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# The Role of Pancreatic Stone Protein as a Predictor of Sepsis in the Intensive Care Unit and Its Correlation With D-Dimer, C-Reactive Protein, and Procalcitonin

Darko Sazdov, Ivica Dimitrov, Androniki Bibovska

Abstract

Pancreatic stone protein (PSP) is secreted by pancreatic acinar cells. PSP is a damage-associated molecular pattern (DAMP) produced in response to sepsis. The study aims to determine the association between PSP values and sepsis criteria, SOFA score, mortality, and values of D-dimer, WBC, CRP, and Procalcitonin on admission to the ICU. This is a monocentric retrospective study that includes 63 patients, with a mean age of 62.5±15.5 years, with PSP values measured on admission to the ICU. Patients were stratified as having normal PSP values, low, moderate, or high risk for sepsis and compared with the classification based on the Third International Consensus Definitions for Sepsis and Septic Shock and to their SOFA score and laboratory parameters, including WBC, CRP, D-dimer, and Procalcitonin. A statistically significant difference was confirmed in the distribution of patients with normal PSP values, with low, moderate and high risk for sepsis according to PSP values in terms of not meeting sepsis criteria (p=0.0000), meeting SIRS criteria (p=0.029), meeting sepsis criteria (p=0.022) and meeting septic shock criteria (p=0.000), while, the difference in terms of severe sepsis criteria was not statistically significant (p=0.88). PSP significantly positively correlated with D-dimers, CRP, and PCT (R =0.4462, p=0.0008; R =0.4971, p=0.00003; and R=0.5825, p=0.000001, respectively). PSP may play a role as a predictor of sepsis severity and mortality in patients in the ICU.

*Keywords:* PSP, sepsis, SOFA, Intensive Care Unit

## Introduction

Pancreatic stone protein (PSP) is a 16 kDa C-type lectin protein produced predominantly by the pancreas and intestine. It is a protein secreted by acinar cells to inhibit the growth and nucleation of calcium carbonate crystals in pancreatic juice. Preclinical studies indicate that PSP is actually a molecular pattern produced in response to sepsis (Hu, 2023). Based on this, the question arises about the role of PSP as a predictor of sepsis, especially in intensive care units. Early recognition of sepsis is essential to prevent complications such as multiorgan dysfunction syndrome (MODS) and death in patients hospitalized in intensive care units. No biomarker has yet been successfully implemented in daily practice with good clinical performance. Pancreatic stone protein (PSP) is a promising biomarker in the context of sepsis.

## Study Objectives

1. To determine the association of PSP value with sepsis criteria in ICU patients.
2. To determine whether there is a connection between PSP value and D-dimer, WBC, CRP values, and procalcitonin measured in ICU patients.
3. To determine the correlation between PSP and mortality in the ICU.
4. To determine the correlation between PSP values and SOFA score on admission to the ICU.

## Methods and Materials

This is a monocentric retrospective study that included 63 patients with an average age of 62.5±15.5 years, who were hospitalized in the general intensive care unit at Acibadem Sistina Hospital in Skopje, North Macedonia.

All patients had the following parameters upon admission to the general intensive care unit:

PSP, sepsis criteria, sofa score, D-dimer, WBC, CRP, procalcitonin.

PSP reference values:

- PSP<100ng/m Normal value
- PSP ≥100-200 ng/ml Low risk of sepsis
- PSP ≥200-300 ng/ml Moderate risk of sepsis
- PSP ≥300ng/ml High risk of sepsis

## Sepsis Criteria

**Table 1:**

*Sepsis Criteria - The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)*

| **SIRS Criteria (≥2 meet SIRS definition)** | | |
|---|---|---|
| Temp >38°C or <36°C | No | Yes |
| Heart rate >90 | No | Yes |
| Respiratory rate >20 or $PaCO_2$ <32 mm Hg | No | Yes |
| WBC >12,000/$mm^3$, <4,000/$mm^3$, or >10% bands | No | Yes |
| **Sepsis Criteria (SIRS + Source of Infection)** | | |
| Suspected or present source of infection | No | Yes |
| **Severe Sepsis Criteria (Organ Dysfunction, Hypotension, or Hypoperfusion)** | | |
| Lactic acidosis, SBP <90 or SBP drop ≥40 mm Hg from normal | No | Yes |
| **Septic Shock Criteria** | | |
| Severe sepsis with hypotension, despite adequate fluid resuscitation | No | Yes |

