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Original

New prediction model for diagnosis of bacterial infection in febrile infants younger than 90 days

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Due to non-specific clinical presentation in febrile infants, extensive laboratory testing is often carried out to distinguish simple viral disease from serious bacterial infection (SBI). Objective of this study was to compare efficacy of different biomarkers in early diagnosis of SBI in infants <90 days old. Also, we developed prediction models with whom it will be possible to diagnose SBI with more accuracy than with any biomarkers independently.

Febrile <90-day-old infants hospitalized in 2-year-period at Department of Pediatrics, University Hospital Centre Split with suspicion of having SBI were included in this study. Retrospective cohort analysis of data acquired from medical records was performed. Out of 181 enrolled patients, SBI was confirmed in 70. Most common diagnosis was urinary tract infection (68.6%), followed by pneumonia (12.9%), sepsis (11.4%), gastroenterocolitis (5.7%) and meningitis (1.4%). Male gender was shown to be a risk factor for SBI in this population (p=0.008). White blood cell count (WBC), absolute neutrophil count (ANC) and C-reactive protein (CRP) were confirmed as the independent predictors of SBI, with CRP as the best one. Two prediction models built by combining biomarkers and clinical variables were selected as optimal with sensitivities of 74.3% and 75.7%, and specificities of 88.3% and 86%. Evidently, CRP is a more superior biomarker in diagnostics of SBI comparing to WBC and ANC. Prediction models were shown to be better in predicting SBI than independent biomarkers. Although both showed high sensitivity and specificity, their true strength should be determined using validation cohort.

Key words: C-reactive protein, biomarkers, fever, infant, bacterial infection.

Fever is among the most frequent reasons for bringing children to the Emergency Department, especially infants during the first three months of life[1]. It is also the main reason for, often unrealistic and exaggerated, parental concern[2]. Despite ingrained parental fear, fever in infants mostly occurs due to the self-limiting viral infection which resolves without need for any specific therapy other than relieving the symptoms[3]. However, in significant percentage of cases underlying cause is bacterial and requires adequate antibiotic treatment to avoid possible complications.

Infants under three months of age, especially newborns, are more susceptible to infections because their immune system is still relatively immature and has not fully developed yet[4]. Also, setting a correct diagnosis is especially challenging because symptoms and signs of infection in children this age are most often non-specific, with elevated body temperature often as the only symptom, especially on examination at the initial stages of disease[5,6].

Because of that, extensive laboratory testing is often carried out, along with initiation of empirical intravenous antibiotic therapy consequently requiring hospitalization[5]. That practice, in addition to the increased risk of side-effects and allergic reactions, also raises the medical costs and increases bacterial resistance to most commonly used antibiotics[7]. Also, hospitalization should be avoided due to

the fact that infants are prone to the hospital-acquired infections during their stay. Therefore, it is necessary, during diagnostic workup, to successfully single out those febrile infants suffering from bacterial infections, especially serious bacterial infections (SBI), and start treating them with antibiotics on time.

Primary objective of this study was to compare efficacy and diagnostic value of white blood cell count (WBC), absolute neutrophil count (ANC), and C-reactive protein (CRP) in the early diagnosis of SBI in febrile infants younger than 90 days. Also, secondary objective was to develop a prediction model with whom it will be possible to diagnose SBI with more accuracy than using any of the biomarkers independently.

Material and Methods

This retrospective cohort study was performed at the Department of Pediatrics of the University Hospital Centre, Split. The Ethics Committee of the University Hospital Centre, Split approved the study (No. 2181-147-01/06/J.B.-16-2) and the parents of the enrolled infants were contacted and signed informed consent. The study included febrile infants aged 0-90 days, who were hospitalized between January 1st, 2014 and December 31st, 2015 with suspicion of having SBI. Other inclusion criteria were gestational age ≥ 37 weeks and rectally measured body temperature ≥ 38°C during the last 24 h. Exclusion criteria were antibiotic treatment during the previous 48 h, previously known immunodeficiency, vaccination during the 5 days before admission, chronic diseases and conditions in medical history and transfer from other medical institutions.

