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Prognostic value of presepsin (soluble CD14-subtype) in diagnosis of ventilator-associated pneumonia and sepsis in trauma patients

Prognostička vrednost presepsina (solubilnog CD 14-podtipa) u dijagnozi pneumonija povezanih sa mehaničkom ventilacijom i sepse kod traumatizovanih bolesnika

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Abstract

Background/Aim. Presepsin (soluble CD14-subtype) is a fragment of CD14 produced in response to bacterial infections and a novel biomarker of pneumonia, sepsis and septic shock. The aim of this study was to compare sensitivity and specificity of persepsin, soluble CD14-subtype (sCD14-ST) with other biomarkers: procalcitonine (PCT), C-reactive protein (CRP) and leukocyte count (Le) in mechanically ventilated injured patients, as a marker of pneumonia, sepsis and septic shock. **Methods.** The prospective study was undertaken in trauma and surgery intensive care unit of the Emergency Center, the Clinical Center of Serbia from January to April 2013. The study included 39 trauma patients requiring mechanical ventilation, and who developed one of the following inclusion criteria: Systemic Inflammatory Response Syndrome (SIRS), ventilator associated pneumonia (VAP), sepsis and/or septic shock. On admission Acute Physiology and Chronic Health Evaluation II (APACHE II) Score and Injury Severity Score (ISS) were calculated. Seventy-two measurements of four biomarkers (presepsin, PCT, CRP and Le) were performed in 39 patients at the moments of diagnosis of SIRS, VAP, sepsis and/or septic shock (21 when SIRS diagnosis was established, 21 after the diagnosis of VAP, 18 at the moment of diagnosis of sepsis and the remaining 12 measurements were conducted while diagnosing the septic shock). The Sequential Organ Failure Assessment (SOFA) score was calculated at these points as well. **Results**. Patients were mainly severely injured (mean ISS = 24.2) and had moderately severe medical condition at admission (mean Apache II score, 14.5). Presepsin concentration significantly differed among all the four groups, except between sepsis and septic shock. The strongest positive correlation of presepsin evinced with PCT ($r = 0.741$, $p < 0.001$). The sCD14-ST indicated better performance in diagnosis of both VAP (AUC = 0.909) and sepsis (AUC = 0.899), compared to PCT (AUCs: 0.863, 0.885, respectively), CRP (AUCs: 0.703, 0.677, respectively) and Le (AUCs: 0.668, 0.700, respectively). **Conclusion.** This study revealed that sCD14-ST is a reliable biomarker for distinguishing sepsis severity. It also showed a good correlation with the infection development as well as worsening in injured patients.

Key words:
presepsin protein, human; pneumonia, ventilator associated; sepsis; shock septic; biomarkers; sensitivity and specificity; diagnosis.

Apstrakt

Uvod/Cilj. Persepsin (solubilni CD14-podtip) je fragment CD14 koji se produkuje kao odgovor na prisustvo bakterijske infekcije i predstavlja novi biomarker u dijagnostici pneumonije, sepse i spetičkog šoka. Cilj ove studije bio je da se uporedi senzitivnost i specifičnost presepsina (solubilnog CD14-podtipa) sa ostalim biomarkerima infekcije: prokalcitoninom (PCT), C-reaktivnim proteinom (CRP) i brojem leukocita (Le) kod povređenih bolesnika na mehaničkoj ventilaciji, kao markera pneumonije, sepse i septičkog šoka. **Metode.** Prospektivna studija sprovedena je u dve jedinice intenzivnog lečenja (JIL) (traumatološka i hirurška) Kliničkog centra Srbije u periodu od januara do aprila 2013. godine. U studiju je bilo uključeno 39 traumatizovanih bolesnika na mehaničkoj ventilaciji kod kojih se razvio neki od sledećih ishoda koji su bili i kriterijumi za

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uključivanje: sisemski inflamatorni odgovor (SIRS), pneumonija povezana sa mehaničkom ventilacijom (VAP), sepsa i/ili septički šok. Na prijemu u JIL *Acute Physiology and Chronic Health Evaluation II* (APACHE II) skor i *Injury Severity Score* (ISS) su računati za svakog bolesnika. Sedamdeset i dva merenja koncentracije četiri biomarkera (presepsin, PCT, CRP i Le) urađena su kod 39 bolesnika u trenutku postavljanja dijagnoze SIRS, VAP, sepse i/ili septičkog šoka. *Sequential Organ Failure Assessment* (SOFA) skor takođe je meren istovremeno. **Rezultati.** Većina bolesnika na prijemu bila je teško povređena (srednja vrednost ISS skora = 24.2) i bila je u srednje teškom stanju (srednja vrednost APACHE II skora = 14.5). Koncentracije presepsina značajno su se razlikovale između sve četiri grupe bolesnika, osim između grupa sa sepsom i septičkim šokom. Najsnažniju pozitivnu korelaciju presepsin je imao sa PCT ($r = 0.741$, $p < 0.001$). sCD14-ST pokazao je bolju prediktivnu vrednost u dijagnozi pneumonije (AUC = 0.909) i sepse (AUC = 0.899) u odnosu na PCT (AUCs: 0.863, 0.855), CRP (AUCs: 0.703, 0.677) i Le (AUCs: 0.688, 0.700). **Zaključak.** Ova studija je pokazala da je sCD14-ST pouzdan biomarker u određivanju težine sepse kao i da je u dobroj korelaciji sa nastankom infekcije i pogoršanjem stanja kod povređenih bolesnika.

Ključne reči:
presepsin protein, humani; pneumonija, respiratorom uzrokovana; sepsa; šok, spetički; biološki pokazatelji; senzitivnost i specifičnost; dijagnoza.

Introduction

Ventilator associated pneumonia (VAP) is one of the most common nosocomial infections appearing in the intensive care unit [1]. Up to 10% of patients receiving mechanical ventilation will eventually develop VAP, with an attributable mortality rate estimated between 1% to 1.5% [2]. In critically injured patients, incidence, morbidity and mortality of VAP are even higher [3].

