# Presepsin values as markers of severity of sepsis

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ABSTRACT

Objectives: Biomarkers are widely used for rapid diagnosis of sepsis. This study evaluated the diagnostic accuracy of presepsin, procalcitonin (PCT), and C-reactive protein (CRP) in differentiating sepsis severity as well as their association with Sepsis-related Organ Failure Assessment (SOFA) score.
Methods: One hundred septic patients from two university clinical centers were enrolled in the study during two time periods. New Sepsis-3 definitions were used for sepsis stratification. Biomarkers and SOFA score were evaluated four times during the illness. A sandwich ELISA kit was used for presepsin measurement. Generalized linear mixed effects model was used to test the changes in biomarkers concentrations and SOFA score values during the illness and to estimate the differences between severity groups. Multivariate analysis was used to test the association of biomarkers with SOFA score.
Results: Presepsin concentrations were significantly higher on admission in patients with septic shock (n = 34) compared to patients with sepsis (n = 66), mean ± SD: 128.5 ± 47.6 ng/mL vs. 88.6 ± 65.6 ng/mL, respectively (p < 0.001). The same was not observed for PCT and CRP; their concentrations did not differ significantly between severity groups. A strong correlation of presepsin with SOFA score was also found (p < 0.0001).
Conclusions: Presepsin had a good diagnostic ability to differentiate septic shock from sepsis in the study groups. PCT and CRP failed in differentiating sepsis severity.

## Background

Sepsis is a life-threatening condition, with poor and highly variable clinical manifestations, difficult to identify and diagnose. Over centuries sepsis has remained a real diagnostic challenge to clinicians, causing millions of death worldwide each year (Angus et al., 2001; Martin et al., 2003). Early recognition of sepsis is crucial for better disease outcome (Dellinger et al., 2013).

Blood cultures are a gold standard for diagnosing sepsis. Despite the great advantages, blood cultures also have some limitations- they are often negative, especially in patients previously treated with antibiotics (Zadroga et al., 2013), and their results are usually obtained over several days. While waiting for blood culture results, treatment of critically ill septic patients may be delayed, increasing the possibility of poor outcome (Ferrer et al., 2009). In the light of this, researchers are trying to find an easy measurable and specific

sepsis biomarker that will aid in identifying septic patients. Among these biomarkers, some of them are already in use as additional tools incorporated in the list of signs and symptoms introduced in 2001 by The International Sepsis Definitions Conference (Levy et al., 2003), such as procalcitonin (PCT) and C-reactive protein (CRP). Soluble CD14 subtype (sCD14-ST), also known as presepsin, was first introduced in 2005 as a molecule specifically increased in patients with sepsis compared to healthy controls and patients presenting with non-infectious systemic inflammatory response syndrome (SIRS) (Yaegashi et al., 2005). It was reported that presepsin specifically increases in patients with bacterial sepsis due to its mechanism of secretion related to bacterial phagocytosis (Arai et al., 2015). PCT and CRP are recognized as acute phase proteins (Nijsten et al., 2000; Pepys, 1982). Their elevated levels are seen in sepsis but also in a large number of different inflammatory conditions. Among new sepsis biomarkers, presepsin aroused interest among researchers. Presepsin is a novel sepsis biomarker. Its diagnostic capacity is still in an investigation phase.

In 2016, The Third International Sepsis Definition Consensus Conference, also known as Sepsis-3, updated and presented new definitions of sepsis and septic shock (Singer et al., 2016). A new

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bedside modified SOFA score was presented, named qSOFA, and recommended for use in identification of septic patients outside the ICUs, and widely recognized SOFA score (Vincent et al., 1996) was recommended for identifying sepsis among ICU critically ill patients. There have been a few studies in which biomarkers measurements were done in septic patients classified according to Sepsis-3 definitions. In a large number of studies, biomarkers were measured and compared between septic patients and healthy controls or non-infectious SIRS patients. The aim of this study was to evaluate the ability of presepsin and other biomarkers to diagnose sepsis and differentiate sepsis severity in our patients classified retro- and prospectively according to Sepsis-3 new definitions, as well as to evaluate the association of sepsis biomarkers with SOFA score, a score designed and strongly recommended to be used in critically ill patients for sepsis recognition.

