# Presepsin as a Novel Biomarker in predicting Inhospital Mortality in COVID-19 Pneumonia Patients

Hebatallah Hany Assal , Safaa Abdelrahman , Maha AlyAlden Abdelbasset , Mai Abdelaziz , Irene Mohamed Sabry , Marwa Moawad Shaban

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**Highlights:**

- Elevated Presepsin in COVID19 patients was associated with inhospital mortality.
- Elevated presepsin levels indicated poor outcomes in COVID-19 patients.
- Presepsin seems to play an important pathogenetic role in COVID ARDS.

**Title:**

Presepsin as a Novel Biomarker in predicting Inhospital Mortality in COVID-19 Pneumonia Patients

**Running title:**

Presepsin in COVID-19 pneumonia

**Authors:**

1-Hebatallah Hany Assal*,MD,Hebatallah.Assal@kasralainy.edu.eg

2-Safaa Abdelrahman[δ],M.D, safaa.mohamed5@gmail.com

3- Maha AlyAlden Abdelbasset[^],M.D, maha.aly@gmail.com

6-Mai Abdelaziz[χ], MD, maiabdelaziz1979@gmail.com

7-Irene Mohamed Sabry*, MD, irene.sabry@yahoo.com

3-Marwa Moawad Shaban* , M.D, marwamoawad@ymail.com

**Corresponding author:**

Hebatallah Hany Assal,MD,Hebatallah.Assal@kasralainy.edu.eg

Tel:01223939861

Address: Department of Chest Medicine, Faculty of Medicine, Cairo University, Al Kasr Al Aini, Old Cairo Cairo,11956, Egypt

**Affiliations:**

*Department of Chest Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt.

[δ]Department of pediatrics , Faculty of Medicine, Cairo University ,Cairo, Egypt

[^]Department of pediatrics, Faculty of Medicine ,Zagazig University, Zagazig, Egypt

[χ]Biochemistry department, Faculty of Medicine, Cairo University, Cairo, Egypt.

**Abstract**

**Objectives:** Different biomarkers such as CRP, serum ferritin and D dimer are used in prognostic assessment of patients with COVID-19 pneumonia. Presepsin(PSP) is a soluble CD14 subtype has recently been proposed as a novel biomarker in sepsis patients. The aim of the current study was to detect the relation of presepsin to the outcome of COVID-19 as well as its relation to other inflammatory biomarkers. **Methods:** Multicenter, retrospective observational study was conducted in Saudi Arabia and Misr International Hospital, Egypt from January 2021 to May 2021. Hospitalized patients who had positive throat swab of SARS-COV2 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, presepsin of enrolled patients were retrospectively collected. Pneumonia severity index (PSI) was used to evaluate the severity of pneumonia. **Results:** 202 hospitalized patients were diagnosed with COVID-19 pneumonia and had positive results of SARS-CoV-2 RNA; were enrolled to our study. Out of 202 hospitalized patients 67 patients (33.17%) required ICU admission. One hundred seventy-six (87.1%) patients survived and were discharged, 26 (12.9%) patients didn't survive. Presepsin 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 in ICU versus non-ICU patients, median (IQR), 800(631-1200) and 446(320-626), respectively (P value<0.001). Elevated levels were also found to be associated with increase length of hospital stay. Levels above 775 pg/ml were found to be associated with in-hospital mortality specificity 80%, sensitivity 73%. **Conclusion:** Elevated presepsin levels indicated poor outcomes in hospitalized COVID-19 pneumonia and was associated with in-hospital mortality.

**Keywords:** Presepsin, Covid-19, inflammatory markers, soluble CD-14, CRP, Ferritin, D-dimer, sepsis.

**Introduction**

COVID-19 caused by SARS-COV2 is currently a challenging pandemic that had 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 interleukin-6 (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, that 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 of lipopolysaccharide of Gram negative bacteria to Toll-like receptors and promotes the activation of the immune response such as cytokines production by effector cells. CD14 has two forms: membrane-bound CD14 (mCD14) and soluble CD14 (sCD14). The 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 (Memar and Baghi, 2019).

Presepsin (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 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:**

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 Ministry of Health, Cairo, Egypt (No: 3-2021/19).