Sepsis is infrequent but significant cause of death in patients with blunt injury. In modern era of intensive care medicine, delays in the initiation of antimicrobial treatment is not rare and while the mortality of patients with sepsis is gradually decreasing, it is still quite high [4]. A cause of this could be found in non-specific symptoms of the infection leading to an inappropriate empirical treatment and increased resistance profile of pathogens. In septic complication, however, it is important to bear in mind not only the fact that the sensitivity of blood cultures for the diagnosis of pneumonia sepsis is less than 25% but also that, when present, the organisms may originate from an extrapulmonary site of infection, in as many as 64% of cases, even if VAP is present [5].

Since clinical criteria have low sensitivity and specificity, there is no "gold standard" for diagnosing either VAP or sepsis [6]. Currently, procalcitonin (PCT) together with C-reactive protein (CRP) and different haematological parameters [white blood cell (WBC) count] are used as markers to diagnose sepsis or severe sepsis [7]. On the other hand, several invasive or semi-invasive methods can be used to diagnose VAP, with certain disadvantages in each of them [8]. Various scores and markers have already been proposed as the promising candidates for evaluating the response of VAP to antibiotic treatment [9]. A number of biomarkers, including soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), interleukin-1-beta, granulocyte colony-stimulating factor, macrophage inflammatory protein-1-alpha and others have been tested recently for patients with suspected or confirmed VAP. However, the obtained results were not promising, but they were even contradictory [10]. Therefore, defining a reliable marker that can enable fast diagnosis of VAP would be of great benefit.

The great efforts have been invested into the assessment of presepsin for sepsis diagnosis [11, 12]. Presepsin or soluble CD14 is a fragment of CD14, the lipopolysaccharide-binding protein complex receptor, produced in a response to bacterial infections. Presepsin is a novel biomarker [soluble amino-terminal fragment of the cluster of differentiation (CD) marker protein CD14] in sepsis that is released into the circulation during monocyte activation [13]. In recent meta-analysis results have demonstrated good overall diagnostic performance of presepsin in sepsis [14].

As far as we know, there are no clinical studies investigating the potential role of presepsin in VAP. Ideal biomarker for VAP will be accurately elevated in serum or broncho-alveolar lavage (BAL) fluid, will respond to adequate therapy and will not be altered in patient without infection complication initially. Also, ideally, biomarker results for VAP diagnosis should be available sooner than obtaining the quantitative culture of BAL fluid, which can take up to 48 hours [15]. Taking into account favorable kinetics of presepsin release as well as its half-life of approximately 4–5 h, this biomarker could be exactly the one we have been searching for.

The aim of this study was to estimate and compare the prognostic value of soluble CD14-subtype (sCD14-ST) with other laboratory (and CRP and Le) and standard biomarkers (PCT) in mechanically-ventilated injured patients as a marker of pneumonia and the severity of infection complications such as sepsis and septic shock.

Methods

Study design

The prospective study was undertaken in trauma and surgery intensive care unit of the Emergency Center, the Clinical Center of Serbia from January to April 2013. Trauma patients requiring mechanical ventilation and who developed one of the following inclusion criteria were included: systemic inflammatory response syndrome (SIRS), VAP, sepsis or septic shock. Exclusion criteria were as follows: the patients younger than 18 years of age, confirmed gastric aspiration, patient receiving antibiotic therapy in the previous 90 days, recent

hospitalization, residence in a nursing home or extended care facility, home therapy and immunodeficiency.

This study was approved by the Ethics Committee of the Faculty of Medicine at the University of Belgrade, Serbia (No. 29/IV-14).

Clinical assessment

Baseline demographic data included age and gender are given in Table 1. On admission, the Acute Physiology and Chronic Health Evaluation II (APACHE II) Score and the Injury Severity Score (ISS) were calculated. The clinical, laboratory and radiographic data were monitored on a daily basis for the development of pneumonia and/or sepsis. The diagnosis of pneumonia and sepsis was made by an intensive care physician. Chest X-rays were interpreted by a radiologist.

Levels of presepsin, PCT, CRP and Le were measured at the moment the clinical diagnosis of VAP was defined, when patients developed septic reaction or septic shock. The Sequential Organ Failure Assessment (SOFA) score was calculated at these points as well.

The biomarkers measurements

Blood was collected with/without heparin as an anticoagulant, using a conventional blood collection tube (Vacutainer, BD, Franklin Lakes, NJ, USA). Collected blood samples were centrifuged (15 min, 3000 rpmi) and plasma/serum aliquots were stored at -80°C, until the measurement was performed. All biomarkers of interest (PCT, CRP and Le) as well as other markers of sepsis were determined at the central laboratory of the Center of Medical Biochemistry, using commercially available methods following the instructions of the manufacturers. The study protocol was approved by the Ethics Committee of the Clinical Center of Serbia.

The presepsin concentration was performed with the Presepsin test (PATHFAST ®, Mitsubishi Chemical Medience Corp., Tokyo, Japan). The test principle is based on non-competitive chemiluminescent enzyme immunoassay (CLEIA). During incubation of the sample with alkaline phosphatase labeled anti-presepsin polyclonal antibody and anti-presepsin monoclonal antibody coated magnetic particles, the presepsin of the sample binds to the anti-presepsin antibodies forming an immunocomplex with enzyme labeled antibody and antibody coated magnetic particles. After removing the unbound substances, a chemiluminescent substrate is added. Following a short incubation, the luminescence intensity generated by the enzyme reaction is measured. The luminescence intensity is related to the presepsin concentration of the sample, calculated by the means of a standard curve [16].

