SHORT COMMUNICATIONS

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Accuracy of serum procalcitonin, C-reactive protein, and soluble CD14 subtype levels in diagnosis of sepsis in children

Tačnost nivoa serumskog prokalcitonina, C-reaktivnog proteina i rastvorljivog CD14 podtipa u dijagnozi sepse kod dece

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Abstract

Background/Aim. Despite the widespread use of procalcitonin, C-reactive protein (CRP), and soluble CD14 subtype (sCD14-ST), their diagnostic accuracy in children with sepsis is not yet clear. The aim of the study was to establish and compare the diagnostic accuracy of procalcitonin, CRP, and sCD14-ST in children admitted to the hospital under suspicion of having sepsis. **Methods**. The study was designed as a retrospective cross-sectional study on children admitted to the Pediatrics Clinic in Kragujevac, Serbia, under suspicion of sepsis, during a 6-month period. Diagnostic accuracy was tested by the construction of receiver operating characteristic (ROC) curves and their comparison in terms of area under the curve (AUC). **Results**. Procalcitonin had the largest AUC [0.75; 95% confidence interval (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:
biomarkers; c-reactive protein; child; diagnosis; presepsin protein, human; sensitivity and specificity; sepsis.

Apstrakt

Uvod/Cilj. Uprkos rasprostranjenom merenju nivoa prokalcitonina, C-reaktivnog proteina (CRP) i rastvorljivog CD14 podtipa (sCD14-ST) u serumu, njihova tačnost u dijagnozi sepse kod dece još nije jasna. Cilj studije bio je da se utvrdi i uporedi dijagnostička tačnost prokalcitonina, CRP-a i sCD14-ST-a kod dece primljene 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 je imao najveću površinu ispod krive [0,75; 95% interval poverenja (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 vs. prokalcitoninu z = 1,054, p = 0,291; CRP vs. sCD14-ST-u z = 0,238, p = 0,812; prokalcitonin vs. 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 ta tri biomarkera.

Ključne reči:
biološki pokazatelji; c-reaktivni protein; deca; dijagnoza; presepsin protein, humani; senzitivnost i specifičnost; sepsa.

Introduction

According to the International Consensus Conference on Pediatric Sepsis held in 2005, sepsis could be defined as a joint occurrence of systemic inflammatory response syndrome with either microbiological confirmation of infection or clinical syndrome associated with a high probability of infection [1]. Apart from these clinical and microbiological criteria, several serum markers of inflammation are used for strengthening the diagnosis of sepsis; procalcitonin (PCT),

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C-reactive protein (CRP), and soluble CD14 subtype (sCD14-ST) ("presepsin") are among the most frequently used inflammatory markers. In a recent systematic review of diagnostic accuracy studies involving PCT, CRP, and sCD14-ST in a patient with sepsis, it was shown that the usefulness of these biomarkers for diagnosing sepsis remains debatable, as well as the significance of the difference in sensitivity and specificity between the three [2].

Diagnostic accuracy is especially problematic in children with sepsis, as recent meta-analysis reported high sensitivity (85%) but low specificity (54%) of PCT [3], and some other studies reported moderate sensitivity (87.5%) and specificity (70.9%) of CRP [4], and high sensitivity (94%) and specificity (100%) of sCD14-ST [5]. However, not all studies confirmed these figures in pediatric patients, thus the true role of these biomarkers for diagnosing sepsis, especially in newly admitted children, remains to be established [6].