Hospitalized patients who had positive throat swab of SARS-COV2 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. CPK , AST ,ALT and Albumin were measured using Dimension EXL -200 ,Siemens Healthcare Diagnostics Inc. Newark, USA. LDH, Ferritin, CRP and D-Dimer were measured using Cobas C311 analyzer, Roche Diagnostics, GmbH, Mannheim, Germany. Heamatological parameters (WBC, Hematocrit, Neutrophil, Lymphocyte and Platelets) were measured using Sysmex XS-500i, Sysmex corporation, Kobe, Japan. PSP measurement in lithium-heparin plasma samples using a chemiluminescent enzyme immunoassay using Pathfast, 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 pneumonia, Pneumonia severity index (PSI) was calculated. PSI uses 20 clinical variables to predict the patient's outcome. The patients are then categorized into five severity classes with increasing likelihood of death within 30 days. Class I–III are low risk groups with cumulative mortality rate <1%; whereas class IV and V are intermediate and high-risk groups with mortality rates ranging from 9–30% (Fine et al., 1997).

**Statistical Analysis**

The data was 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 standard deviation (SD), and categorical data as number and percentage (%), the normality of data was examined using Shapiro-Wilk test. Association with mortality was performed by Chi square test, independent t-test or Mann Whitney test. Comparison between length of hospital stay in patients with elevated PSP level versus patients with low PSP level was done by independent t-test.

Multivariate logistic regression analysis was performed to test for the preferential effect DM on the relation between presepsin level and survivorship. Two-sided *p* values 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 continues data. The prognostic utility of presepsin and other inflammatory marker was done using receiver operating characteristic curve (ROC-curve), the AUC above 0.6 considered acceptable for test capability. P considered significant if < 0.05.



**Results:**

Two hundred and two hospitalized patients were diagnosed with COVID-19 pneumonia and had positive results of SARS-CoV-2 RNA; were enrolled to our study.

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

Regarding the severity of the disease, patients were stratified into groups according to the pneumonia severity index (PSI). Fifty seven (28.2%) patients had PSI score ≥ 91 (risk class IV &

V), they were considered to have severe COVID pneumonia i.e: high risk groups while the rest of the patients 71.8% had PSI <90 (risk class I, II , III) were considered patients with mild COVID pneumonia, i.e: low risk groups.

Out of 202 hospitalized patients 67 patients (33.17%) required ICU admission. One hundred seventy-six (87.1%) patients survived and were discharged, 26 (12.9%) patients didn't survive.

The factors associated with COVID-19 mortality were summarized in table 2 in which older age, diabetes and hypertension were significantly associated with mortality (P = 0.01, < 0.001 , =0.05 respectively). Moreover, PSI score was significantly higher in non-survived patients, P < 0.001 as well as LDH, Ferritin, CRP, ESR, D-dimer, TLC, neutrophil, NLR (P < 0.001), while lymphocyte count was significantly lower in non-survivor.(Table 2)

The mean and median level of PSP was 707.4 pg/ml and 545 pg/ml respectively, and ranged about (116-14681) pg/ml, with significant higher elevation in non-survived group, median (IQR) was 978.5 (755.7-1400), P < 0.001. (Table 1 & 2 & Fig 1). To adjust for the effect of DM as a confounder. We performed a multivariate logistic regression. The analysis showed that presepsin was still a significant predictor of mortality (OR=0.997, 95%CI=0.996-0.999, p<0.005)

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

The performances of PSP, NLR, Ferritin,CRP as well as PSI score in predicting inhospital mortality from COVID-19 pneumonia sepsis were evaluated using ROC curves (Fig. 3). The levels of PSP as well as PSI score and NLR demonstrated good performance in predicting the prognosis of COVID-19 pneumonia(area under the curve=0.84, 0.87,0.83 respectively)(Table 3)

PSP showed linear positive correlation with PSI and biomarkers of inflammation NLR, D-dimer, Ferritin, CRP and ESR as well as negative correlation with lymphocytic count (Table 4) (Fig5a-5g)

Patients were divided into two groups according to the proposed cut off value of presepsin (775 pg/ml). Patients with PSP levels greater than 775 pg/ml (148 patients) had significant increase in length of hospital versus patients with PSP level less than 775 pg/ml (54 patients) (mean±SD 17.02±6.78 versus 12.48±5.8, p< 0.001). (Fig 4)

**Discussion:**

Presepsin(PSP) is a soluble CD14 subtype has recently been proposed as a novel biomarker in sepsis patients. Several studies had proved its role in risk stratifying patient 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 soluble CD14 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 from a dose–response mechanism of the host-pathogen interaction, that occurs in the initial phase of the pathogen recognition, and remains elevated during several days on the basis of the disease severity (Zaninotto et al., 2020)

Investigating the role of PSP in COVID patients 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 COVID19 pneumonia to detect its relation to the outcome of COVID19 as well as its relation to other inflammatory biomarkers.