Quantitative analysis of PCT was performed by using an automated electrochemiluminescence immune analyzer (Elecsys BRAHMS PCT, Roche Diagnostics, Mannheim, Germany). CRP was determined by nephelometry (BN II, Siemens, Erlangen, Germany). Both parameters, PCT and CRP, are routinely available from the central laboratory of our hospital. For their determination, serum samples were used. The leukocyte counts were established by automatic laser mediated counting.

Table 1

Patients characteristics

Characteristics of patients	Values
Age (year), mean ± SD	47.9 ± 15.2
Gender, n (%)	
males	33 (84.6)
females	6 (15.4)
APACHE II categories, n (%)	
1–10	12 (30.8)
11–20	18 (46.2)
21–30	9 (23.1)
31–40	-
> 40	-
APACHE II, mean ± SD	14.4 ± 6.0
Severity of injuries, n (%)	
mild (ISS < 9)	7 (17.9)
moderate (ISS: 9–15)	11 (28.2)
severe (ISS: 16–24)	14 (35.9)
profound (ISS: 25–75)	7 (17.9)
ISS, mean ± SD	24.2 ± 12.8
Infection status, n (%)	
SIRS	21 (29.2)
VAP	21 (29.2)
Sepsis	18 (25.0)
Septic shock	12 (16.6)

SD – standard deviation; Apache II – Acute Physiology and Chronic Health Evaluation; ISS – Injury Severity Score; SIRS – systemic inflammatory response syndrome; VAP – Ventilation Associated Pneumonia.

Definitions

Trauma was defined as presence of injury to more than one body area or system or the presence of major traumatic brain injury alone. The APACHE II is a severity-of-disease classification system applied within 24 h of admission of a patient to an intensive care unit (ICU).

SIRS is defined by the presence of at least two of the following signs: body temperature lower than 36 °C or higher than 38 °C, heart rate faster than 90 beats per minute, tachypnea (high respiratory rate) with more than 20 breaths per minute, leukocyte count lower than 4000 cells/mm³ or higher than 12,000 cells/mm³ or the presence of more than 10% immature neutrophils.

VAP is diagnosed when new persistent pulmonary infiltrates, not otherwise explainable, appear on chest X-rays > 48 h after admission to the ICU, with the presence of one systemic and two pulmonary criteria. Patients with pulmonary contusion show worsening of X-ray findings as diagnosed by a radiologist. The systemic criteria are as follows: fever >38 °C, leukopoenia (count lower than 4,000 WBC/mm^3) or leukocytosis (count higher than 12,000 WBC/mm^3); for adults older than 70 years of age, the systemic criteria also include altered mental status, with no other recognized cause. The pulmonary criteria are as follows: new onset of purulent sputum (or a change in the character of the sputum, increased respiratory secretions or increased suctioning requirements), worsening gas exchange (desaturations, increased oxygen requirements or increased ventilator demand), new onset or worsening cough, and dyspnoea, tachypnoea, rales or bronchial breath sounds. Positive chest X-ray is defined as a progressive or new infiltrate, consolidation, pleural effusion or cavitation. Sputum change is defined as the new onset of purulent sputum or a change in the character of the sputum [17]. Respiratory samples for a bacteriological examination were collected from BAL.

Sepsis was defined as the worsening of clinical condition with at least one acute sepsis-related organ dysfunction, with one of the clinical variables: significant edema or positive fluid balance, hyperglycemia (plasma glucose > 7.7 mmol/L) in the absence of diabetes, organ dysfunction variables: arterial hypoxemia (Pao2/Fio2 < 300), acute oliguria (urine output < 0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation), increase of the creatinine level > 44.2 μmol/L, coagulation abnormalities, ileus, thrombocytopenia, hyperbilirubinemia (plasma total bilirubin level > 70 μmol/L) and tissue perfusion variables: hyperlactatemia (> 1 mmol/L) or decreased capillary refill or mottling. In order to exclude the possibility of extra-pulmonary infection source, only the patients with bacteremia having the same pathogens isolated from the respiratory sample were included.

Septic shock was defined as sepsis accompanied by arterial hypotension (systolic blood pressure – SBP < 90 mm Hg, mean arterial pressure – MAP < 70 mm Hg, or a SBP decrease > 40 mm Hg in adults or less than two sd below normal for the age) [18].

Statistical analysis

Statistical analysis was done using STATA 12.0 software (Stata Corporation, College Station, Texas, USA). For continuous variables the Kolmogorov-Smirnov test was performed to assess the assumption of normality. Thus, normally distributed continuous data were presented as mean ± standard deviation (SD) and were compared between the groups by using the Student's *t*-test, and skewed data were presented as median [inter-quartile range (IQR)] and were compared using the Mann-Whitney *U* test. Bonferroni correction was applied for all the multiple comparisons. Categorical data were presented as frequency (percentage) and compared using χ^2 test or Fisher exact-test, where appropriate. Spearman's correlation test was used to assess the correlation between presepsin and other biomarkers and variables describing medical condition severity (ISS, SOFA and Apache II). Receiver operation characteristic (ROC) analysis was done and c-statistic was calculated for each inflammation marker, in order to examine their diagnostic accuracy. The comparison of four different area under curve (AUC) was done by using χ^2 test within ROCCOMP command (Delong, Delong and Clarke-Pearson method), with post hoc Bonferroni correction [19]. For all the comparisons *p*-values ≤ 0.05 were considered as statistically significant difference with 95% confidence interval (CI).

Results

Patients' and injury characteristics

In 39 patients (33 males and 6 females) who sustained trauma, spending more than 48 hours on mechanical ventilation, 72 measurements of four biomarkers were performed. Blood was drawn at the moment of SIRS, VAP, sepsis or septic shock diagnosis. Twenty one of all those measurements were performed when SIRS was diagnosed, other 21 measurements were conducted at the moment of VAP diagnosis, further 18 measurements at the moment of sepsis diagnosis and 12 measurements coincided with septic shock diagnosis (Table 1).

