ACCEPTED MANUSCRIPT

Accepted manuscripts are the articles in press that have been peer reviewed and accepted for publication by the Editorial Board of the *Vojnosanitetski Pregled*. They have not yet been copy edited and/or formatted in the publication house style, and the text could still be changed before final publication.

Although accepted manuscripts do not yet have all bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: article title, the author(s), publication (year), the DOI.

Please cite this article **ACCURACY OF SERUM PROCALCITONIN, C-REACTIVE PROTEIN AND SOLUBLE CD14 SUBTYPE LEVELS IN DIAGNOSIS OF SEPSIS IN CHILDREN**

**TAČNOST SERUMSKOG PROKALCITONINA, C-REAKTIVNOG PROTEINA I sCD14-ST U DIJAGNOZI SEPSE KOD DECE**

**Authors** Sanja Knežević Rangelov, Slobodan M Janković, Vojnosanitetski pregled (2019); Online First May, 2019.

**UDC:**

**DOI:** [https://doi.org/10.2298/VSP1801200057K](https://doi.org/10.2298/VSP1801200057K)

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
ACCURACY OF SERUM PROCALCITONIN, C-REACTIVE PROTEIN AND SOLUBLE CD14 SUBTYPE LEVELS IN DIAGNOSIS OF SEPSIS IN CHILDREN

TAČNOST SERUMSKOG PROKALCITONINA, C-REAKTIVNOG PROTEINA I sCD14-ST U DIJAGNOZI SEPSE KOD DECE

Sanja Knežević Rangelov

Faculty of Medical Sciences, University of Kragujevac

Slobodan M Janković

Univerzitet u Kragujevcu, Fakultet medicinskih nauka

Correspondence to:

Short title: PROCALCITONIN, CRP AND SOLUBLE CD14 SUBTYPE IN CHILDREN WITH SEPSIS
Abstract

Background/Aim. Despite widespread use of procalcitonin, C-reactive protein and soluble CD14 subtype (sCD14-ST), their diagnostic accuracy in children with sepsis is not yet clear. The aim of our study was to establish and compare diagnostic accuracy of procalcitonin, C-reactive protein and sCD14-ST in children admitted to hospital under suspicion of having sepsis. Methods. The study was designed as retrospective cross-sectional study on children admitted to Pediatrics Clinic in Kragujevac, Serbia under suspicion of sepsis, during the 6 months period. Diagnostic accuracy was tested by construction of Receiver-operator curves and their comparison in terms of area under the curve. Results. Procalcitonin had the largest area under the curve (0.75; 95% CI 0.63 – 0.88), followed by CRP (0.68; 95%CI 0.54-0.81) and sCD14-ST (0.65; 95% CI 0.52 – 0.79). Differences between the areas under the ROC curves were not significant (CRP vs. procalcitonin z = 1.054, p = 0.291; CRP vs. sCD14-ST z = 0.238, p = 0.812; procalcitonin vs. sCD14-ST z = 1.089, p = 0.286). Conclusion. Our study showed relatively low sensitivity and moderate specificity of procalcitonin, C-reactive protein and sCD14-ST in diagnosing sepsis among children, as well as similar diagnostic accuracy of the three biomarkers.

Key words: c-reactive protein; diagnostic test; scd14-st; procalcitonin; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Uprkos rasprostranjenom merenju nivoa prokalcitonina, C-reaktivnog proteina i rastvorljivog CD14 podtipa (sCD14-ST) u serumu, njihova tačnost u dijagnozi sepse kod dece još nije jasna. Cilj ove studije je bio da utvrdi i uporedi dijagnostičku tačnost prokalcitonina, C-reaktivnog proteina i sCD14-ST-a kod dece primljenih u bolnicu zbog sumnje na sepsu. Metode. Studija je bila dizajnirana kao retrospektivna studija preseka i sprovedena na deci primljenoj u Pedijatrijsku kliniku Kliničkog centra Kragujevac tokom šestomesečnog perioda pod sumnjom na sepsu. Dijagnostička tačnost je bila testirana konstrukcijom Kriva prijemnik-operator (KPO) za svaki od testova i poređenjem površina ispod njih. Rezultati. Prokalcitonin ima najveću površinu ispod krive (0.75; 95%CI 0.63 –
0.88), zatim slede CRP (0.68; 95%CI 0.54-0.81) i sCD14-ST (0.65; 95% CI 0.52 – 0.79). Razlike između površina ispod KPO krivih nisu bile značajne (CRP naprema prokalcitoninu z = 1.054, p = 0.291; CRP naprema sCD14-ST-u z = 0.238, p = 0.812; prokalcitonin naprema sCD14-STu z = 1.089, p = 0.286). **Zaključak.** Naša studija je ukazala na relativno nisku senzitivnost i umerenu specifičnost prokalcitonina, CRP-a i sCD14-ST-a u dijagnozi sepse kod dece, kao i sličnu dijagnostičku tačnost ova tri biomarkera.