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

In a case series done by Fukada et al who investigated PSP level, CRP, procalcitonin, Krebs von den Lungen-6 (KL-6) KL-6 in hospitalized COVID 19 patients. PSP and CRP were higher on admission in the moderate-to-severe group than in those in the mild group. Additionally, serial PSP measurements showed increase in patient showing progression of the disease requiring invasive mechanical ventilation. On the other hand, severe patients who showed improvement of their COVID pneumonia had concomitantly decreasing PSP level. Fukada et al found PSP levels to be increased early before KL-6 levels in patients presenting with moderate disease progressing to severe, demonstrating 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 presepsin showed significant positive correlation with PSI score as well as inflammatory markers (NLR, D-dimer, Ferritin, CRP,

ESR). However PSP was superior than NLR, Ferritin, CRP in predicting inhospital mortality from COVID-19 pneumonia (area under the curve=0.84,0.83,0.77,0.67 respectively).(Table3 & 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 characterized 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). Post mortem pathological exam 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 were significantly elevated in patients with ARDS compared to patients with cardiogenic pulmonary edema. Also when comparing PSP levels in ARDS patients with infectious etiology versus non-infected ARDS patients( hemorrhagic shock, aspiration and multiple transfusion) no significant difference was found (Shan et al., 2019). Martin et al found sCD14 to be increased markedly in BAL of patients with ARDS and proposed that CD14-dependent mechanisms may contribute to lung inflammation in ARDS (Martin et al., 1997). A study was done to examine the effects of CD14 on the release of pro inflammatory 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 above mentioned evidence, it seems that PSP act as a key component in ARDS associated inflammatory cascade. Hence CD14 blockade may be a promising therapeutic approach in patients with COVID ARDS and needs to be investigated in further studies.

Being a retrospective study had added some limitations. First, presepsin 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 of Shan et al, blood samples for determination of presepsin were collected at enrollment and 4 days later. It was found that in ARDS patients whose plasma presepsin level increased over 4 days had a trend toward 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 where the increasing levels indicates unresponsiveness to treatment and points toward a poor outcome.

Second, the question of weather PSP levels were elevated as a part of the intense immune response characteristic to severe COVID pneumonia or due to concomitant bacterial co infection in COVID patients needs to be investigated in further studies. In other words Presepsin level would be

better compared between patients presenting with COVID pneumonia and patients presenting with other non COVID causes of pneumonia (bacteria ,fungal and other viruses) after adjusting with age and pneumonia severity scores. This would provide us with better understanding of its pathogenic role.

## Conclusion

PSP was found to be significantly elevated in patients presenting with severe COVID 19 and levels above 775pg/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 management decisions regarding intensive care monitoring and further interventions.

## Declaration of Competing Interest

The authors declare that there is no conflict of interests.

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## Ethical approval:

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

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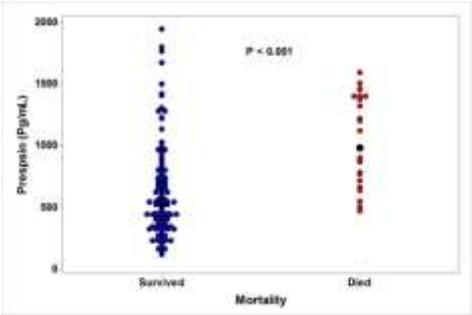