Based upon medical charts review, patients were divided into two groups: a group of patients with serious bacterial infection (SBI) and a group of patients without a serious bacterial infection (nonSBI). The SBI group included patients who met the same criteria for SBI already described in previous studies. Those criteria were: (a) sepsis/bacteremia microbiologically confirmed by positive blood culture or bacterial meningitis diagnosed by positive cerebrospinal fluid culture; (b) urinary tract infection (UTI) confirmed by positive urine culture ($>10^5$ colony forming units/ml of a single microorganism in a sample collected by sterile method); (c) chest radiographic features consistent with pneumonia (lobar consolidation or an infiltrate) confirmed by pediatric radiologist; (d) bacterial gastroenteritis confirmed by positive stool culture; (e) cellulitis with an appropriate physical examination[8,9]. Patients with other discharge diagnoses were included in the nonSBI group. None of the patients received pneumococcal or meningococcal vaccine.

By using available medical records, for each enrolled patient a series of data were collected: gender, birth weight and birth length, age at the time of admission, body weight and length, maximum measured body temperature and the results of tests performed at the time of admission, including complete blood count (CBC) with differential, CRP, blood cultures, urine cultures, coprocultures, cerebrospinal fluid cultures and the results of viral antigen isolation from blood samples, stool or nasopharyngeal lavage (RSV, rotavirus and adenovirus). Using WBC and the number of segmented and non-segmented neutrophils, absolute neutrophil count (ANC) was calculated for each patient with the following formula:

ANC=0.01xWBC x (non-segmented neutrophils (%) + segmented neutrophils (%)

Statistical analysis

Differences between continuous variables were tested for statistical significance using Mann Whitney test. The values of categorical variables were compared between groups using Chi-square test. For all statistical calculations, the value of $p<0.05$ was considered statistically significant. Optimal sensitivity and specificity of biomarkers were determined from the ROC curves using Youden indicator. Positive (LR+) and negative (LR-) likelihood ratios were also used as a measure of diagnostic usefulness. ROC analysis and Mann Whitney test were carried out using GraphPad Prism 7.6 (GraphPad Software, La Jolla, California, USA). Logit function was used for logistic regression and the best model was chosen by information theoretic approach using Akaike information criterion (AIC). Logistic regression was performed using XLSTAT application (Addinsoft, New York, NY, USA).

Results

During the observed period of time, 5141 children aged 0-18 years were hospitalized and 790 of them (15.4%) were infants up to 90 days old. Of them, 187 (23.7%) were hospitalized for febrile illness with suspicion of having SBI. Having met the inclusion criteria and none of exclusion criteria, 181 of them were included in the study.

Based upon the discharge diagnoses, subjects were allocated to SBI group (n=70) or nonSBI group (n=111). No subjects remained unallocated.

Table I shows demographic characteristics of study groups and they were comparable for age, body weight and body length. Significant predominance of male gender was found in SBI group. Statistically significant difference between the groups was also found for birth weight and birth length.

The most common diagnosis in SBI group was urinary tract infection (68.6%), followed by sepsis (11.4%), meningitis (1.4%), pneumonia (12.9%) and gastroenterocolitis (5.7%). The most common isolated causative pathogen was *Escherichia coli*, which was found in 81.3% of patients with urinary tract infection and in 60% of all patients in SBI group. Other isolated pathogens were: beta-hemolytic group B Streptococcus (GBS, *Streptococcus agalactiae*), *Enterobacter cloacae, Klebsiella pneumoniae* (ESBL+), *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus epidermidis* (MRSE), unfermentable gram-negative bacilli and coagulase-negative *Staphylococcus sp.*

In the SBI group, WBC, ANC, CRP and maximum measured body temperature were found statistically significantly elevated (Fig. 1). Sensitivity, specificity and the calculated optimal cut-off value of biomarkers and maximum measured body temperature are shown in Table II. CRP proved to be the most useful biomarker for differentiation between SBI and nonSBI groups, with both sensitivity and specificity of 80% at the cut-off value of 13.3 mg/L. The diagnostic values of biomarkers and maximum measured body temperature are shown using ROC curves (Fig. 2).