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

Methods

The study was designed as a retrospective, observational cross-sectional study on children admitted to Pediatric Clinic in Kragujevac, Serbia (part of the Clinical Center of Kragujevac) under suspicion of sepsis during the first 6 months of 2017. The Inclusion criteria were the following: age below 18 years, admission to the hospital, values of PCT, sCD14-ST, and CRP measured upon admission, and suspicion of sepsis regardless of the source of the infection. The exclusion criteria were the following: septic shock, incomplete patient file, and antibiotic treatment during the last 15 days prior to admission. The study sample was not random but consecutive, as all patients 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 a peripheral vein on admission, and sera were separated by centrifugation and sent to the central laboratory of the Clinical Center of Kragujevac. PCT was measured by electrochemiluminescence method (COBAS, Roche), CRP by immunoturbidimetry (AU680 and AU400, Beckman Coulter Analyzers), and sCD14-ST by chemiluminescence (PATHFAST immunoanalyzer, 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 PCT, sCD14-ST, and CRP on admission, age, gender, 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 upon admission if not stated otherwise). The existence of sepsis was confirmed based on the criteria set by the International Consensus Conference on Pediatric Sepsis. The study was approved by the Institutional Review Board of Pediatric Clinic in Kragujevac.

The sample size was calculated based on the following assumptions: power of the study at least 80%, probability of type one error 0.05, the difference between the areas under the receiver operating characteristic (ROC) curves (AUC) tested by Student's *t*-test for independent samples, expected difference between the AUCs taken from the study of Julián-Jiménez et al. [7] (0.79 vs. 0.72) and standard deviation of AUCs measurement of 0.15. The calculation was performed using G-power software version 3.1 [8].

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 χ^2 test. AUCs were calculated for PCT, 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]. The significance of differences between the AUCs was tested by the De Long's method [10] using MedCalc software. All other calculations were performed by the Statistical Software for Social Sciences (SPSS) version 20.0.

Results

The study included 80 children, out of which 36 had sepsis according to the International Pediatric Sepsis Consensus Conference criteria. Characteristics of the groups with and without sepsis are shown in Table 1. The Kolmogorov-Smirnov test showed that, on admission, only white cell count and creatinine serum level in children without sepsis were normally distributed ($p = 0.200$ and $p = 0.210$, respectively), precluding the use of parametric tests for comparison of the study groups.

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

In the group of children without sepsis, 22 (50.0%) had a microorganism isolated: *Enterococcus* spp. 2 (9.1%), *Salmonella enteritidis* 1 (4.5%), *Streptococcus*

Table 1

Clinico-epidemiologic characteristics of the study groups on admission

Variable	Children with sepsis (n = 36)	Children without sepsis (n = 44)	Significance of difference
Age in months, median (IQR)	15 (1.3–56.0)	9 (1.25–41.0)	Mann-Whitney *U* test = 659.5; 0.200
Gender (m/f), n (%)	13/23 (36.1/63.9)	21/23 (47.7/52.3)	Pearson χ^2 test= 1.093; 0.296
Febrile, n (%)	29 (80.5)	25 (56.8)	Pearson χ^2 test = 5.086; 0.024*
White cells count ($\times 10^9$/L), median (IQR)	15.2 (11.1–18.9)	13.4 (10.8–18.8)	Mann-Whitney *U* test = 752.0; 0.699
Serum creatinine (μmol/L), median (IQR)	43.0 (39.0–48.0)	42.0 (34.0–47.5)	Mann-Whitney *U* test = 651.5; 0.392
CRP (mg/L), median (IQR)	76.6 (9.9–131.0)	17.1 (3.5–67.7)	Mann-Whitney *U* test = 450.5; 0.001*
Procalcitonin (ng/mL), median (IQR)	2.130 (0.144–5.220)	0.261 (0.108–0.615)	Mann-Whitney *U* test = 218.5; 0.001*
sCD14-ST (pg/mL), median (IQR)	259.0 (163.0–535.5)	189.0 (127.0–267.5)	Mann-Whitney *U* test = 498.0; 0.004*
Primary site of bacterial infection and diagnosis at discharge from the hospital, n (%)	Blood, sepsis – 14 (38.9) Cerebrospinal fluid, meningitis – 8 (22.2) Lungs, bacterial bronchopneumonia – 6 (16.7) Urine, pyelonephritis – 2 (5.6) Gut, gastroenterocolitis, bacterial – 6 (16.7)	Viral bronchopneumonia – 10 (22.7) Gastroenterocolitis, viral – 13 (29.6) Omphalitis – 5 (11.4) Cystitis – 4 (9.1) Viral pharyngitis – 6 (13.6) Not found – 6 (13.6)	na