**Figure 1:** Presepsin level in survivor versus non survivor group.

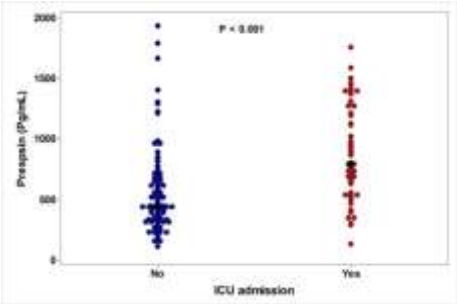


**Figure 2**: Presepsin level in patients who required ICU admission versus patients who did not.

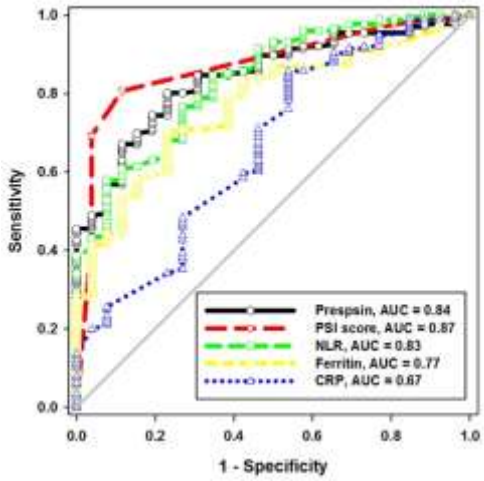


**Figure 3:** Receiver operating characteristic(ROC) curves of the presepsin, PSI score,Ferritin, CRP and NLR in predicting patients' in-hospital mortality. *PSI: pneumonia severity index, CRP:C-reactive protein, NLR: Neutrophil to lymphocyte ratio.*