## Reference Values of WBC, D-D-Dimer, CRP, and Procalcitonin

- WBC 4-11 *10^9/L
- CRP <0.5 mg/dl
- PCT <0.5 ng/ml (Normal);
  0.1-0.5 ng/ml (Local inflammation, infection);
  0.5-2ng/ml (Low- systemic anwer on inflammation);
  2-10 ng/ml (Strong - systemic answer on inflammation);
  >10 ng/ml (Bacterial sepsis / septic shock)
- D-Dimer < 0.5 ug/ml F. EU

## Inclusion and Exclusion Criteria

Patient data was obtained from the CEREBRAL+ electronic system of Acibadem Sistina Clinical Hospital, which contains all medical documentation for treated patients.

### Inclusion criteria

All patients who had PSP taken upon admission to the ICU.

### Exclusion criteria

- Death within 24 hours of ICU admission;
- Patients under 18 years of age;

## Statistical Analysis

The statistical processing of the data received from the research was made in the statistical program Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois) version 25.0. For the data distribution, the Kolmogorov-Smirnov and the Shapiro-Wilk W test were used. Qualitative variables are presented with absolute and relative numbers. Quantitative variables are presented with average, minimum, and maximum values, standard deviation, median, and interquartile range. For comparison of qualitative data, Fisher's exact test was used; quantitative variables were compared with the Kruskal-Wallis test. Correlation between two variables was analyzed with Spearman's rank correlation coefficient.

The statistical significance was defined for $p < 0.05$.

## Ethical Aspects of the Study

For this study, the researchers have received approval from the Committee for Ethical Issues at the Acibadem Sistina Hospital No. 02-2673/02.

## Results

The study included 63 patients, 42(66.7%) male and 21(33.7%) female. The patients were aged 18 to 89 years, with a mean age of 62.5±15.5 years.

Table 2 shows the distribution of patients according to sepsis criteria.

**Table 2:**

*Distribution of Patients According to Sepsis Criteria*

| **Sepsis criteria** | **n (%)** |
|---|---|
| Doesn't fulfill criteria for sepsis | 15 (23.81) |
| Criteria for SIRS | 8 (13) |
| Criteria for sepsis | 16 (25.4) |
| Criteria for severe sepsis | 4 (6.35) |
| Criteria for septic shock | 20 (31.75) |

Patients in our study most often had PSP values of 300 ng/ml and higher, and belonged to the group with high risk for sepsis – 34 (53.97%), followed by 12 (19.0%) patients with PSP values of 200 to 300 ng/ml who have a moderate risk for sepsis, 9 (14.29%) patients with PSP values of 100 to 200 ng/ml with a low risk for sepsis, and, 8 (12.7%) patients with PSP values lower than 100 ng/ml who have no risk for sepsis.

Table 3 shows the distribution of PSP values in patients with different sepsis criteria. Patients with normal PSP values most often did not meet the criteria for sepsis (87.5%), patients with low risk for sepsis according to PSP most often met the criteria for SIRS (44.44%), patients with moderate risk for sepsis according to PSP met the criteria for sepsis (58.33 %), patients with high risk for sepsis according to PSP most often met the criteria for septic shock (55.88 %).

A statistically significant difference was confirmed in the distribution of patients with normal PSP values, with low, moderate and high risk for sepsis according to PSP values in terms of not meeting sepsis criteria ( p=0.0000), meeting SIRS criteria (p=0.029), meeting sepsis criteria ( p=0.022) and meeting septic shock criteria ( p=0.000), while the difference in terms of severe sepsis criteria was not statistically significant (p=0.88). The impact of PSP was confirmed as significant for 4 out of 5 sepsis criteria.

**Table 3:**

*Distribution of PSP Values in Patients With Different Criteria for Sepsis*

| Variable | PSP (Pancreatic stone protein) | | | | | p-level |
|---|---|---|---|---|---|---|
| | N | Normal value n (%) | Low risk for sepsis n (%) | Moderate risk for sepsis n (%) | High risk for sepsis n (%) | |
| Doesn't fulfill criteria for sepsis | 15 | 7 (87.5) | 2 (22.22) | 2 (16.67) | 4 (11.76) | ***p=0.0000 |
| Criteria for SIRS | 8 | 1 (12.5) | 4 (44.44) | 1 (8.33) | 2 (5.88) | *p=0.029 |
| Criteria for sepsis | 16 | 0 | 2 (22.22) | 7 (58.33) | 7 (20.59) | *p=0.022 |
| Criteria for severe sepsis | 4 | 0 | 1 (11.11) | 1 (8.33) | 2 (5.88) | p=0.88 |
| Criteria for septic shock | 20 | 0 | 0 | 1 (8.33) | 19 (55.88) | ***p=0.000 |
| total | 63 | 8 | 9 | 12 | 34 | |