The secondary objective of this study was, using a combination of studied biomarkers and demographic indicators, to develop a prediction model in which we followed the principle of

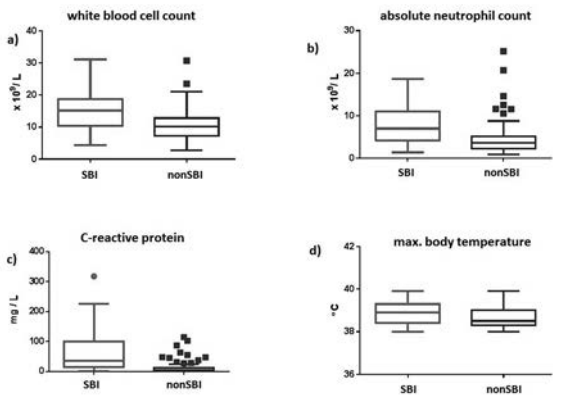

Fig. 1. Display of biomarker findings and maximum measured body temperature by subject groups using box and whiskers plot
(a) White blood cell count is higher in SBI group (median 15.2 x10^9/L, IQR 10.40-18.73 in SBI group as opposed to median 10.2 x10^9/L, IQR 7.30-12.80 in nonSBI group; p<0.0001) **(b)** Absolute neutrophil count is higher in SBI group (median 6.97 x10^9/L, IQR 4.21-10.98 in SBI group as opposed to median 3.66 x10^9/L, IQR 2.32-5.18 in nonSBI group; p<0.0001) **(c)** C-reactive protein (CRP) level is higher in SBI group (median 35.7 mg/L, IQR 14.25-100.2 in SBI group as opposed to median 4.2 mg/L, IQR 1.7-11.9 in nonSBI group; p<0.0001) **(d)** Maximum measured body temperature is statistically significantly higher in SBI group (median 38.9°C, IQR 38.4-39.3 in SBI group as opposed to median 38.5°C, IQR 38.3-39.0 in nonSBI group; p=0.0257)
SBI – serious bacterial infection group; nonSBI – patients without serious bacterial infection group; IQR – interquartile range

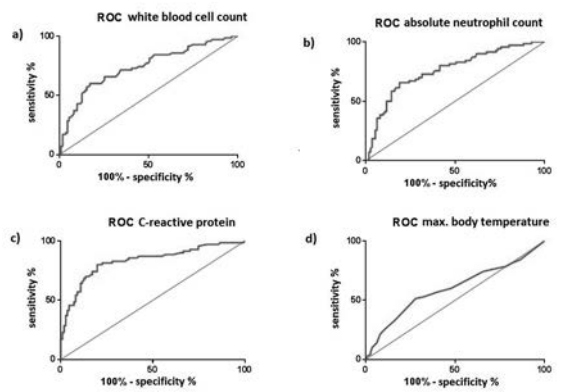

Fig. 2. Diagnostic value of biomarkers and maximum measured body temperature in predicting serious bacterial infection shown using receiver operating characteristic (ROC) curves
(a) AUC for white blood cell count is 0.74 (95%CI 0.66-0.82), **(b)** AUC for absolute neutrophil count is 0.76 (95%CI 0.69-0.83), **(c)** AUC for C-reactive protein (CRP) level is 0.83 (95%CI 0.77-0.9), **(d)** AUC for maximum measured body temperature is 0.6 (95%CI 0.51-0.69)
AUC- area under the curve, CI- confidence interval

parsimony, i.e. Ockham's razor, keeping in mind the future validation of this model. The model using a combination of CRP, WBC, gender and maximum measured body temperature was the one with the greatest Akaike weight. However, model with same variables, just without maximum measured body temperature, is equally good. Given sample size, we were not able to decisively show whether maximum measured body temperature adds more accuracy to the simpler model or it is just a superfluous variable (Table III and Table IV). Both models yielded similar diagnostic characteristics when applied to the patient cohort on which they were developed. More complex model (model No. 10) yielded LR+ of 6.35 (95% CI 3.25-13.13) and LR- 0.29 (95% CI 0.47-0.17) at the cut-off value of 0.4 (40%) probability for SBI. Simpler model (model No. 8) showed LR+ of 5.4 (95% CI 3.02-11.83) and LR- of 0.28 (95% CI 0.45-0.16) at the cut off value of 0.36 (36%) probability for SBI.

Discussion

The aim of this study was to determine the diagnostic value and effectiveness of the most common biomarkers in clinical practice. We have shown that WBC, ANC and CRP are significantly higher in the group of infants who suffer from SBI, compared to those without SBI. The CRP seems to have higher diagnostic value than ANC and WBC. Various studies confirm our results that CRP poses greater diagnostic value versus WBC[8,10-12] and ANC[10,13]. Only one study has shown better performance of ANC than CRP.[14]

The optimal WBC cut-off value of $13.4x10^9$/L determined in this study is somewhat lower than the value $15x10^9$/L commonly used in other studies[8,10,11,13,15-18]. However, with its sensitivity of 60% and specificity 83%, the WBC in this study proved to be more sensitive and equally specific, comparing to results from those studies. Still, our results also confirm that it does not have sufficient diagnostic value to be used independently as a predictor of SBI and it is recommended to be used in combination with other biomarkers. With standalone use, 40% of children would be a falsely classified as negative for SBI.