Study participants were predominantly middle-aged (mean age 47.9 ± 15.2 years) and males [n = 33 (84.6 %)]. They were mainly severely injured according to the mean ISS of 24.2. The majority of the patients had moderately severe medical condition on admission, as indicated by mean APACHE II score 14.5 (Table 1).

Biomarkers concentrations

Distribution of serum presepsin, PCT, CRP and Le in patients with SIRS, VAP, sepsis and/or septic shock are shown in Figure 1. Median, minimum and maximum concentrations of biomarkers is summarized in Table 2.

Comparisons of biomarkers between four groups are shown in Table 3. Presepsin concentration significantly differed among all four groups, except between sepsis and septic shock. These differences were highly significant ($p < 0.001$) with the exception of the difference between the

patients with VAP and sepsis, which was less prominent [median (IQR) 663.0 (271.5) vs. 988.0 (746.8); $p = 0.012$]. PCT was significantly higher in every consequent group, except for the septic shock group compared to sepsis [12.5 (4.4) vs. 11.5 (7.0); $p = 0.215$)]. CRP and Le significantly differed only between the SIRS and septic shock [124.0 (112.0) vs. 220.3 (143.4); $p = 0.012$] and [11.0 (8.3) vs.17.5 (7.0); $p = 0.024$, respectively].

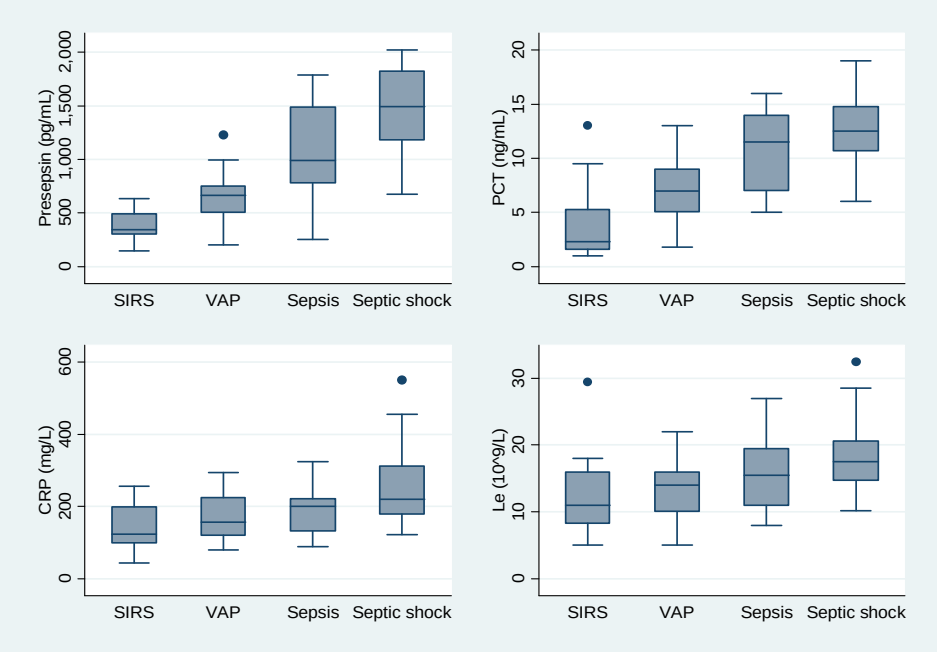

Fig. 1 – Distribution of presepsin, procalcitonin (PCT), C-rective protein (CRP) and leukocytes (Le) in 39 trauma patients at the moment of diagnosis of systemic inflammatory response syndrome (SIRS) (n = 21), ventilator associated pneumonia (VAP) (n = 21), sepsis (n = 18) or septic shock (n = 12).

Table 2

Concentration of presepsin, procalcitonin (PCT), C-reactive protein (CRP) and leucocytes (Le) in the trauma patients

Biomarker	SIRS	VAP	Sepsis	Septic shock
	Median (IQR) Min–Max	Median (IQR) Min–Max	Median (IQR) Min–Max	Median (IQR) Min–Max
Presepsin (pg/mL)	343.0 (202.0) 144–633	663.0 (271.5) 199–1230	988.0 (746.8) 252–1789	1494.0 (674.3) 674–2020
PCT (ng/mL)	2.3 (3.8) 1–13	7.0 (4.5) 1.8–13	11.5 (7.0) 5–16	12.5 (4.4) 6–19
CRP (mg/L)	124.0 (112.0) 43–256	157.0 (119.5) 79–294	200.0 (101.3) 88–324	220.3 (143.4) 122–550.4
Le (10^9/L)	11.0 (8.3) 5–29.4	14.0 (6.5) 5–22	15.5 (8.9) 8–27	17.5 (7.0) 10.2–32.4

SIRS – systemic inflammatory response syndrome; VAP – ventilator-associated pneumonia; IQR – interquartile range.

Table 3

Comparisons of presepsin, procalcitonin (PCT), C-reactive protein (CRP) and leucocytes (Le) between groups*

Biomarkers	Presepsin	PCT	CRP	Le
SIRS vs. VAP	< 0.001	0.024	0.630	0.406
SIRS vs. Sepsis	< 0.001	< 0.001	0.222	0.258
SIRS vs. Septic shock	< 0.001	< 0.001	0.012	0.024
VAP vs. Sepsis	0.012	0.012	0.587	0.202
VAP vs. Septic shock	< 0.001	< 0.001	0.378	0.144
Sepsis vs. Septic shock	0.132	0.215	0.185	0.285

***Mann-Whiney *U* test with Bonferroni correction.**
SIRS – systemic inflammatory response syndrome; VAP – ventilator-associated pneumonia.