p (Fisher's exact test), * Sig p<0.05, ***sig p<0.0001

The comparison of patients without risk, with low, moderate, and high risk for sepsis according to PSP in terms of D- D-dimer, leukocyte, C-reactive protein, and procalcitonin values showed a statistically significant difference in terms of D- dimer values (p=0.0045), CRP (p=0.0003) and PCT (p=0.0001), and non-significant for WBC values (p=0.32) (Table 4).

Post-hoc analyses show significantly higher values of D-dimers, CRP, and PCT in patients with high risk of sepsis compared to patients with normal PSP (p=0.0025, p=0.00021, and p=0.00018, respectively).

D-dimer values in patients at high risk for sepsis versus patients with normal PSP were 9.08 ± 8.8 and 0.97 ± 0.8. ug /ml FEU, respectively; 24.29 ± 12.9 and 4.91 ± 3.9 mg /dl, respectively for CRP; 19.80 ± 28.8 and 1.63 ± 4.4 ng/ml, respectively for PCT (Table 4).

**Table 4:**

Comparison of PSP With Laboratory Parameter Values

| Variable | Statistical parameters | PSP (Pancreatic stone protein) | | | |
|---|---|---|---|---|---|
| | | **Normal value** | **Low risk for sepsis** | **Moderate risk for sepsis** | **High risk for sepsis** |
| **D-Dimer ug /ml FEU** | n | 6 | 7 | 9 | 31 |
| | mean ± SD | 0.97 ± 0.8 | 4.12 ± 2.6 | 4.83 ± 4.6 | 9.08 ± 8.8 |
| | median (IQR) | 0.72(0.54-1.01) | 3.73(2.3-5.6) | 3.48(1.62-7.6) | 6.1(2.2-12.6) |
| | p-level | H=13. 05 * *p=0.0045<br>post- hoc normal value vs high risk for sepsis **p=0.0025 | | | |
| **WBC * 10^9/L** | n | 8 | 9 | 12 | 34 |
| | mean ± SD | 12.19 ± 6.2 | 17.06 ± 9.4 | 18.39 ± 6.7 | 15.56 ± 9.7 |
| | median (IQR) | 10.37(8.6-14.3) | 13.3(12.4-20.3) | 18.25(14.8-23.7) | 13.8(8.6-22.4) |
| | p-level | H=3. 54 p =0.32 | | | |
| **CRP mg /dl** | n | 8 | 9 | 12 | 34 |
| | mean ± SD | 4.91 ± 3.9 | 18.53 ± 13.8 | 15.19 ± 15.21 | 24.29 ± 12.9 |
| | median (IQR) | 3.53(2.9-6.6) | 16.6(9.8-20.0) | 11.1(4.8-21.2) | 24.1(14.9-31.5) |
| | p-level | H=19. 1 * **p=0.0003<br>post- hoc normal value vs high risk for sepsis ***p=0.00021 | | | |
| **PCT ng /ml** | n | 8 | 9 | 12 | 34 |
| | mean ± SD | 1.63 ± 4.4 | 1.32 ± 1.7 | 9.80 ± 28.5 | 19.80 ± 28.8 |
| | median (IQR) | 0.06(0.04-0.13) | 0.79(0.29-1.45) | 1.17(0.12-3.33) | 4.84(1.31-24.6) |
| | p-level | H=21. 39 * **p=0.0001<br>post- hoc normal value vs high risk for sepsis ***p=0.00018 | | | |

H (Kruskal-Wallis test, post-hoc Mann-Whitney U test), **sig p<0.01, ***sig p<0.0001

PSP was significantly positively correlated with D-dimer, CRP, and PCT (R =0.4462, p = 0008; R =0.4971, p = 0.00003; and R = 0.5825, p = 0.000001, respectively), and non-significantly correlated with WBC (p = 0.99) (Table 5, Figure 1).

PSP values increased with increasing D – D-dimer, CRP, and PCT values, and vice versa.

