung with cellular fibromyxoid exudates (Xu et al., 2020). Shan et al found that PSP levels were significantly elevated in patients with ARDS compared with patients with cardiogenic pulmonary oedema. In addition, when comparing PSP levels in patients with ARDS with infectious aetiology versus noninfected patients with ARDS (haemorrhagic shock, aspiration and multiple transfusion), no significant difference was found (Shan et al., 2019). Martin et al found sCD14 to be increased

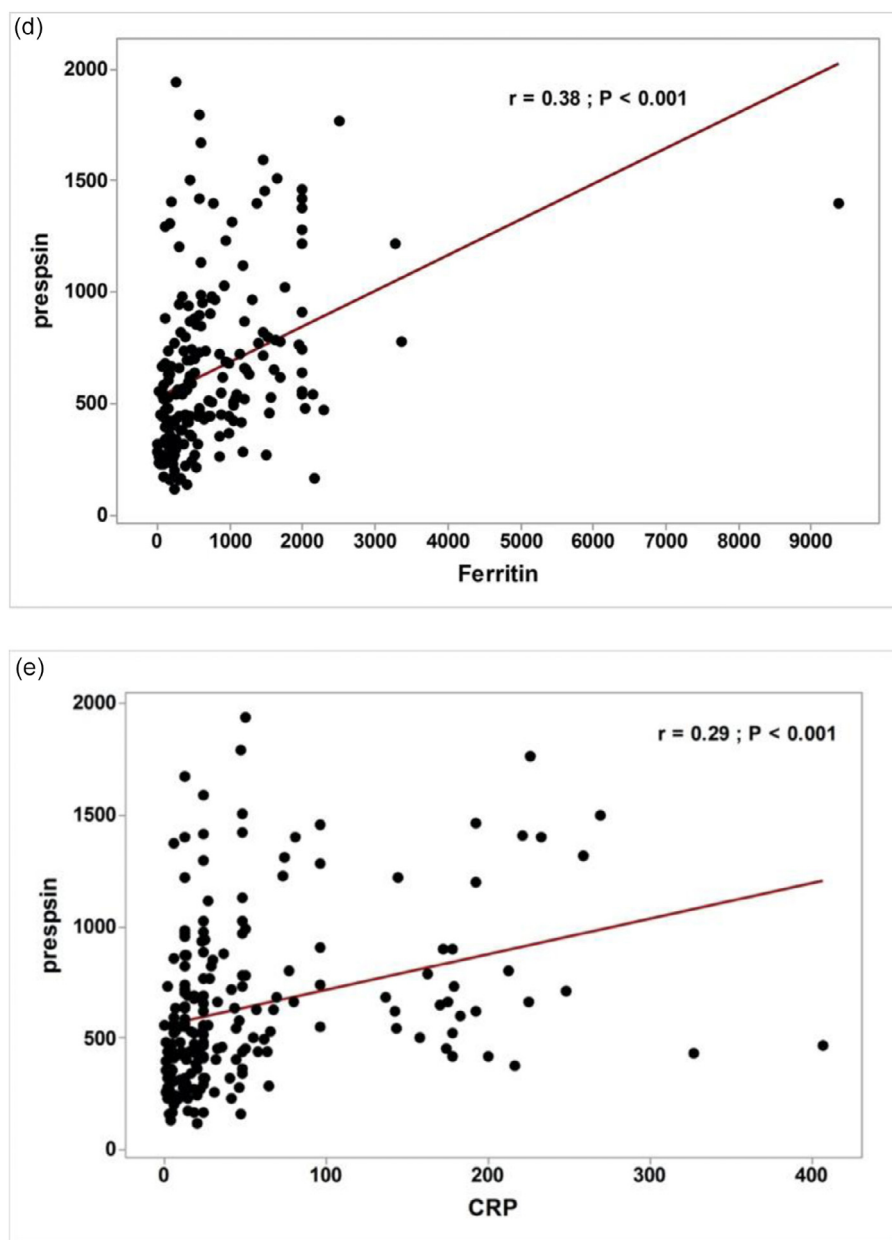


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markedly in bronchoalveolar lavage of patients with ARDS and proposed that CD14-dependent mechanisms may contribute to lung inflammation in ARDS (Martin et al., 1997). A study was carried out to examine the effects of CD14 on the release of proinflammatory cytokines from harvested human bronchial epithelial cells. IL-8 and IL-6 were found to increase in a concentration dependent manner upon stimulation with sCD14 (Striz et al., 1998). From the previously mentioned evidence, it seems that PSP acts as a key component in ARDS-associated inflammatory cascade. Hence, CD14 blockade may be a promising therapeutic approach in patients with COVID-19 ARDS and needs to be investigated further.