## Materials and methods

### Patients' inclusion and exclusion criteria

A prospective observational study was conducted in two university clinical centers: University Clinical Center of Kosovo, Clinic of Infectious Diseases in Pristina, Kosovo, and University Clinical Center of Zagreb, University Hospital for Infectious Diseases in Zagreb, Croatia. More than half of patients were treated in the Intensive Care Units of both hospitals, and the other part of enrolled patients were treated in the Department of Neuroinfections and Blood-stream Infections at the Clinic of Infectious Diseases, in Pristina. Patients enrollment in the study was done in two separated time periods in the participatig centers in the study. Between end of February 2015 and end of May 2016, in the study were enrolled the first half of patients admitted at the Clinic of Infectious Diseases in Pristina, Kosovo. Between end of February 2018 and end of December 2018, in the study were enrolled the second half of patients admitted at the University Hospital of Infectious Diseases in Zagreb, Croatia.

The study was compliant with the 2008 Helsinki Declaration. After obtaining informed consent from patients or their supervisor, one hundred patients (48 male, 52 female) were included in the study. Before the start of the study, the ethical approval was obtained from the Ethics Committee of both University Clinical Centers, in Prishtina and in Zagreb.

Patients' inclusion criteria were: age $\geq 18$ years old; infection suspected or documented; and at least two of the following criteria determined by the Sepsis-3 Consensus Conference 2016 as clinical criteria for sepsis suspicion: altered mentation, systolic blood pressure <100 mmHg, and respiratory rate $\geq 22$ breaths/ min. All consecutive sepsis suspected patients on admission, aged $\geq 18$ years, of both genders, previously healthy subjects, and patients with history of chronic organ dysfunction (chronic kidney failure, chronic obstructive pulmonary disease, diabetes, heart failure NYHA IV), recent surgery or recent invasive procedure, patients on immunosuppressive therapy after organ transplantation, or with documented malignancy, were enrolled in the study. Patients' exclusion criteria were: age <18 years, incapability for obtaining informed consent, and evidence of a different diagnosis. After being included in the study, patients were excluded if a different diagnosis was documented: metastatic meningitis, pulmonary tromboembolism, hemorrhagic fever, leptospirosis, etc.

### Disease stratification

Patients were stratified into sepsis group and septic shock group according to Sepsis-3 Consensus Conference Definitions. All consecutive sepsis suspected patients with qSOFA$\geq 2$ on admission, were included in the study. Patients with persistent hypotension that could not be corrected with fluid resuscitation requesting the use of vasoactive agents, were classified as septic shock patients (34/100). The first half of patients included in the study were retrospectively classified as sepsis or septic shock patients according to Sepsis-3 definitions criteria, or excluded when the criteria were not met. The other half of patients were prospectively stratified according to new Sepsis-3 definitions criteria.

Patients were followed until discharge or until ICU or hospital death. Thirty-two patients died over the course of the disease.

### Data collection

Demographics and clinical features, as well as laboratory parameters of enrolled patients were collected.

The following hemodynamic parameters were collected daily: mental status, heart rate, respiratory rate, ventilation status, mean arterial pressure, fever, urine output. To evaluate the mental status, Glasgow Coma Scale (GCS) was calculated. At four time points, on admission (T0), after 24 hours (T1), after 72 hours (T2) and on Day 7 (T3), the following laboratory parameters were recorded: red blood cell count, hemoglobin, hematocrit, white blood cell count, platelet count, serum creatinine, serum total bilirubin, serum liver enzymes (aspartate aminotransferase-AST and alanine aminotransferase-ALT), partial tromboplastin time (PTT), international normalized ratio (INR), electrolytes (sodium and potassium), blood gas analysis, CRP, PCT, and presepsin concentrations.