Similar conclusion goes for ANC, as well. ANC has shown the diagnostic value similar to that of WBC, but slightly more sensitive, with a sensitivity of 65.7% and specificity of 81% for the cut-off value $5.7x10^9$/L. Diagnostic value coincides with the results of studies conducted by other researchers, but using the cut-off values of 10000/ mm^3 and 10600/ mm^3.[13,14]

Given that there is no consensus on the specific cut-off value for CRP that should be used to distinguish high and low risk of SBI in infants with fever, each author chooses the value to be used. Typically, in studies it varies in the range from 20 to 70 mg/L[19], provided that for the population up to 90 days old most frequently used value is 20 mg/L[8,11,12,20]. Our cut-off value of 13.3 mg/L is somewhat lower than theirs, but close to the one used in a research by Zarkesh et al.[10], whose diagnostic value of CRP (sensitivity 81.6% and specificity 89.8%) shows results comparable to ours.

Similar applies to the maximum measured body temperature. Different cut-off values which are considered a fever in various studies also represent a problem[21]. Although this study demonstrates that fever is statistically

Table I. Demographic Characteristics of Study Subjects (n=181).

	SBI *(n=70)*	Non-SBI *(n=111)*	P value
Gender (male, female) (%)	71.14%, 27.14%	53.15%, 46.84%	0.008
Age (days)*	46.50 (20.00 to 72.00)	47.00 (29.00 to 70.00)	0.41
Body weight (g)*	4950 (4088 to 5985)	4780 (4250 to 5600)	0.53
Body length (cm)*	57.25 (54.00 to 60.00)	57.00 (54.00 to 60.00)	0.51
Birth weight (g)*	3800 (3325 to 4103)	3470 (3120 to 3800)	0.0011
Birth length (cm)*	52.00 (50.00 to 53.00)	51.00 (50.00 to 52.00)	0.025

SBI: serious bacterial infection group; Non-SBI: patients without serious bacterial infection group; IQR: interquartile range. Data is presented as median (IQR)

Table II. Diagnostic Properties of Biomarkers and Maximum Measured Body Temperature.

Biomarker	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratios	
				Positive	Negative
White blood cell count	13.4 x 10^9/L	60% (47.59-71.53%)	82.88% (74.57-89.37%)	3.5 (1.87-6.72)	0.48 (0.38-0.7)
Absolute neutrophil count	5.7 x 10^9/L	65.71% (53.4-76.65%)	81.08% (72.55-87.89%)	3.4 (1.9-6.33)	0.42 (0.26-0.64)
C-reactive protein	13.3 mg/L	80% (68.73-88.61%)	80.81% (71.54-87.14%)	4.02 (2.4-6.89)	0.25 (0.13-0.44)
Maximum body temperature	38.85 °C	51.43% (39.17-63.56%)	72.07% (62.76-80.17%)	1.84 (1.05-3.2)	0.67 (0.45-0.97)

CI: confidence interval

significantly higher in infants with SBI, maximum measured body temperature as an independent indicator has poor diagnostic predictive value. Similar results are shown in a French study[22]. However, in conjunction with other biomarkers, it still contributes to improving the accuracy of detection of SBI.

In the studied population of hospitalized children, the most frequent SBI was urinary tract infection, with the most common isolated causative pathogen being Escherichia coli. This is consistent with results of previously published studies[9,10,21,23,24].

Our results have showed significant predominance of male gender in SBI group, with male to female ratio 2.6:1, as opposed to nonSBI group where gender is equally distributed. These findings imply that male gender is a risk factor for the development of SBI in infants up to 90 days old. Other authors suggest a similar conclusion[1,22,25-27], so it is important to take gender into consideration during the evaluation of febrile infants. Although most studies found no link between gender and SBI[10,12,20,28-31], that discrepancy should be considered from the epidemiological and population point of view. These studies were generally carried out in countries with widespread circumcision of young boys. Various previous studies have shown that this process significantly, up to 10 times, reduces the incidence of urinary tract infections in infants younger than three months[32-35]. As our research, as well as others[9,10,21,23,24], showed that urinary tract infection is the most common SBI in this population of children, we believe that is the cause of discrepancy in the results. Therefore, uncircumcised boys aged up to three months, such as our patients, are at increased risk for the development of SBI. Also, the reason may be a relatively small sample size in this study.