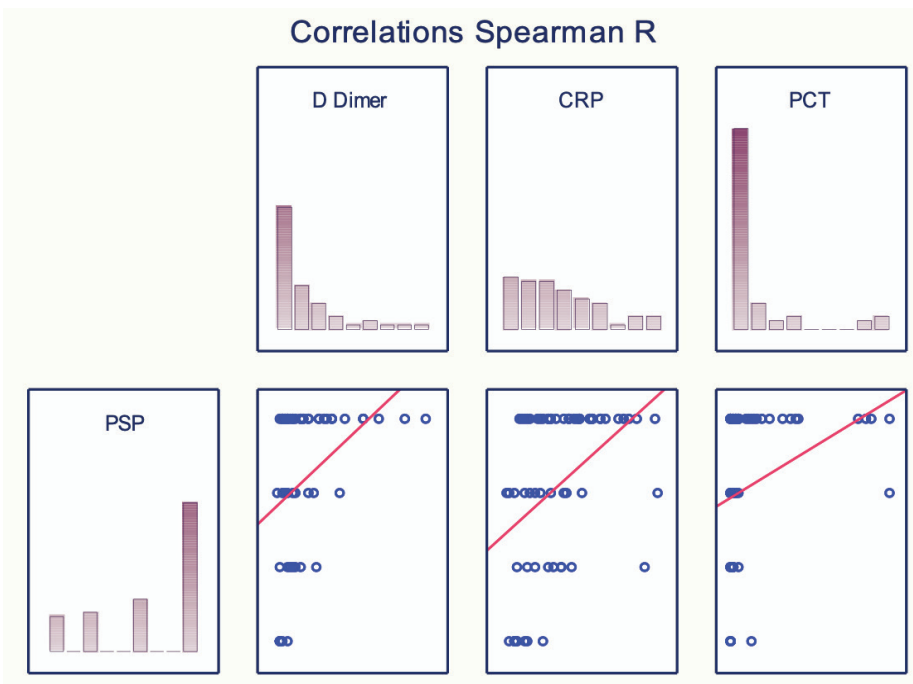
**Table 5:**

*Correlations of PSP with D- dimer, CRP, and PCT*

| | Spearman R | t(N-2) | p-level |
|---|---|---|---|
| D-Dimer | 0.4462 | 3.5604 | 0.0008 |
| WBC | 0.0014 | 0.0107 | 0.99 |
| CRP | 0.4971 | 4.4736 | 0.00003 |
| PCT | 0.5825 | 5.5504 | 0.000001 |

**Figure 1**

*PSP Correlations With D- D-dimer, CRP, and PCT*



Patients with high risk of sepsis according to PSP values (44.12%) were the most common, followed by patients with moderate risk of sepsis (33.33%), patients without risk (12.5%), and patients with low risk of sepsis (11.11%). The differences in the distribution of deceased and living patients in relation to PSP were insufficient to be confirmed as statistically significant (p = 0.18) (Table 6).

**Table 6:**

*Distribution of Deceased and Living Patients With Respect to PSP*

| **Deceased** | **PSP (Pancreatic stone protein)** | | | | | **p-level** |
|---|---|---|---|---|---|---|
| | **N** | **Normal value n (%)** | **Low risk for sepsis n (%)** | **Moderate risk for sepsis n (%)** | **High risk for sepsis n (%)** | |
| Yes | 21 | 1 (12.5) | 1 (11.11) | 4 (33.33) | 15 (44.12) | p=0.18 |
| No | 42 | 7 (8 7. 5 8 ) | 8 (88.89) | 8 (66.67) | 19 (55.88) | |

p (Fisher's exact test)

On admission to the ICU, patients' SOFA scores varied significantly depending on the PSP values (p = 0.038). The SOFA score 0-1 had only 1 (11.11%) patient from the group with low risk of sepsis. Patients with normal PSP and low risk of sepsis had a Sofa score of 2-3 more often compared to patients with high and moderate risk (25% vs 22.22% vs 8.82% vs 8.33%). Sofa score of 4 - 5 was most often calculated in patients with moderate risk, followed by patients with normal PSP, with low and high risk of sepsis (58.33% vs 25 % vs 11.11 % vs 8.82 %). Sofa score of 6-7 was most commonly calculated in patients with normal PSP compared to patients with moderate, high and low risk of sepsis according to PSP (25% vs 16.67 % vs 11.76 % vs 11.11 %), Sofa score 8-9 was most often found in patients with normal PSP compared to patients with low, high and moderate risk of sepsis according to PSP (25% vs 22.22 % vs 20.59 % vs 8.33 %), Sofa score 10-11 was more common in patients with high risk compared to patients with low and moderate risk for sepsis (26.47% vs 11.11 % vs 8.33 % vs 0 %), and, Sofa score 12-14 was more common in patients with high risk for sepsis compared to the other groups (23.53 % vs 11.11 % vs 0 % vs 0%) (Table 7).