For evaluating organ dysfunction, Sepsis-related (Sequential) Organ Failure Assessment (SOFA) score (Vincent et al., 1996) was calculated at all four time points: T0, T1, T2, and T3.

Routine laboratory parameters and CRP were tested immediately. For PCT and presepsin levels measurements, blood was collected at all four time points, frozen until the end of the study, and then measured.

### Sample collection for sepsis biomarker measurements

A 5 ml blood sample was taken from cubital vein after initial skin desinfection with 70% alcohol. Blood samples were collected using sodium citrate or ethylenediamine tetraacetic acid (EDTA) as anticoagulants. Blood was centrifuged for 15 minutes at 1000 x g within 30 minutes of collection, then serum samples were stored at $-40\,^{\circ}$C for later PCT and presepsin concentration testing.

PCT levels were measured in each center: Institute of Biochemistry, Pristina, University Clinical Center of Kosovo, and University Hospital for Infectious Diseases in Zagreb, Croatia. In both centers, quantitative analysis of PCT was performed using an automated electrochemiluminescence immunoanalyzer (ELECSYS* BRAHMS* PCT; Roche Diagnostics, Mannheim, Germany). Presepsin measurements were done in PROLAB "biochemical laboratory in Pristina, by professionally trained staff. ELISA kits for presepsin measurement were imported from the manufacturer Nordic Biosite based in Sweeden, after obtaining permission for import from Agency for Medicinal Products of Kosovo. Kits were used for reserach purposes only. A sandwich enzyme-linked immune-sorbent assay– Human Presepsin ELISA Kit from Nordic Biosite, was used for presepsin measurement.

### Statistical analysis

Categorical variables were reported as frequency and percentage. Continuous variables were reported as medians, 25th and 75th percentiles and means $\pm$ one standard deviation ($\pm$SD). Simple comparisons were done for categorical variables using the chi-square test or Fisher's exact test as appropriate, and the Wilcoxon

rank-sum test for continuous variables. Generalized linear mixed effects model was used to test the changes in presepsin concentrations during the illness and to estimate the difference between two severity groups (sepsis and septic shock), after adjustments for baseline presepsin values. Receiver Operating Characteristic (ROC) curves and areas under the ROC curve (AUC) were calculated to test the importance of initial presepsin concentrations for sepsis severity. Based on optimal cutoff values of presepsin for discriminating between severity groups, according to ROC curve analysis, the sensitivity and specificity of the found threshold values were calculated. Generalized mixed effects model was used to test the changes in SOFA scores during the illness and to estimate the difference between two severity groups after an adjustment for baseline values. Adjustments were done because baseline score values have a strong impact on subsequent values. Multivariate analysis was performed to assess the association of presepsin, procalcitonin and C-reactive protein values and SOFA score, after an adjustment for day of hospitalization. For all statistical tests, significance was set at an alpha level of 0.05. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina, USA).

## Results

### Association of presepsin concentrations with severity of sepsis

Presepsin concentrations significantly decreased over the course of the study ($p < 0.0001$) (Table 1 and Figure 1).

The results showed that the higher the presepsin concentrations on admission in septic patients, and the slower its decrease, the more severe clinical presentation and: the greater the possibility of having septic shock. Severity of disease was strongly associated with presepsin concentrations and day of measurement. Figure 1 shows that presepsin concentrations significantly decreased over the course of the study ($p < 0.0001$) and that severity groups differed. The differences were greater after 24 and 72 hours. Adjustments were done because baseline presepsin values have a strong impact on subsequent values.

To test the importance of initial presepsin values for severity of sepsis, the Receiver Operating Characteristic (ROC) curve was constructed (Figure 2). Presepsin values above 110 ng/ml were significantly associated with septic shock, Fisher's exact test $p = 0.003$. At the set cutoff value of 110 ng/mL, sensitivity and specificity were 0.727 and 0.617, respectively. In Figure 2, we can notice a sharp increase in specificity with values above 110 ng/mL. The calculated area under the ROC curve (AUC) was 0.703.