IQR – interquartile range; m – male; f – female; CRP – C-reactive protein; *statistically significant difference; na – not applicable.

pneumoniae 1 (4.5%), *Klebsiella* spp. 1 (4.5%), *Staphylococcus* spp. 5 (22.8%), *Proteus* spp. 2 (9.1%), *Escherichia coli* 6 (27.4%), *Pseudomonas* spp. 2 (9.1%), *Herpes* virus 1 (4.5%) and *Enterobacter* 1 (4.5%). The isolation sites in this group were as follows: umbilical skin in 5 (22.8%) cases, blood in 2 (9.1%) cases, urine in 8 (36.4%) cases, tracheal aspirate in 3 (13.6%) cases, skin in 3 (13.6%) cases, and stool in 1 (4.5%) case.

ROCs for PCT, CRP, and sCD14-ST measured at the admission of the children to the hospital are shown in Figure 1.

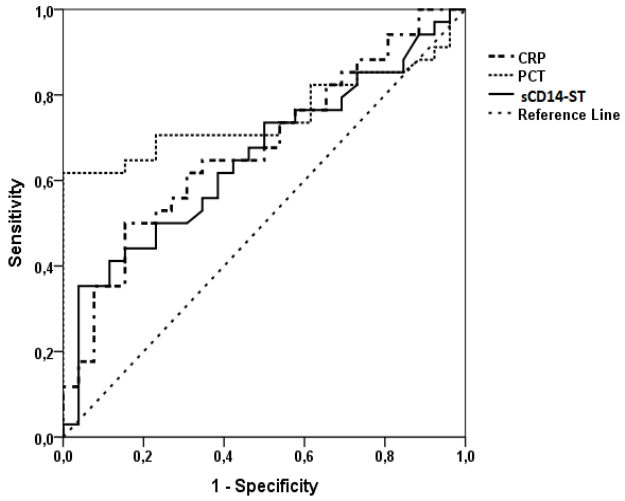

Fig. 1 – Receiver operating characteristic (ROC) curves for procalcitonin (PCT), C-reactive protein (CRP), and soluble CD14 subtype (sCD14-ST) if diagnosing sepsis in children on admission to a hospital.

PCT had the largest AUC (0.753 ± 0.065), followed by CRP (0.716 ± 0.057) and sCD14-ST (0.686 ± 0.061). The sensitivity and specificity of PCT, CRP, and sCD14-ST calculated for cut-off values determined by the Manhattan method are shown in Table 2.

Table 2

Cut-off values, sensitivity and specificity of procalcitonin (PCT), C-reactive protein (CRP), and soluble CD14 subtype (sCD14-ST) for diagnosing sepsis in children on admission to hospital

Parameter	PCT	CRP	SCD14-ST
Cut-off value	1.42 ng/mL	22.1 mg/L	319.5 pg/mL
Sensitivity (%)	61.8	63.9	55.6
Specificity (%)	100	75.0	88.6

Discussion

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

When compared with the 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 the diagnostic value of these biomarkers in children with sepsis. However, such results could be explained in one of the following ways: (1) due to the retrospective character of our study, the validity of

diagnosing sepsis, established by the consensus criteria, could not have been checked, and it depended on the performance of the attending physicians; (2) other studies could have overestimated the diagnostic accuracy since many of them included in the control group either healthy children or patients easily differentiated from those who had sepsis [11]. 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 [12], 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.

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 the presence of sepsis in children but rather taken into account together with the clinical picture. Further research in this area is necessary, especially on groups of children with a narrower age range (newborns, infants, toddlers, etc.).

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