Table 4

C-statistic of presepsin, procalcitonin (PCT), C-reactive protein (CRP) and leukocytes (Le) in prediction of infection or sepsis

Biomarker	Non-VAP vs. VAP			Non-sepsis vs. sepsis		
	AUC	95% CI	*p*	AUC	95% CI	*p*
Presepsin	0.908	0.842–0.975	0.000	0.899	0.818–0.980	0.000
PCT	0.863	0.765–0.961	0.000	0.885	0.810–0.960	0.000
CRP	0.703	0.57–0.835	0.007	0.677	0.553–0.800	0.011
Le	0.668	0.527–0.809	0.026	0.700	0.579–0.820	0.004

VAP – ventilator-associated pneumonia; AUC – area under the curve; CI – confidence interval.

Correlation between presepsin and other markers

The strongest positive correlation presepsin evinced with PCT ($r = 0.741$, $p < 0.001$) (Figure 2). Presepsin was in significant positive correlation with other inflammation markers and with SOFA score ($r = 0.575$; $p < 0.001$) which represents the extent of the organ function/failure and was measured at the moment of each infectious condition. The similar correlations with abovementioned variables were observed for PCT, while CRP correlated with APACHE II and ISS as well.

ROC analysis

Diagnostic accuracy of the four sepsis biomarkers (presented as the ROC curves) in discrimination of non-VAP (SIRS) and VAP conditions (VAP + sepsis + septic shock) are shown in Figure 3 while for non-sepsis (SIRS + VAP) and sepsis conditions (sepsis + septic shock), they are shown in Figure 4. The summary of the c-statistic or the AUC for those four markers is shown in Table 5. According to the AUCs, presepsin evinced better performance in diagnosis of both VAP (AUC = 0.908) and sepsis (AUC = 0.899), than PCT (AUC = 0.863; 0.885, respectively), CRP (AUC = 0.703; 0.677, respectively) and Le (AUC = 0.668; 0.700, respectively). However, the AUCs comparison revealed that AUC for presepsine was significantly greater only when compared to AUC for Le ($\chi^2 = 10.92$, $p = 0.006$) in discriminating between non-VAP and VAP conditions. Considering non-sepsis and sepsis conditions, AUC for presepsin was significantly higher than AUC for CRP ($\chi^2 = 11.40$, $p = 0.004$) and Le ($\chi^2 = 11.67$, $p = 0.003$). However, presepsin showed as good diagnostic accuracy as PCT.

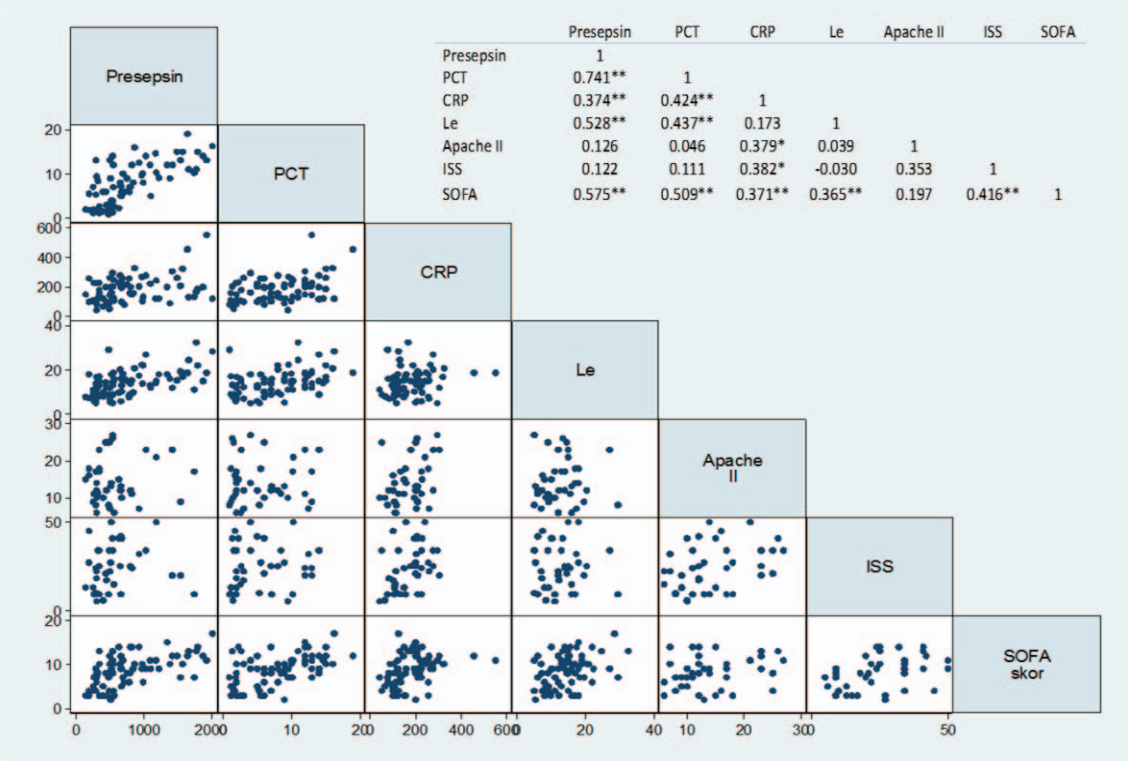

Fig. 2 – Correlation of presepsin with other inflammation markers, Acute Physiology and Chronic Health Evaluation (APACHE II) score, Injury Seventy Score (ISS) and Sequential Organ Failure Assessment (SOFA) score. (*$p < 0.05$; **$p < 0.001$).