The distribution of presepsin concentrations on admission in two severity groups is shown in Figure 3. Vertical line shows threshold value of 110 ng/mL. We can notice that more patients in the septic shock group had values of presepsin above 110 ng/mL, in comparison to septic patients without shock, where most patients had values of presepsin under the set cutoff value of 110 ng/mL.

### Association of CRP and PCT levels with sepsis severity

Table 2 shows values of CRP and PCT on admission, in patients with sepsis and septic shock.

There were no significant differences in CRP levels on admission between patients with sepsis and septic shock, mean ± SD, 201.6 ± 97.0 mg/L vs. 219.8 ± 146.3 mg/L, respectively ($p = 0.824$). Baseline PCT levels did not differ between patients with sepsis and those with septic shock; mean ± SD, 20.0 ± 28.5 ng/mL vs. 32.9 ± 39.2 ng/mL ($p = 0.099$), respectively.

### Association of sepsis biomarkers with SOFA score

Multivariate analysis of association of sepsis biomarkers and SOFA score, after an adjustment for day of treatment, showed that presepsin was strongly associated with SOFA score ($p < 0.0001$), PCT less but still significantly ($p = 0.004$), whereas CRP was not associated with SOFA score ($p = 0.1827$) and subsequently severity of the disease (Table 3).

Presepsin was a better predictor of multiple organ dysfunction syndrome compared to other tested sepsis biomarkers.

## Discussion

When evaluating differences in presepsin concentrations between two severity groups, we found significantly higher presepsin concentrations in septic shock patients compared to septic patients, especially in the first 72 hours. This study revealed that presepsin concentrations had a good capacity for distinguishing disease severity. Interestingly, we did not find association of CRP and PCT levels with severity of sepsis. PCT and CRP levels did not differ significantly between two severity groups.

Comparison of these results for association of sepsis biomarkers with severity of disease to those found in other studies was difficult because most studies in which sepsis biomarkers capability for discriminating sepsis severity was evaluated, either used old sepsis definitions or analyzed, in addition to sepsis group patients, patients with SIRS or healthy controls. However, most studies related to diagnostic accuracy of presepsin reported that presepsin has a good discriminating capacity between sepsis severity groups.

**Table 1**
Presepsin concentrations (ng/mL) in two severity groups.

| | Sepsis | Septic shock | Overall | | Sepsis | Septic shock | Overall |
| | *Presepsin on admission (ng/mL)* | | | | *Presepsin after 72 hours (ng/mL)* | | |
|---|---|---|---|---|---|---|---|
| N | 66 | 34 | 100 | **N** | 60 | 24 | 84 |
| Mean | 88.6 | 128.5 | 102.2 | **Mean** | 54.3 | 87.7 | 63.9 |
| SD | 65.6 | 47.6 | 62.8 | **SD** | 55.4 | 54.4 | 56.8 |
| Median | 92.3 | 127.2 | 106.9 | **Median** | 29.4 | 85.3 | 47.3 |
| 25th percentile | 28.2 | 106 | 43.6 | **25th percentile** | 7.3 | 39.7 | 9.7 |
| 75th percentile | 125.4 | 154.3 | 140.8 | **75th percentile** | 111.1 | 128.3 | 118.4 |
| | ***Presepsin after 24 hours (ng/mL)*** | | | | ***Presepsin on Day 7 (ng/mL)*** | | |
| N | 62 | 30 | 92 | **N** | 57 | 18 | 75 |
| Mean | 77.5 | 126.5 | 93.5 | **Mean** | 26 | 28.2 | 26.5 |
| SD | 61.5 | 52.1 | 62.7 | **SD** | 33.7 | 32.2 | 33.1 |
| Median | 66.3 | 122.1 | 105.4 | **Median** | 9.7 | 15.7 | 13.2 |
| 25th percentile | 19.7 | 111.1 | 33.9 | **25th percentile** | 2.5 | 8.4 | 3.9 |
| 75th percentile | 126.2 | 152.9 | 132 | **75th percentile** | 43.4 | 33.4 | 43.4 |