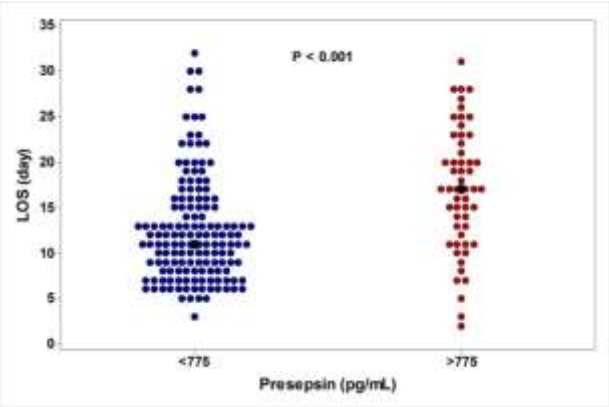


**Figure 4:** Relationship between presepsin values and hospital stay.

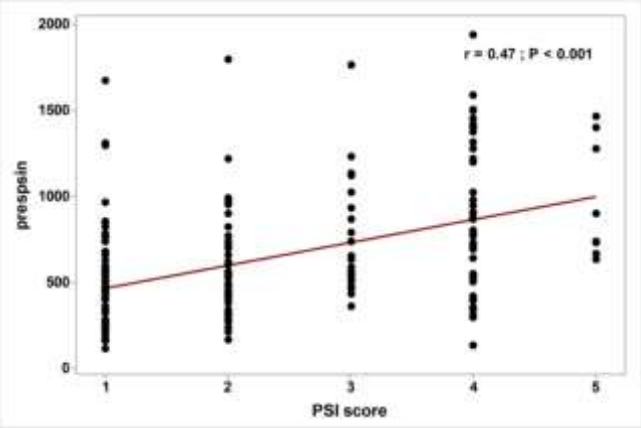


**Figure 5a:** Correlation between Presepsin and PSI score

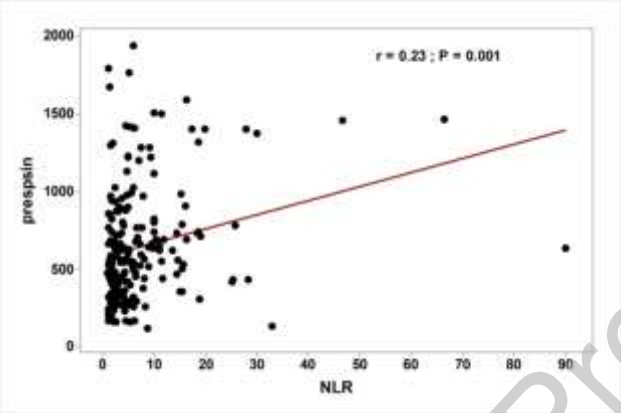


**Figure 5b:** Correlation between presepsin and neutrophil lymphocyte ratio

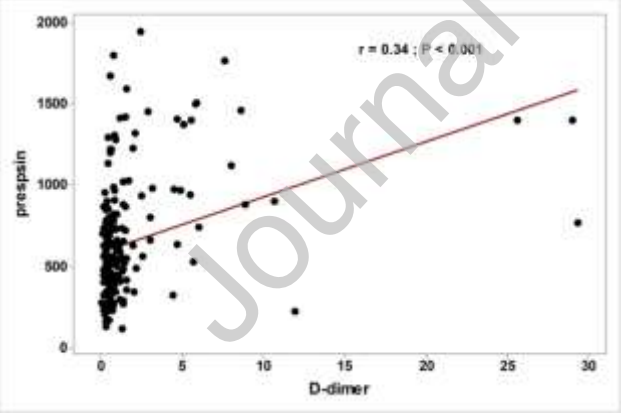


**Figure 5c:** Correlation between presepsin and D-dimer

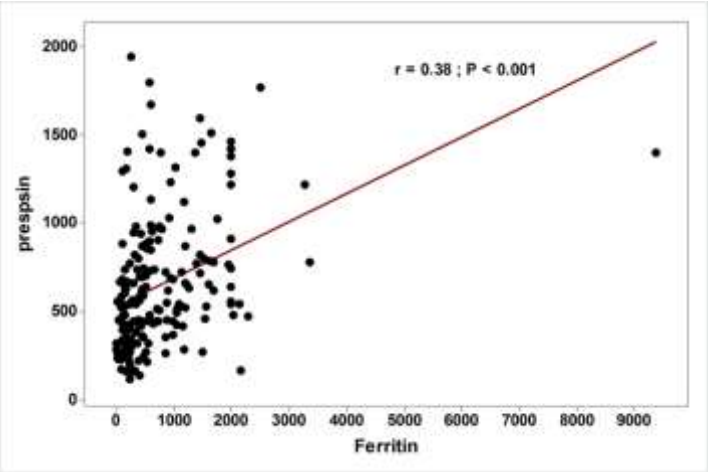


**Figure 5d:** Correlation between presepsin and ferritin levels

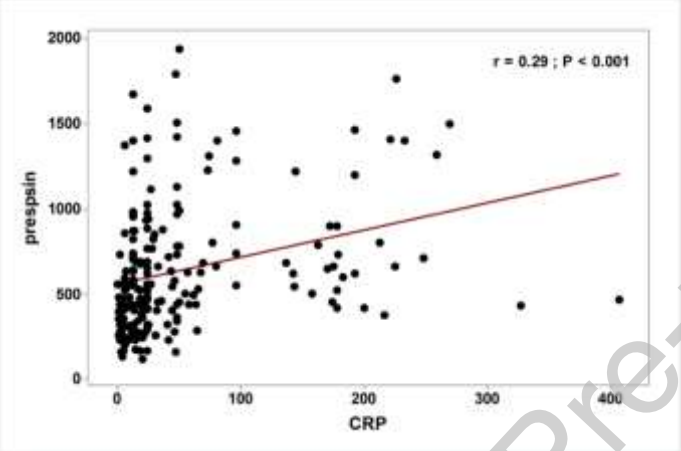


**Figure 5e:** Correlation between presepsin and CRP level

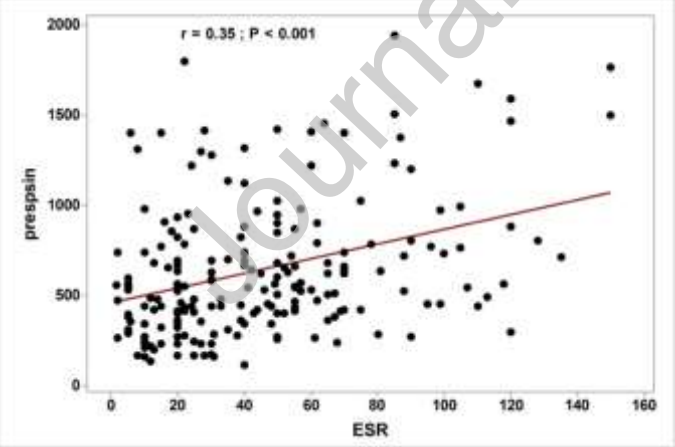


**Figure 5f:** Correlation between presepsin and ESR levels

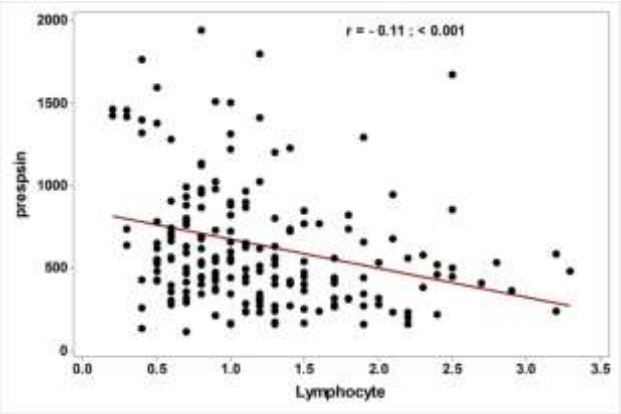


**Figure 5g:** Correlation between presepsin and lymphocyte count

**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×10^3/Ul** | 6.3(1.2-28.9) |
| **Neutrophil count×10^3/uL** | 4.4(0.7-27) |
| **Lymphocyte count×10^3/uL** | 1(0.2-3.3) |
| **Platelet count ×10^3/uL** | 213(50-693) |
| **Hematocrit** | 39.8(19-61.4) |
| **NLR** | 4.2(0.9-90) |

LDH: Lactate dehydrogenase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, CPK: Creatine phosphokinase, AST: aspartate aminotransferase, ALT: alanine transaminase, TLC: Total leucocytic count, NLR: Neutrophil to lymphocyte ratio.