Patients at high risk for sepsis according to PSP more frequently had SOFA scores of 10-11 and 12-14 compared to other patient groups.

**Table 7:**

*Comparison of the SOFA score with PSP on admission to the intensive care unit*

| Sofa score on reception in the ICU | PSP (Pancreatic stone protein) | | | | | p-level |
|---|---|---|---|---|---|---|
| | N | Normal value n (%) | Low risk for sepsis n (%) | Moderate risk for sepsis n (%) | High risk for sepsis n (%) | |
| 0-1 | 1 | 0 | 1 (11.11) | 0 | 0 | |
| 2-3 | 8 | 2 (25) | 2 (22.22) | 1 (8.33) | 3 (8.82 ) | |
| 4-5 | 13 | 2 (25) | 1 (11.11) | 7 (58.33) | 3 (8.82) | |
| 6-7 | 9 | 2 (25) | 1 (11.11) | 2 (16.67) | 4 (11.76) | *p=0. 038 |
| 8-9 | 12 | 2 (25) | 2 (22.22) | 1 (8.33) | 7 (20.59) | |
| 10-11 | 11 | 0 | 1 (11.11) | 1 (8.33) | 9 (26.47) | |
| 12-14 | 9 | 0 | 1 (11.11) | 0 | 8 (23.53) | |

P (Fisher's exact test) *sig $p<0.05$

A statistically significant positive correlation was found between PSP and SOFA score on admission (R=0.4343, p=0.0004). PSP values increased with increasing SOFA score, and vice versa (Table 8).

**Table 8:**

*Correlation between PSP and SOFA score reception in the ICU*

| PSP with SOFA score on reception in the ICU | Spearman R | t(N-2) | p-level |
|---|---|---|---|
| | 0.4343 | 3. 7659 | 0.0004 |

Our study included 66.7% male patients and 33.7% female patients with a mean age of 62.5±15.5 years.

A statistically significant difference was confirmed in the distribution of patients with normal PSP values, with low, moderate and high risk for sepsis according to PSP values in terms of not meeting sepsis criteria (p=0.0000), meeting SIRS criteria (p=0.029), meeting sepsis criteria (p=0.022) and meeting septic shock criteria (p=0.000), while the difference in terms of severe sepsis criteria was not statistically significant (p=0.88).

PSP is a new biomarker that can be used for screening and diagnosis of infection and sepsis, but also as a prognostic marker for determining the severity and mortality of patients with infection and sepsis.

PSP significantly positively correlated with D-dimers, CRP, and PCT (R=0.4462, p=0.0008; R=0.4971, p=0.00003; and R=0.5825, p=0.000001, respectively), and insignificantly with WBC (p=0.99). (Table 5, Figure 1). PSP values increased with increasing D-dimers, CRP, and PCT values, and vice versa.

## Discussion

Pancreatic stone protein/regenerating protein (PSP/Reg) was first discovered in the 1970s and named lithostathine because it was believed to help prevent the formation of calcium pancreatic stones. It was found to have a role in regeneration and cell proliferation and is a part of the so-called regenerating (Reg) gene family. A breakthrough study by Graf et al. (2002) revealed that even physiologic stress and mild stress, such as anesthesia, can produce a measurable elevation of the level of PSP. After these initial findings, Keel et al. (2009) did a study to determine if PSP/Reg levels were dependent on pancreatic involvement. Therefore, they compared the levels of PSP/Reg and several other biomarkers and complement proteins in patients with polytrauma without pancreatic damage and in healthy subjects. PSP/Reg levels are increased after trauma, and this level is correlated to the degree of damage. They also showed that PSP/Reg engages neutrophils and can be used as a biomarker for complications in the period after trauma, indicated by a significant increase of PSP in patients who developed infection (111.4 g/ml) and sepsis (146.4 ng/ml). CRP, IL-6, and PCT levels were also increased, but didn't discriminate between septic and non-septic patients (Keel, 2009).