Abbreviations: SD-standard deviation.
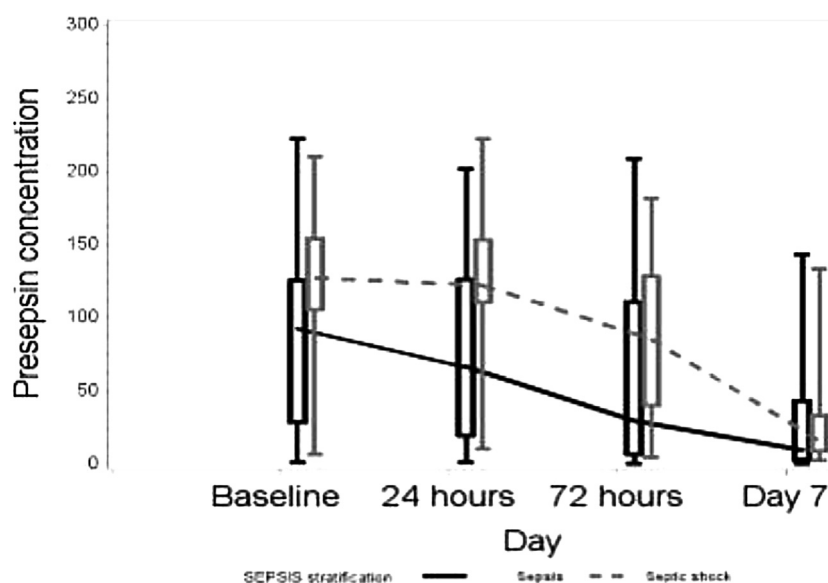
**Figure 1.** Presepsin concentrations (ng/mL) in two severity groups.
Black line: sepsis patients; black dotted line: septic shock patients. The vertical left side of the figure shows presepsin concentrations expressed in ng/mL. The lower horizontal line shows presepsin concentrations at four time points: on admission, after 24 hours, after 72 hours, and on Day 7.
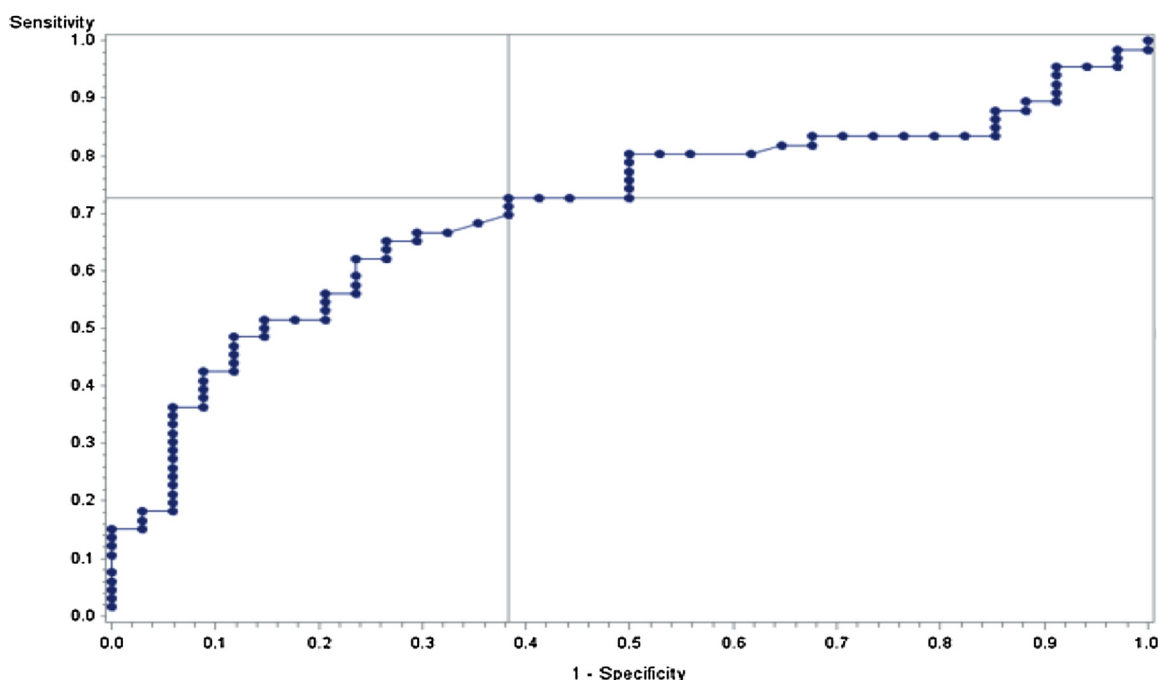