**Ključne reči:**
c-reactivni protein; dijagnostički test; scd14-st; prokalcitonin; senzitivnost i specifičnost.

**Introduction**

According to International Consensus Conference on Pediatric Sepsis held in 2005 it could be defined as joint occurrence of systemic inflammatory response syndrome with either microbiological confirmation of infection or clinical syndrome associated with high probability of infection. Apart from these clinical and microbiological criteria several serum markers of inflammation are used for strengthening diagnosis of sepsis, and procalcitonin (PCT), C-reactive protein (CRP) or sCD14-ST („presepsin“) are among the most frequently used. In a recent systematic review of diagnostic accuracy studies involving PCT, CRP and sCD14-ST in patient with sepsis it was shown that usefulness of these biomarkers for diagnosis of sepsis remains debated as well as significance of difference in sensitivity and specificity between the three.

Diagonal accuracy is especially problematic in children with sepsis, as recent meta-analysis reported high sensitivity (85%) but low specificity (54%) of procalcitonin, and some other studies moderate sensitivity (87.5%) and specificity (70.9%) of CRP and high sensitivity (94%) and specificity (100%) of sCD14-ST. However, not all studies confirmed these figures in pediatric patients, so true role of these biomarkers for diagnosis of sepsis, especially in newly admitted children remains to be established.

The aim of our study was to establish and compare diagnostic accuracy of PCT, CRP and sCD14-ST in children admitted to hospital under suspicion of having sepsis.
Methods

The study was designed as retrospective, observational cross-sectional study on children admitted to Pediatrics Clinic in Kragujevac, Serbia (part of Clinical Center Kragujevac) under suspicion of sepsis, during the first 6 months of 2017. The Inclusion criteria were age below 18 years, admission to the hospital, values of both procalcitonine, sCD14-ST and CRP measured on admission, suspicion of sepsis regardless of the source of infection. The exclusion criteria were septic shock, incomplete patient file and antibiotic treatment during the last 15 days before admission. The study sample was not random, but consecutive, as all patients who were admitted to the hospital during the study period due to suspicion of sepsis were enrolled if the criteria for inclusion and exclusion were satisfied.

Blood samples were taken from peripheral vein on admission and sera were separated by centrifugation and sent to central laboratory of Clinical Center Kragujevac. Procalcitonin was measured by electrochemiluminiscence method (COBAS, Roche), CRP by immunoturbidimetry (AU680 and AU400, Beckman Coulter Analyzers) and sCD14-ST by chemiluminiscence (PATHFAST immunoanalyser, Mitsubishi Chemical Europe). The laboratory was accredited by the Serbian Interlaboratory Control body. The following variables were collected from the patients files: serum levels of procalcitonine, sCD14-ST and CRP on admission, age, sex, serum level of creatinine, white cell count, results of microbiological analysis of blood and tissue samples, data about body temperature on admission, data about chest x-ray if available and vital parameters (all variables were measured on admission if not stated otherwise). Existence of sepsis was confirmed on the basis of criteria set by the International Consensus Conference on Pediatric Sepsis. The study was approved by the Institutional Review Board (IRB) of Pediatrics Clinic in Kragujevac.