The differences in birth weight and length between the groups, although statistically significant, might reflect that males are overrepresented in SBI group so we do not think that they play a role in risk stratification. This conclusion is in accordance with the results of other studies[9,27].

Given the non-specific clinical presentation, invasiveness of the current diagnostic gold standards and the need for an early start of antibiotic treatment in infants where it is

Table III. Optimal Model Selection Using Akaike Information Criterion (AIC).

Model no.	Model variables	Deviance	AIC	Number of variables	ΔAIC	wAICi	Evidence ratio
1	WBC	210.04	214.38	1	38.86	$1.265 \cdot 10^{-9}$	$2.74 \cdot 10^{8}$
2	ANC	213.06	217.06	1	41.54	$3.309 \cdot 10^{-10}$	$1.05 \cdot 10^{9}$
3	CRP	181.24	185.24	1	9.72	0.003	129
4	CRP, gender	177.22	183.22	2	7.69	0.007	46.9
5	CRP, WBC	173	179.08	2	3.55	0.059	5.91
6	CRP, ANC	176	182.26	2	6.74	0.012	29
7	CRP, ANC, WBC	173.07	181.07	3	5.55	0.022	16.1
8*	CRP, WBC, gender	167.78	175.78	3	0.26	0.305	1.14
9	CRP, ANC, WBC, gender	167.73	177.73	4	2.21	0.115	3.0
10*	CRP, WBC, gender, Tmax	165.52	175.52	4	0	0.347	
11	CRP, ANC, WBC, gender, Tmax	165.47	177.48	5	1.96	0.130	2.66

WBC: white blood cell count, ANC: absolute neutrophil count, Tmax: maximum measured body temperature, ΔAIC: difference in AIC between considered model and model with minimum AIC, wAICi: Akaike weight. *: models chosen as optimal

required, the role of biomarkers in the diagnosis of febrile infants up to three months of age is extremely important, primarily to distinguish between bacterial and viral infections. Although there are numerous biomarkers, some of the most commonly used being: WBC, ANC, CRP and procalcitonin (PCT), there is still no biomarker sufficiently sensitive and specific to determine with certainty whether the infant is suffering from SBI or not.

Therefore, the secondary objective of this study was, using a combination of evaluated biomarkers and demographic characteristics, to develop a prediction model which will be more efficient in diagnosing SBI. Keeping in mind the future validation of the model, we applied the principle of parsimony, i.e. Ockham's razor, and selected the models with the minimum number of parameters and maximum specificity and sensitivity. Two selected models were shown to be superior both in terms of model selection and LR+ when compared to CRP alone, thus suggesting their potential use as tools to confirm candidate diagnosis. On the other hand, LR- values are very similar between any of the models and CRP. However, in order to determine true diagnostic values of selected models and biomarkers (with their proposed cut-offs) a study on validation cohort should be conducted.

CRP is a more superior biomarker in diagnostics of SBI comparing to WBC and ANC. Prediction models were shown to be better in predicting SBI than independent biomarkers. Although both showed high sensitivity and specificity, their true strength should be determined using validation cohort.

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Table IV. Parameters and Diagnostic Characteristics of the Best Models.

Model	Parameter	Odds ratio for parameter (95% CI)	Cut-off value	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Likelihood ratio	
						Positive (95% CI)	Negative (95% CI)
No. 10	CRP	1.031 (1.016-1.046)	40% probability	74.3 (62.4-84)	88.3 (80.8-93.6)	6.35 (3.25-13.13)	0.29 (0.17-0.47)
	WBC	1.142 (1.052-1.239)					
	Gender (male)	2.734 (1.204-6.210)					
	Tmax	1.783 (0.836-3.806)					
No. 8	CRP	1.033 (1.017-1.049)	36% probability	75.7 (64-85.2)	86 (78.7-92.2)	5.4 (3.02-11.83)	0.28 (0.16-0.45)
	WBC	1.131 (1.044-1.226)					
	Gender (male)	2.499 (1.120-5.577)					

WBC: white blood cell count, ANC: absolute neutrophil count, Tmax: maximum measured body temperature, CI: confidence interval

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