**Figure 2.** Receiver Operating Characteristic curve (ROC curve) for presepsin values and severity of sepsis.

Similarly to our results, a great number of studies report significantly higher levels of presepsin in septic shock patients compared to septic patients without shock (Liu et al., 2013; Behnes et al., 2014; Masson et al., 2015; Klouche et al., 2016).

We found a few studies published over the past two years, with sepsis stratification of enrolled patients according to new Sepsis-3 definitions. In one study (Ali et al., 2016), patients were classified as SIRS group with or without sepsis, they were not classified as sepsis and septic shock groups, so our data are not comparable. In another study (de Guadiana Romualdo et al., 2017), patients were classified as sepsis and non-sepsis patients with documented infection. Similarly to our results, they found a good capacity of presepsin to differentiate septic shock from sepsis on admission. In

a most recent article published in 2019, a prospective observational study on 91 patients, which retrospectively classified patients according to new Sepsis-3 definitions criteria into non-sepsis, sepsis and septic shock, presepsin was found to have the highest diagnostic accuracy for discriminating non-sepsis from sepsis and septic shock group as well as between sepsis groups compared to PCT and CRP (Yamamoto et al., 2019).

At the set cutoff value of presepsin for predicting septic shock, we found sensitivity of 72.7% and specificity of 61.8%. The AUC for predicting septic shock was 0.703. We could not compare the observed cutoff value with those found in other studies because no other study used the same technique for measuring presepsin concentrations and had stratified patients according to Sepsis-3
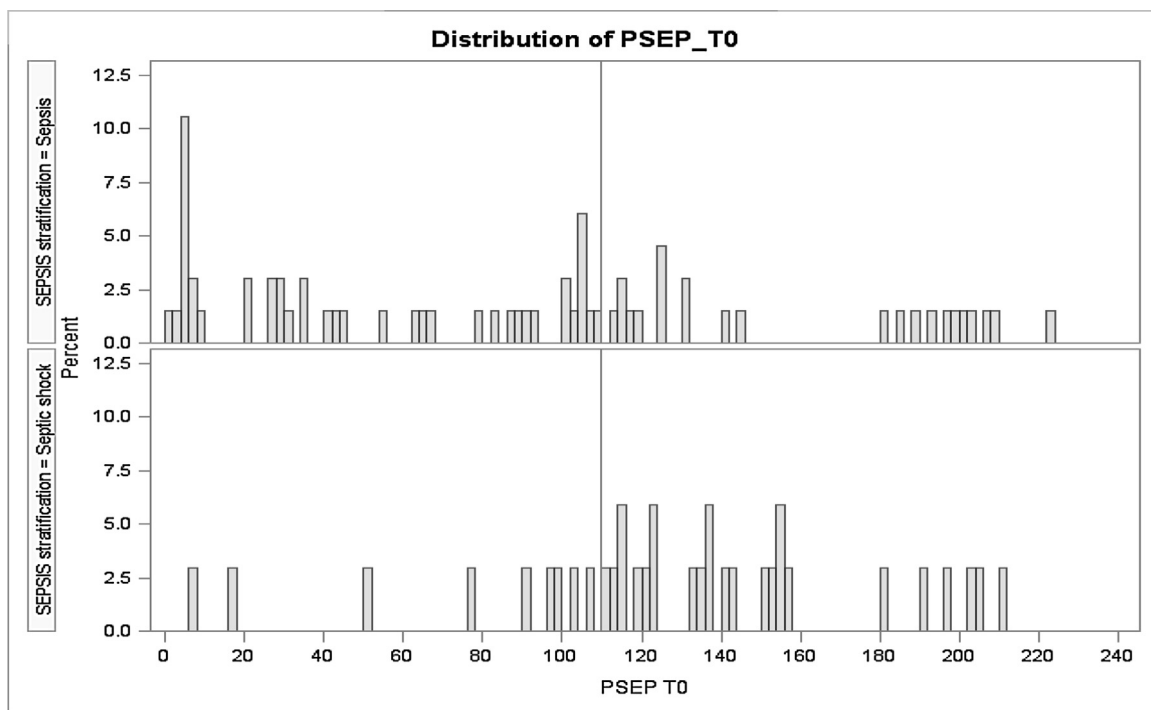