The sample size was calculated on the basis of the following assumptions: power of the study at least 80%, probability of type one error 0.05, difference between the areas under the ROC curves (AUC) tested by Student's T-test for independent samples, expected difference between the AUCs taken from the study of Julian Himenez et al. (0.79 vs 0.72) and standard deviation of AUCs measurement of 0.15. The calculation was performed using Gpower software version 3.1.
Statistics. Distributions of data from the study were tested for normality by Kolmogorov-Smirnov test and then described by measures of central tendency (median) and variability (interquartile range). The differences among the study groups in regard to continuous variables were tested for significance by the Mann Whitney U test, and those in rates by the Chi Square test. AUCs were calculated for procalcitonine, CRP and sCD14-ST, together with 95% confidence intervals (CI). Optimal cut-off values were determined by the Manhattan method using online calculator created by the Charite – Universitätsmedizin Berlin 9. Significance of differences between the AUCs was tested by the De Long’s method using MedCalc software. All other calculation were performed by the Statistical Software for Social Sciences (SPSS) version 20.0.

Results

There were 80 children who took part in the study, 36 of them having sepsis according to the International pediatric sepsis consensus conference criteria. Characteristics of the groups with and without sepsis are shown in the Table 1. The Kolmogorov-Smirnov test showed that only white cell count and creatinine serum level on admission in children without sepsis were normally distributed (p=0.200 and p=0.210, respectively), precluding use of parametric tests for comparison of the study groups.

In the group of children with sepsis 24 (66.7%) had an microorganism isolated: 2 Enterococcus sp. (8.3%), 1 Salmonella enteritidis (4.2%), 1 Micrococcus luteus (4.2%), 1 Streptococcus beta-haemolyticus (4.2%), 1 Serratia sp. (4.2%), 2 Streptococcus pneumoniae (8.3%), 5 Klebsiella sp. (21%), 4 Staphylococcus sp. (16.6%), 4 Escherichia coli (16.5%), 2 Pseudomonas sp. (8.3%) and 1 Neisseria meningitidis (4.2%). The isolation sites in this group were as following: cerebrospinal fluid in 7 cases (29.2%), blood in 7 cases (29.2%), urine in 2 cases (8.3%), tracheal aspirate in 7 cases (29.2%) and stool in 1 case (4.1%).

In the group of children without sepsis 22 (50.0%) had an microorganism isolated: 2 Enterococcus sp. (9.1%), 1 Salmonella enteritidis (4.5%), 1 Streptococcus pneumoniae (4.5%), 1 Klebsiella sp. (4.5%), 5 Staphylococcus sp. (22.8%), 2 Proteus sp. (9.1%), 6 Escherichia coli (27.4%), 2 Pseudomonas sp. (9.1%), 1 Herpes virus (4.5%) and 1 Enterobacter (4.5%). The isolation sites in this group were as following: umbilical skin in 5
cases (22.8%), blood in 2 cases (9.1%), urine in 8 cases (36.4%), tracheal aspirate in 3 cases (13.6%), skin in 3 cases (13.6%), and stool in 1 case (4.5%).

Receiver-operator curves (ROC) for procalcitonin, C-reactive protein (CRP) and sCD14-ST measured at admission of the children to hospital are shown in the Figure 1. Procalcitonin had the largest area under the curve (0.753 ± 0.065), followed by CRP (0.716 ± 0.057) and sCD14-ST (0.686 ± 0.061). Sensitivity and specificity of procalcitonin, CRP and sCD14-ST calculated for cut-off values determined by Manhattan method are shown in the Table 2.

Discussion

Our study showed that PCT, CRP and sCD14-ST had relatively low sensitivity and much higher specificity for diagnosing sepsis in children. Besides, significant difference in diagnostic accuracy of these the biomarkers was not observed.

When compared with results of other studies and meta-analyses, values of sensitivity for PCT, CRP and sCD14-ST in our study were much lower (almost 20%), which could underestimate diagnostic value of these biomarkers in children with sepsis. However, such result could be explained in one the following ways: (1) due to retrospective character of our study, validity of diagnosis of sepsis established by the consensus criteria could not have been checked, and it depended on performance of attending physicians; (2) other studies could have overestimated diagnostic accuracy as many of them included as control group either healthy children of patients easily differentiated from those who had sepsis. Although several studies confirmed higher diagnostic accuracy of sCD14-ST (comparing area under the ROC curves) than that of CRP and PCT in patients with sepsis, our results did not show any significant difference.