**Table (2):** Epidemiological, inflammatory markers and length of hospital stay comparison between survivor and non-survivor groups

| Factors | Survival (n=176) | Non survival (n=26) | P value |
|---|---|---|---|
| **Age(years)*** | 54.038±9.035 | 47.835±12.552 | 0.01§ |
| **Gender:**<br>**Female,N(%)**<br>**Male,N(%)** | <br>39(22.16%)<br>137(77.84%) | <br>4(15.38%)<br>22(84.62%) | 0.48ɬ |
| **Diabetic,N(%)** | 55(31.25%) | 17(65.38%) | 0.001ɬ |
| **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%) | < 0.001ɬ |
| **PSI risk class,N(%)**<br>**I**<br>**II**<br>**III**<br>**IV**<br>**V** | <br>76(43.18%)<br>46(26.14%)<br>20(11.36%)<br>30(17.05%)<br>4(2.27%) | <br>1(3.85%)<br>0<br>2(7.69%)<br>18(69.23%)<br>5(19.23%) | <br><br><br>< 0.001ɬ<br><br> |
| **Presepsin pg/ml** # | 516.5(343.3-720) | 978.5(755.8-1400) | < 0.001$ |
| **LDH U/L** # | 318.5(244.5-412) | 532(425.25-665.2) | < 0.001$ |
| **Ferritin ng/ml** # | 413.5(175.8-901.5) | 1289(669.7-1765.7) | < 0.001$ |
| **CRP mg/L** # | 24(10.3-48) | 48(12.7-179.3) | < 0.001$ |
| **ESR mm/hr** # | 35(20-57) | 59.5(40-87.8) | < 0.001$ |
| **D-dimer mg/L** # | 0.6(0.4-1.1) | 1.8(0.9-6.4) | < 0.001$ |
| **TLC×10^3/Ul** # | 6.1(4.5-8.3) | 10.55(6.7-12.8) | |
| **Neutrophil ×10^3/Ul** # | 4.15(2.6-6.2) | 8.5(5.5-12.1) | < 0.001$ |
| **Lymphocyte ×10^3/Ul** # | 1.1(0.7-1.7) | 0.7(0.4-1) | < 0.001$ |
| **NLR**# | 3.7(1.8-6.5) | 14.8(5.4-21.3) | < 0.001$ |
| **LOS**# | 12(9-17) | 18.5(8-22.3) | 0.08 |

ICU:Intensive care unit, PSI: pneumonia severity index, TLC: Total leucocytic count, NLR: Neutrophil to lymphocyte ratio, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LOS: Length of hospital stay. *: Data are represented as mean and stander deviation (SD), #:data are represented as median and inter quartile range (IQR), and categorical data as number (N) and percentage (%); §: independent t-test, $: Mann Whitney test, ɬ: chi square test, P considered significant if < 0.05.

**Table 3:** Diagnostic utility of Presepsin and other inflammatory markers

| Marker | Cut-off level | Senstivity | 95% CI | Specificity | 95% CI | PPV | NPV |
|---|---|---|---|---|---|---|---|
| Presepsin 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 |

CI: Confidence interval, PPV: positive predictive value, NPV: negative predictive value, NLR: Neutrophil to lymphocyte ratio

**Table 4:** Correlation between Presepsin and clinical and laboratory markers of inflammation:

| Factors | Presepsin | |
|---|---|---|
| | R | P |
| PSI score | 0.29 | < 0.001 |
| Lymphocytes | -0.20 | 0.004 |
| NLR | 0.46 | < 0.001 |
| D-dimer | 0.24 | 0.001 |
| Ferritin | 0.22 | 0.001 |
| CRP | 0.23 | 0.001 |
| ESR | 0.27 | < 0.001 |

*: Person correlation, the sign before "r" denoting the direction of relationship, $P < 0.05$ considered significant. PSI: pneumonia severity index, NLR: Neutrophil to lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.