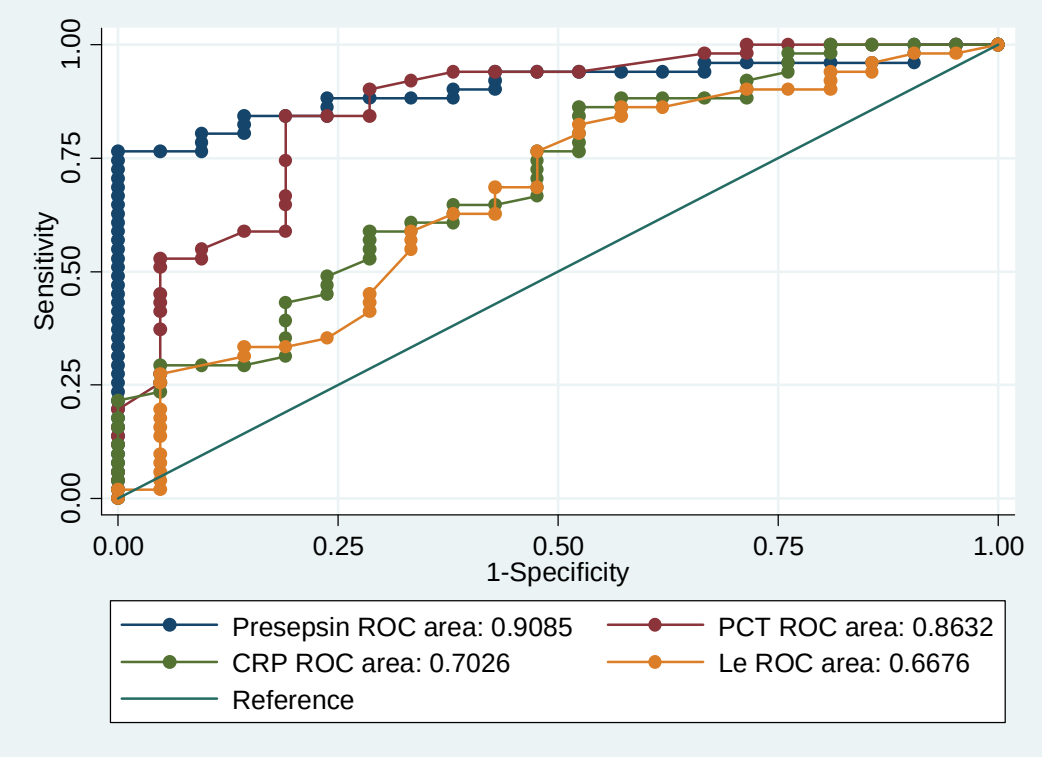

Fig. 3 – Receiver operation characteristic (ROC) curve for presepsin, procalcitonin (PCT), C-reactive protein (CRP) and leukocytes (Le) in the non-infection group [systemic inflammatory response syndrome (SIRS)] and the infection group [sepsis, ventilator-associated pneumonia (VAP) and septic shock].

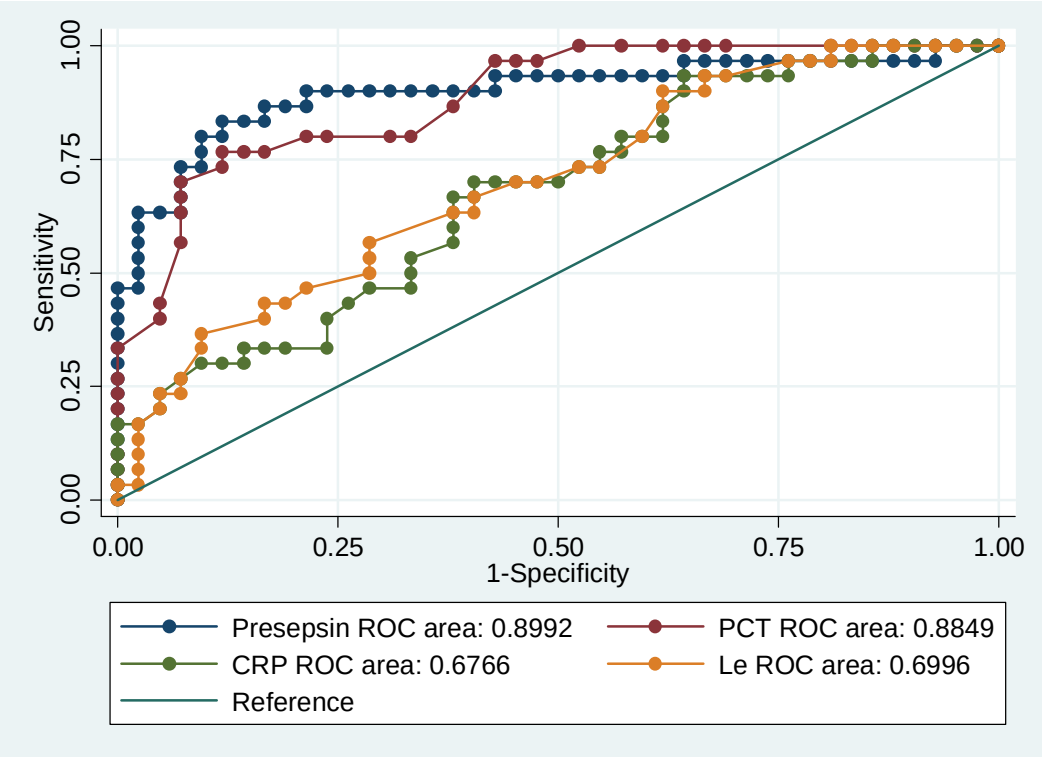

Fig. 4 – Receiver operation characteristic (ROC) curve for presepsin, procalcitonin (PCT), C-reactive protein (CRP) and leukocytes (Le) in the non-septic group [Systemic Inflammatory Response Syndrome (SIRS) and ventilator-associated pneumonia (VAP)] and the septic group (sepsis and septic shock).

Table 5
Comparisons of the area under curves (AUCs) with Bonferroni correction

Biomarker	Non-VAP vs. VAP	Non-sepsis vs. sepsis
Presepsin vs. PCT	0.414	0.744
Presepsin vs. CRP	0.228	0.004
Presepsin vs. Le	0.006	0.003
PCT vs. CRP	0.186	0.012
PCT vs. Le	0.162	0.001
CRP vs. Le	0.717	0.777

VAP – ventilator-associated pneumonia; PCT – procalcitonin; CRP – C-reactive protein; Le – leukocytes.