Several studies have also investigated the potential role of PSP/Reg as a prognostic biomarker, enabling clinicians to better identify high-risk patients who would benefit from more aggressive treatment (Lopes et al., 2022). A study from 2012 evaluated 107 patients admitted to a mixed surgical and non-surgical ICU. 33 were diagnosed with severe sepsis and 74 with septic shock. The authors measured levels of PSP, PCT, CRP, and IL-6 24 hours from admission. They also computed APACHE II (Acute Physiology and Chronic Health Evaluation II), SAPS (Simplified Acute Physiology Score) II and III, and SOFA scores for admitted patients in the first 24 hours after admission. Acute phase protein levels and APCHE II and SAPS II, and SAPS III scores were significantly higher in patients with septic shock compared to patients with severe sepsis. For PSP/Reg, this was a five-fold difference between these two groups of patients. But regardless of disease severity, only levels of PSP/Reg and SPAS II score showed a statistically significant difference between patients

who survived and those who didn't. Our monocentric retrospective study included 63 adult patients admitted to the Surgical Intensive Care Unit and showed similar results. 34 of these patients or 53.97%, had a PSP value of 300 ng/ml and higher, and belonged to the group with high risk for sepsis, followed by 12 patients (19.0%) with a PSP value of 200 to 300 ng/ml and a moderate risk for sepsis, and 9 patients (14.29%) with a PSP value between 100 and 200 ng/ml and a low risk for sepsis. When compared to the clinical criteria for sepsis, our study revealed a statistically significant difference in the distribution of patients with different levels of PSP and clinical signs of SIRS, sepsis, and septic shock.

The use of PSP as a biomarker for sepsis was assessed in different settings and different patient populations alone or in combination, and was compared to other commonly used and new biomarkers.

Klein et al. (2015) did a study to test the ability of PSP/Reg to predict the occurrence of infection in 120 cardiac surgery patients. For this purpose, they measured the levels of PSP, CRP, and Leucocytes on the first 3 days after surgery and found increased levels of PSP/Reg with infection and sepsis, even 48 hours before other biomarkers (Klein et al, 2015).

Klien et al. (2021) also tested the PSP/Reg as a screening tool for infection and sepsis in 90 patients with burns covering more than 15% of their total body surface area (TBSA). In this study, PSP/Reg, CRP, PCT, and Leucocyte levels were measured daily, 3 days after admission, to test the ability to discriminate between patients with inflammation, infection, and sepsis. Levels of PSP/Reg demonstrated a steep increase in those with sepsis, especially septic shock, even 72 hours before other biomarkers (Klein et al., 2021).

A prospective multicenter study in 14 centers across Europe, including 243 ICU patients, confirmed these results (Pugin et al., 2021). Authors compared the clinically established diagnosis of sepsis with the trend of PSP, PCT, and CRP. The results revealed that levels of PSP in patients admitted to the ICU can sometimes increase up to 5 days before the clinical diagnosis of sepsis is made. This was 3 days before PCT and 2 days before CRP. Clinical signs of sepsis correlated with the highest level of PSP, which was above 450 ng/ml on the day of sepsis, compared to the non-sepsis group, where levels of PSP were under 200 ng/ml (Pugin et al, 2021). In our study, we only measured the values of PSP, white blood cells, CRP, and D-dimers at admission. We did not follow up with separate measurements on subsequent days.

In a 2022 study from China by Xiang et al Z and colleagues, 105 emergency department patients were assessed without prior selection. Levels of PSP of 126.4 ng/ml were more effective in detecting infections compared to PCT and CRP. When PSP was combined with CRP and PCT, diagnostic accuracy improved significantly, achieving a perfect AUROC of 1.0 in distinguishing infected from non-infected patients (Xiang et al., 2022).

In a separate investigation by De Hond et al. (2022), conducted in the emergency department of a tertiary hospital, researchers explored the potential of PSP as a diagnostic marker for infection and sepsis. Of the 156 patients included, 47.4% were diagnosed with infection and 16.7% with sepsis. The results supported the clinical utility of PSP/Reg in helping differentiate sepsis from both uncomplicated infections ($p = 0.032$) and non-infectious presentations ($p = 0.022$). In this setting, PSP showed greater diagnostic performance than CRP and white blood cell counts. Additionally, patients with sepsis exhibited significantly elevated PSP levels compared to those with milder infections or no infection in both cohorts (De Hond et al., 2022).