**Figure 3.** Distribution of presepsin concentrations on admission in two severity groups.
Abbreviations: PSEP-presepsin; T0-on admission; vertical line in the middle of the figure-threshold value of 110 ng/mL. The upper left half of the figure shows percentage of patients with sepsis at the corresponding presepsin value. The lower left half of the figure shows percentage of patients with septic shock at the corresponding presepsin value. The horizontal line shows presepsin values on admission, expressed in ng/mL.

**Table 2**
Concentrations of CRP and PCT on admission in two severity groups.

| | Sepsis | Septic shock | Overall | | Sepsis | Septic shock | Overall |
|---|---|---|---|---|---|---|---|
| | **CRP on admission (mg/L)** | | | | **PCT on admission (ng/mL)** | | |
| **N** | 66 | 34 | 100 | **N** | 66 | 34 | 100 |
| **Mean** | 201.6 | 219.8 | 207.8 | **Mean** | 20 | 32.9 | 24.4 |
| **SD** | 97 | 146.3 | 115.7 | **SD** | 28.5 | 39.2 | 32.9 |
| **Median** | 196.9 | 198.5 | 197 | **Median** | 6 | 14.2 | 8.5 |
| **25th percentile** | 125.6 | 138.5 | 128 | **25th percentile** | 2.3 | 4.3 | 2.9 |
| **75th percentile** | 252.2 | 264.5 | 259.5 | **75th percentile** | 21.9 | 48.8 | 29 |

Abbreviations: SD-standard deviation; CRP-C-reactive protein; PCT-procalcitonin.

new definitions. Some studies have found higher sensitivity and specificity of their cutoff values set for predicting septic shock (Liu et al., 2013; Behnes et al., 2014), or higher sensitivity but lower specificity (Klouche et al., 2016), or lower sensitivity and higher specificity (Ali et al., 2016; de Guadiana Romualdo et al., 2017).

Interestingly, in our study, CRP and PCT did not show any significant correlation with disease severity.

When comparing the diagnostic accuracy of presepsin with the one of PCT and CRP, in recent studies (de Guadiana Romualdo et al., 2017; Yamamoto et al., 2019), CRP was not found to have any discriminating value in relation to sepsis severity groups, which is in line with our results. However, different to our results, some studies (Shozushima et al., 2011; Behnes et al., 2015; de Guadiana Romualdo et al., 2017; Yamamoto et al., 2019) found PCT to perform a good diagnostic value, even though when compared to presepsin, the latter showed a better diagnostic accuracy.