Discussion

The number of severely injured patients treated in the ICU and requiring prolonged mechanical ventilation is significant, leading to high incidence of VAP, as shown earlier [20]. The accurate diagnosis of infection, especially pneumonia, in the ICU settings is challenging and is linked with decrease in morbidity and mortality.

During VAP development the beginning of treatment cannot be accurately suggested. It is usually associated with the ICU rounds and changes in the chest X-ray findings, which can lead to delayed clinical decision-making. Moreover, using clinical decision, as suggested by many guidelines, can postpone appropriate antibiotic regimens. Lower or upper respiratory sputum sample techniques are still the most reliable diagnostic method for ventilator-associated pneumonia. However, it takes at least two days to obtain the results. The case is the same with blood cultures, which are frequently used for sepsis confirmation. Therefore, defining a reliable marker that can enable fast diagnosis of VAP would be of great benefit.

In the present study we evaluated prognostic value of presepsin in diagnosis of VAP and sepsis in critically injured patients requiring mechanical ventilation, i.e., its potential to differentiate the local infection (VAP) from SIRS, as well as to differentiate VAP from sepsis and septic shock. In our study levels of presepsin were significantly higher in patients who developed VAP compared to those with SIRS and significantly higher in patients with sepsis compared to those with VAP or SIRS. These results are in line with few studies that measured levels of sCD14-ST in blood samples for local infection diagnosis [21–23]. In study of Shozushima et al. [22] presepsin levels were significantly higher in patients with local infection, sepsis, and severe sepsis than in patients without infection. Similarly, Popov et al. [23] showed significantly higher values of presepsin in the group of patient with infectious complications than in those without infections following cardiac surgery. In our study, however, we measured biomarkers levels only after the clinical diagnosis of infection was made. Regularly measuring sCD14-ST levels can possibly hasten diagnosis, even before significant clinical changes are present (e.g., sputum, fever, chest X-ray change) [7].

Presepsin in our study evinced an excellent ability to differentiate both, non-VAP vs. VAP diagnoses and non-septic vs. septic diagnoses, as shown by the high area under the ROC curves (0.908 and 0.899, respectively). Considering pneumonia, presepsin was only investigated in severe community acquired pneumonia (sCAP) treated in the ICU. Similarly to our findings, in a study by Klouche et al. [24] presepsin evinced a great capacity to differentiate sCAP from severe sepsis and septic shock. They also observed significantly higher concentrations of presepsin in patients with pneumonia compared to those with the non-infectious respiratory failure. The similar was observed in a study by Liu et al. [25] where presepsin levels corresponded with level of infection, i.e., presepsin was higher in patients with sCAP than in those with CAP.

Presepsin was studied more profoundly in patients with sepsis [14, 26–28]. Its elevation represents a dose–response mechanism of the host reaction to pathogen. In our study presepsin level was significant for differentiating the severity of sepsis, as shown in the mentioned studies. In addition to this, we observed significant positive correlation of presepsin with SOFA score, a clinical score which depicts the degree of patients' organ failure. This finding suggests that presepsin is a marker which closely corresponds to sepsis pathogenesis. The association of presepsin level with severity of disease scores were also observed Shozushima et. al. [22] (CAP severity score) and Liu et al. [25] (APACHE II score).

The most meaningful result of our study was that presepsin indicated a better performance in the diagnosis of VAP and sepsis than commonly used laboratory markers (PCT and WBC). PCT is one of the most frequently used markers for diagnosis of local infection and sepsis complications [29, 30]. Although procalcitonin-guided strategy used to treat suspected bacterial infections could reduce antibiotic exposure, PCT tends to rise transiently in non-septic conditions and SIRS, like invasive trauma, surgery and physical exercise, as shown in the previous studies and which is not the case with presepsin [26, 31, 32]. In our study, in the presence of pneumonia and sepsis, the levels of PCT raised significantly, however diagnosis can be delayed due to the fact that PCT value increased 4 hours after infection and peaked one day after infection while presepsin concentration increased in 2 hours after infection, reaching the peak value after 3 hours [13]. In spite of the fact that presepsin in our study showed significant positive correlation with other laboratory markers of sepsis (PCT, CRP, WBC), presepsin expressed the strongest positive correlation with PCT. This finding is in accordance with other clinical studies that have also pointed out the im-

portance of PCT and the presepsin measurements in the patients with sepsis, as diagnostic and prognostic markers [33].

Conclusion

In the era of terrifying increase of pathogens resistance, great efforts have been made to define the new tools for excellence in early diagnosis of infections. Some of them are novel biomarkers which can hasten the process. Keeping in mind that the best preventive techniques for VAP are not specifically defined or are not available, real time control of infection relies on its diagnosis. Our study suggests that presepsin (sCD14-ST) is reliable biomarker for diagnosis of VAP in severely injured patients requiring mechanical ventilation, as well as for distinguishing sepsis severity in these patients.