Our study has several limitations that could affect the results. First, the age range of our patients was very wide, as we included both newborns and adolescents. Since there are inherent age-related differences in response to infection, cut-off values that we calculated could not have been appropriate completely for both very young and older children.

In conclusion, our study showed relatively low sensitivity and moderate specificity of PCT, CRP and sCD14-ST in diagnosing sepsis among children, as well as similar
diagnostic accuracy of the three biomarkers. PCT, CRP and sCD14-ST should not be relied upon completely when assessing presence of sepsis in children, but rather taken into account together with clinical picture. Further research in this area is necessary, especially on groups of children with more narrow age range (newborns, infants, toddlers, etc.).

Acknowledgements

The authors are grateful to the group of trainees from educational event held in Sarajevo, November the 3rd, 2017, for their active watching while the authors were writing the manuscript.

REFERENCES


Table 1.

Characteristics of the study groups on admission.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Children with sepsis (n = 36)</th>
<th>Children without sepsis (n = 44)</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in months (Median and IQR*)</td>
<td>15 (1.3 – 56.0)</td>
<td>9 (1.25 – 41.0)</td>
<td>Mann Whitney U test = 659.5, p = 0.200</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>13/23 (36.1%/63.9%)</td>
<td>21/23(47.7%/52.3%)</td>
<td>Pearson Chi-Square = 1.093, p = 0.296</td>
</tr>
<tr>
<td>Febrile</td>
<td>29 (80.5%)</td>
<td>25 (56.8%)</td>
<td>Pearson Chi-Square = 5.086, p = 0.024**</td>
</tr>
<tr>
<td>White cells count ( x 10⁹/l) (Median and IQR*)</td>
<td>15.2 (11.1 – 18.9)</td>
<td>13.4 (10.8 – 18.8)</td>
<td>Mann Whitney U test = 752.0, p = 0.699</td>
</tr>
<tr>
<td>Serum creatinine (μM/l) (Median and IQR*)</td>
<td>43.0 (39.0 – 48.0)</td>
<td>42.0 (34.0 – 47.5)</td>
<td>Mann Whitney U test = 651.5, p = 0.392</td>
</tr>
<tr>
<td>CRP TAG (mg/l) (Median and IQR*)</td>
<td>76.6 (9.9 – 131.0)</td>
<td>17.1 (3.5 – 67.7)</td>
<td>Mann Whitney U test = 459.5, p = 0.001**</td>
</tr>
<tr>
<td>Procalcitonin (ng/ml) (Median and IQR*)</td>
<td>2.130 (0.144 – 5.220)</td>
<td>0.261 (0.108 – 0.615)</td>
<td>Mann Whitney U test = 218.5, p = 0.001**</td>
</tr>
<tr>
<td>sCD14-ST (pg/ml) (Median and IQR*)</td>
<td>259.0 (163.0 – 535.5)</td>
<td>189.0 (127.0 – 267.5)</td>
<td>Mann Whitney U test = 498.0, p = 0.004**</td>
</tr>
<tr>
<td>Primary site of bacterial infection and diagnosis at</td>
<td>Blood, Sepsis - 14(38.9%)</td>
<td>Viral bronchopneumonia - 10(22.7%)</td>
<td>N/A*</td>
</tr>
</tbody>
</table>

*Median and interquartile range (IQR) **Significance level: **p < 0.01, *p < 0.05
### Table 2.

Cut-off values, sensitivity and specificity of procalcitonin, CRP and sCD14-ST for diagnosing sepsis in children on admission to hospital.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Procalcitonin</th>
<th>CRP</th>
<th>SCD14-ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cut-off value</td>
<td>1.42 ng/ml</td>
<td>22.1 mg/l</td>
<td>319.5 pg/ml</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>61.8%</td>
<td>63.9%</td>
<td>55.6%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>75.0%</td>
<td>88.6%</td>
</tr>
</tbody>
</table>
Fig. 1 – ROC curves for procalcitonin (PCT), CRP and sCD14-ST if diagnosing sepsis in children on admission to a hospital.