Being a retrospective study added some limitations. First, PSP was not measured serially to detect its relation to response to treatment and to compare it with declining inflammatory markers in recovering patients. In the study conducted by Shan et al, blood samples for determination of PSP were collected at enrolment and 4 days later. It was found that patients with ARDS whose

plasma PSP level increased over 4 days had a trend towards an increased risk of death compared with those whose plasma level decreased over time (Shan et al., 2019). Hence, it appears that the decreasing levels of PSP over time indicates the appropriateness of initiated therapy and vice versa, in which the increasing levels indicates unresponsiveness to treatment and points towards a poor outcome.

Second, the question of whether PSP levels were elevated as a part of the intense immune response characteristic to severe COVID-19 pneumonia or owing to concomitant bacterial coinfection in patients with COVID-19 needs to be investigated further. In other words, PSP level would be better compared between patients presenting with COVID-19 pneumonia and patients presenting with other non-COVID-19 causes of pneumonia (bacteria, fungi and other viruses) after adjusting for age and pneumonia severity scores. This would provide us with better understanding of its pathogenic role.



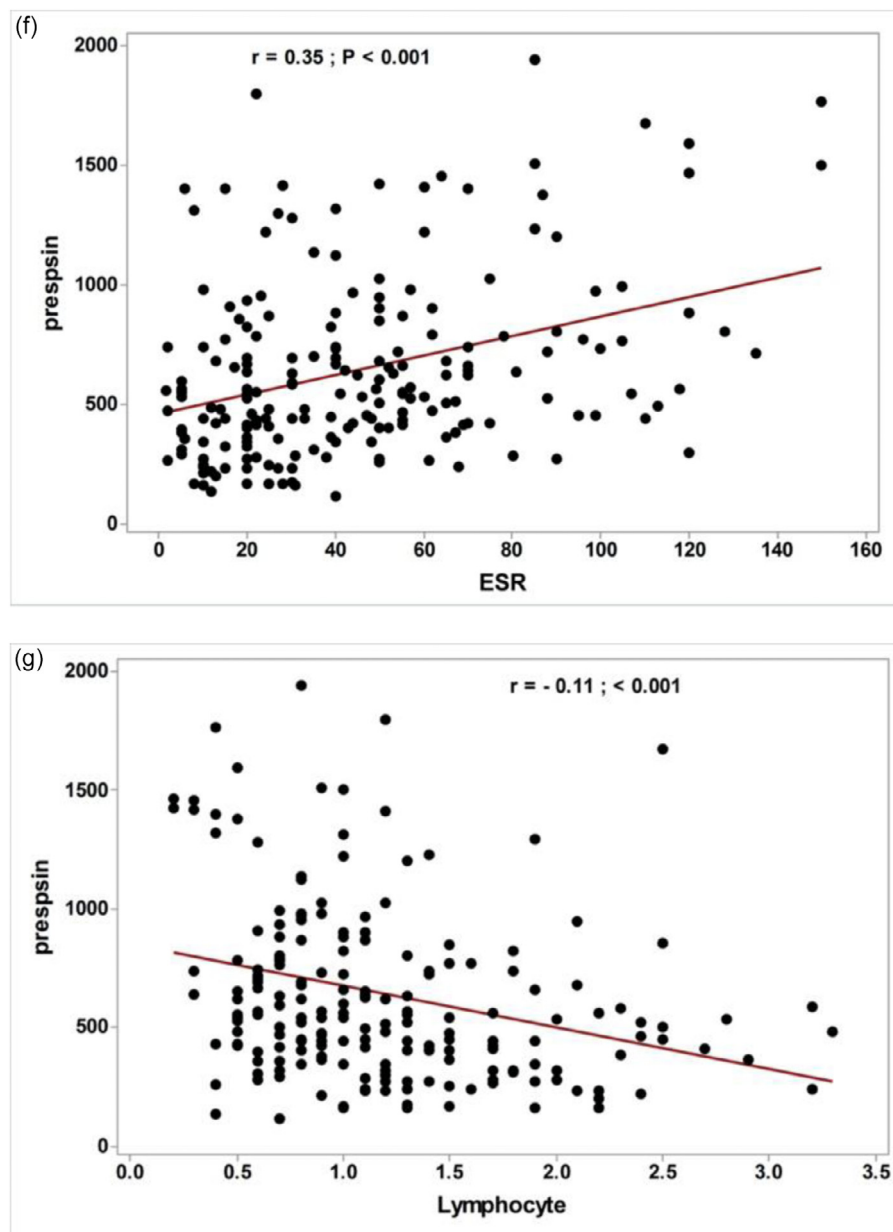


Fig. 5. Continued

## Conclusion

PSP was found to be significantly elevated in patients presenting with severe COVID-19, and levels above 775 pg/ml was significantly associated with in-hospital mortality (sensitivity 73% and specificity 80%). Elevated PSP level indicates poor outcomes and should alert the physicians in making decisions regarding intensive care monitoring and further interventions.

## Ethical approval

This study was approved by the institutional review board of Ministry of Health, Cairo, Egypt (No: 3-2021/19).

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## Conflict of interests

The authors declare that there are no conflicts of interests.

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