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R E F E R E N C E S

1. *Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD*, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302(21): 2323–9.
2. *Bekaert M, Timsit JF, Vansteelandt S, Depuydt P, Vésin A, Garrouste-Orgeas M*, et al. Attributable mortality of ventilator-associated pneumonia: A reappraisal using causal analysis. Am J Respir Crit Care Med 2011; 184(10): 1133–9.
3. *Agbaht K, Lisboa T, Pobo A, Rodriguez A, Sandiumenge A, Diaz E,* et al. Management of ventilator-associated pneumonia in a multidisciplinary intensive care unit: Does trauma make a difference. Intensive Care Med 2007; 33(8): 1387–95.
4. *Dombrovskiy VY, Martin AA, Sunderram J, Paz HL*. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. Crit Care Med 2007; 35(5): 1244–50.
5. *Nair GB, Niederman MS*. Ventilator-associated pneumonia: Present understanding and ongoing debates. Intensive Care Med 2015; 41(1): 34–48.
6. *Kalanuria AA, Zai W, Mirski M*. Ventilator-associated pneumonia in the ICU. Crit Care 2014; 18(2): 208.
7. *Pierrakos C, Vincent J*. Sepsis biomarkers: A review. Crit Care 2010; 14(1): R15.
8. *Palazzo SJ, Simpson T, Schnapp L*. Biomarkers for ventilator-associated pneumonia: Review of the literature. Heart Lung 2011; 40(4): 293–8.
9. *Fagon JY*. Biological markers and diagnosis of ventilator-associated pneumonia. Crit Care 2011; 15(2): 130.
10. *Póvoa P*. Serum markers in community-acquired pneumonia and ventilator-associated pneumonia. Curr Opin Infect Dis 2008; 21(2): 157–62.
11. *Chenevier-Gobeaux C, Borderie D, Weiss N, Mallet-Coste T, Claessens YE*. Presepsin (sCD14-ST), an innate immune response marker in sepsis. Clin Chim Acta 2015; 450: 97–103.
12. *Sandquist M, Wong HR*. Biomarkers of sepsis and their potential value in diagnosis, prognosis and treatment. Expert Rev Clin Immunol 2014; 10(10): 1349–56.
13. *Cinel I, Opal SM*. Molecular biology of inflammation and sepsis: a primer. Crit Care Med 2009; 37(1): 291–304.
14. *Zhang X, Liu D, Liu YN, Wang R, Xie LX*. The accuracy of presepsin (Scd14-ST) for the diagnosis of sepsis in adults: A meta-analysis. Crit Care 2015; 19: 323.
15. *Waters B, Muscedere J*. A 2015 Update on Ventilator-Associated Pneumonia: New Insights on Its Prevention, Diagnosis, and Treatment. Curr Infect Dis Rep 2015; 17(8): 496.
16. *Okamura Y, Yokoi H*. Development of a point-of-care assay system for measurement of presepsin (sCD14-ST). Clin Chim Acta 2011; 412(23–24): 2157–61.
17. *American Thoracic Society*. Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171(4): 388–416.
18. *Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM*, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 39(2): 165–228.
19. *DeLong ER, DeLong DM, Clarke-Pearson DL*. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics 1988; 44(3): 837–45.
20. *Jovanovic B, Milan Z, Markovic-Denic L, Djuric O, Radinovic K, Doklestic K*, et al. Risk factors for ventilator-associated pneumonia in patients with severe traumatic brain injury in a Serbian trauma centre. Int J Infect Dis 2015; 38: 46–51.
21. *Kojic D, Siegler BH, Uhle F, Lichtenstern C, Nawroth PP, Weigand MA*, et al. Are there new approaches for diagnosis, therapy guidance and outcome prediction of sepsis. World J Exp Med 2015; 5(2): 50–63.
22. *Shozushima T, Takahashi G, Matsumoto N, Kojika M, Okamura Y, Endo S*. Usefulness of presepsin (sCD14-ST) measurements as a marker for the diagnosis and severity of sepsis that satisfied diagnostic criteria of systemic inflammatory response syndrome. J Infect Chemother 2011; 17(6): 764–9.
23. *Popov D, Plyushch M, Ovseenko S, Abramyan M, Podshchekoldina O, Yaroustovsky M*. Prognostic value of sCD14-ST (presepsin) in cardiac surgery. Kardiochir Torakochirurgia Pol 2015; 12(1): 30–6.
24. *Klouche K, Cristol JP, Devin J, Gilles V, Kuster N, Larcher R*, et al. Diagnostic and prognostic value of soluble CD14 subtype (Presepsin) for sepsis and community-acquired pneumonia in ICU patients. Ann Intensive Care 2016; 6: 59.
25. *Liu B, Yin Q, Chen Y, Zhao Y, Li C*. Role of Presepsin (sCD14-ST) and the CURB65 scoring system in predicting severity and outcome of community-acquired pneumonia in an emergency department. Respir Med 2014; 108(8): 1204–13.
26. *Masson S, Caironi P, Fanizza C, Thomae R, Bernasconi R, Noto A,* et al. Circulating presepsin (soluble CD14 subtype) as a marker of host response in patients with severe sepsis or septic shock: Data from the multicenter, randomized ALBIOS trial. Intensive Care Med 2015; 41(1): 12–20.
27. *Vodnik T, Kaljevic G, Tadic T, Majkic-Singh N*. Presepsin (sCD14-ST) in preoperative diagnosis of abdominal sepsis. Clin Chem Lab Med 2013; 51(10): 2053–62.
28. *Endo S, Suzuki Y, Takahashi G, Shozushima T, Ishikura H, Murai A*, et al. Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study. J Infect Chemother 2012; 18(6): 891–7.
29. *Shehabi Y, Sterba M, Garrett PM, Rachakonda KS, Stephens D, Harrigan P,* et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A random-

ized controlled trial. Am J RespirCrit Care Med 2014; 190(10): 1102–110.

30. *Tanriverdi H, Tor M, Kart L, Altin R, Atalay F, SumbSümbüloglu V*. Prognostic value of serum procalcitonin and C-reactive protein levels in critically ill patients who developed ventilator-associated pneumonia. Ann Thorac Med 2015; 10(2): 137–42.
31. *Wacker C, Prkno A, Brunkhorst FM, Schlattmann P*. Procalcitonin as a diagnostic marker for sepsis: A systematic review and meta-analysis. Lancet Infect Dis 2013; 13(5): 426–35.
32. *Schuetz P, Amin DN, Greenwald JL*. Role of procalcitonin in managing adult patients with respiratory tract infections. Chest 2012; 141(4): 1063–73.
33. *Enguix-Armada A, Escobar-Conesa R, García-De La Torre A, De La Torre-Prados MV*. Usefulness of several biomarkers in the management of septic patients: C-reactive protein, procalcitonin, presepsin and mid-regional pro-adrenomedullin. Clin Chem Lab Med 2016; 54(1): 163–8.

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