Despite the fact that PCT and CRP are helpful markers in the diagnosis of sepsis, they are often increased in a large number of non-sepsis inflammatory conditions, such as myocardial infarction (Kafkas et al., 2008), surgery (Maisner et al., 1998), trauma (Maier et al., 2009), pancreatitis (Rau et al., 2007), etc. Recently, presepsin values have been investigated in other non-sepsis conditions, such

**Table 3**
Association of biomarkers with SOFA score after adjustment for day of treatment.

| Effect | DAY | ODDS ratio | Standard Error | Pr > \|t\| |
|---|---|---|---|---|
| **Intercept** | | 1.2905 | 0.0867 | <.0001 |
| **Presepsin** | | 0.0027 | 0.0006 | <.0001 |
| **Procalcitonin** | | 0.0024 | 0.0008 | 0.004 |
| **CRP** | | 0.0004 | 0.0003 | 0.1827 |
| **Day** | 1 | 0.0922 | 0.0891 | 0.3013 |
| **Day** | 2 | 0.0845 | 0.0861 | 0.3271 |
| **Day** | 3 | 0.1076 | 0.0778 | 0.1677 |
| **Day** | 4 | 0 | | |

as rheumatoid arthritis (Tsujimoto et al., 2018), trauma (Koch et al., 2018), kidney injury (Nakamura et al., 2014), etc. All those studies have shown increased presepsin concentrations in patients with a disease other than sepsis, only when an infection was present.

SOFA score is strongly associated with disease severity, as previously reported by others (Degoricija et al., 2006; Liu et al., 2013; Behnes et al., 2014; Klouche et al., 2016; Godnic et al., 2015). It is expected that higher SOFA scores would be found in patients with septic shock, knowing that SOFA score calculates not only the number of organs failing but also the severity of organ dysfunction.

Our study revealed a strong correlation of presepsin with SOFA score, thus letting us believe that presepsin may be a specific sepsis biomarker. Different to our findings, a recent article reported that initial presepsin concentrations do not correlate with SOFA score (Brodska et al., 2018).

The present study has some advantages. First, since our patients were diagnosed by infectious diseases specialists, the possibility of misdiagnosing sepsis was obviously smaller compared to other studies done in emergency departments or medical ICUs by other field specialists. Second, no patients with other inflammatory conditions were enrolled in the study.

A great finding of our study is the accuracy of presepsin for diagnosing sepsis and its capability for differentiating between sepsis severity groups, as well as its strong correlation with SOFA score, a score designed to be specifically used for identifying septic patients. The correlation of presepsin with SOFA score supports the view that presepsin is a valuable marker for diagnosing and differentiating sepsis severity.

On the other hand, the present study revealed a poor diagnostic ability of PCT for differentiating sepsis severity, which has not been reported previously.

However, this study has some limitations. Patients' enrollment was done in two study periods. Even though we tried to comply with new Sepsis-3 definitions, the first part of enrolled patients were classified retrospectively and lactate levels were not measured as they were not at the time the criteria for recognizing septic shock. Finally, microbiological documentation of sepsis was low. We assume that the low percentage of microbiological documentation of sepsis was partially due to antibiotic treatment of included patients, prior to admission to our hospitals.

## Conclusions

This study shows that serum presepsin concentration on admission reflects the severity of disease. Presepsin was a better predictor of multiple organ dysfunction syndrome compared to other tested sepsis biomarkers. The strong correlation of presepsin with SOFA score makes this marker a valuable tool for identifying septic patients. PCT and CRP concentrations did not differ between sepsis severity groups.

## Funding source

## Authors' contribution

This article was conceived, designed and written by A.A-B; data were analyzed and interpreted by BB; data collection was done by AA-B and AA; presepsin measurements were done by MK and AA-B; revision of the article was done by BB and ShD.

## Ethical approval

Ethical approval was obtained from the Ethics Committee of both University Clinical Centers, in Prishtina and in Zagreb.

## Conflict of interest

Authors declare no conflict of interest.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

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