A recent systematic review and meta-analysis conducted by Mai et al. (2024) evaluated the diagnostic performance of Pancreatic Stone Protein (PSP) across 14 studies. The pooled analysis demonstrated a sensitivity of 0.88, a specificity of 0.78, and an AUC of 0.90 (Mai et al., 2024). When compared to other established biomarkers, the pooled sensitivity of PSP in this meta-analysis was notably higher than that reported by Chen et al. (2023) for the neutrophil-to-lymphocyte ratio (NLR), which showed a sensitivity of 0.79, though the specificity was lower than NLR's 0.91. (Chen, 2023) A similar trend was observed in the comparison between PSP and calprotectin, where PSP demonstrated higher sensitivity (0.88 vs. 0.77), while calprotectin exhibited greater specificity (0.85 vs. 0.78) (Gao et al., 2022). In contrast, Poggi et al.'s (2022) meta-analysis of presepsin reported superior diagnostic performance, with pooled sensitivity and specificity values of 0.93 and 0.91, respectively (Poggi et al., 2022).

Different cut-off values have been used to distinguish infection, sepsis, and septic shock in various studies. Prazak et al. (2021), in a meta-analysis, including 5 studies and 631 patients, confirmed infection in 371 631 patients using a PSP cut-off of 44.18 ng/ml. The overall sensitivity and specificity were 0.66 and 0.83, respectively. The cut-off value for risk of sepsis in our study was 100ng/ml, and the risk level increased with higher levels of PSP values. Combining PSP with CRP increased both the sensitivity and specificity for differentiating patients with and without infection (Prazak et al., 2021).

Higher levels of PSP/reg (above 33.9 ng/mL), together with purulent sputum, yielded a specificity of 97% for detecting pathogenic organisms in sputum samples. On the other hand, lower levels and non-purulent sputum had a sensitivity of 92% in excluding bacterial infections (Scherr et al., 2013).

Apart from its use as a diagnostic tool in early detection of infection and sepsis in different patient populations and different settings, studies show a correlation between levels of Pancreatic Stone Protein (PSP) and higher SOFA scores, which suggests a direct link between levels of PSP and the extent of organ dysfunction (Que et al., 2012; Zuercher et al., 2023). We also computed the SOFA score for each patient on admission and compared it to the PSP level. A statistically significant positive correlation was found between PSP and SOFA score on admission (R=0.4343, p=0.0004). PSP values increased with increasing SOFA score, and vice versa, similar to the aforementioned study by Paguin et al (2022) (Table 8).

Zuercher et al. (2023) in their systematic review and individual patient level meta-analysis set to evaluate the performance of PSP in predicting intensive care unit (ICU) mortality and infection severity among critically ill adults admitted to the hospital for infection. Among the 678 patients included, the pooled ICU mortality was 17.8%. PSP was strongly associated with ICU mortality (OR = 2.7, 95% credible interval (CrI) [1.3–6.0] per one standard deviation increase; age, gender, and sepsis severity adjusted OR = 1.5, 95% CrI [0.98–2.8]). The AUC was 0.69 for PSP, 95% confidence interval (CI) [0.64–0.74]. PSP showed a very good discriminative ability for both investigated study endpoints, ICU mortality and infection severity; better in comparison to CRP, similar to PCT. Combinations of biomarkers did not improve their predictive ability (Zuercher et al., 2023). In a different study of only levels of PSP/Reg and SPAS II score and not disease severity, a statistically significant difference was found between patients who survived and those who didn't. In patients with septic shock, PSP/reg was the only biomarker associated with in-hospital mortality (P = 0.049). Risk of mortality increased continuously for each ascending quartile of PSP/reg (Pugin et al., 2021).

The differences in the distribution of deceased and living patients with respect to PSP in our study were insufficient to be confirmed as statistically significant (p=0.18).

## Conclusion

Pancreatic Stone Protein (PSP) has emerged as a promising biomarker in the intensive care unit (ICU). It shows promising results for early detection of sepsis, monitoring of systemic inflammation, and prognosis of critically ill patients. Its quick response to infectious and inflammatory stimuli makes it a valuable tool for timely clinical decision-making, especially when traditional markers may lag. Incorporating PSP into routine ICU protocols could enhance diagnostic accuracy, promote early intervention, and ultimately improve patient outcomes. Larger multicenter studies are needed to standardize PSP thresholds and fully establish its role alongside other biomarkers in critical care practice.

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