Biomarkers to diagnose sepsis

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Abstract

Background: Sepsis is a life-threatening organ dysfunction that arises when a host responds insufficiently to an infection as bacteria enter the bloodstream. In recent years, SOFA scoring system has been used to identify poor organ functioning. Microbiological blood tests represent a gold standard in sepsis diagnostics. Reliable biomarkers for early detection of sepsis would greatly facilitate rapid and efficient treatment of sepsis.

Methods: In a prospective non-interventional study we studied the diagnostic value of C-reactive protein (CRP), procalcitonin (PCT), neutrophil CD64 index, neutrophil granulocyte count and immature neutrophil count in patients with sepsis and patients with severe infection without sepsis. A total of 46 consecutive intensive-care-unit patients admitted for severe infection and 10 healthy controls were included. The patients were treated routinely according to the principles of good clinical practice.

Results: Statistically significant differences between the two groups of patients have been established for the CD64 index, the PCT and the immature neutrophil count, whereas the differences in the CRP and the neutrophil granulocyte count are statistically non-significant. The highest diagnostic values were measured for the immature neutrophil count (AUC 0.91) and PCT (AUC 0.84). The combination of biomarkers has been shown to have same predictive values as the immature neutrophil count and the PCT.

Conclusions: The CD64 index was one of the less discriminating for drawing distinction between sepsis and severe infection without sepsis in intensive-care–unit patients.

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1. Background

Sepsis is one of the commonest causes of death due to infection. In the USA hospitalizations for septicemia or sepsis increased from 621,000 in 2000 to 1,141,000 in 2008 (1). In Slovenia, the incidence of severe sepsis in adults is estimated at 118 cases per 100,000 inhabitants (2).

The sepsis mortality is between 17.4 % and 42.9 % (3). In developed countries mortality due to sepsis exceeds the mortality due to myocardial infarction (4). Sepsis is the most expensive condition treated in U.S. hospitals, costing more than $20 billion in 2011, and increasing on average by 11.9 % annually (5).

A consensus conference in 1991 defined "sepsis" as the combination of an infection with two or more features of the so-called "systemic inflammatory response syndrome" (SIRS) (6): altered body temperature > 38 °C or < 36 °C, ele-

vated pulse rate, elevated respiratory rate and abnormal white blood cell count 12.0×10^9/L or $< 4.0 \times 10^9$/L (7). However, this definition lacked specificity. Therefore, an updated definition defines sepsis as a systemic organ failure due to inappropriate immune response to the inciting microorganism (8).

For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 or more points (Table 1) (9).

Patients with suspected infection who are likely to have a prolonged ICU stay or to die in hospital can be promptly identified using qSOFA, i.e., alteration in mental status, systolic blood pressure ≤ 100 mm Hg, or respiratory rate ≥ 22/min (8,9). The mortality rate depends on the severity of illness. In septic shock the hospital mortality exceeds 50 % (10,11).

Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality (12). Patients with septic shock can be identified by persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg and by the serum lactate level > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation (8,13).

Table 1: SOFA score. (9).

		Score				
System		**0**	**1**	**2**	**3**	**4**
Respiration	PaO_2/ FiO_2, mmHg (kPa)	> 400 (> 53.3)	< 400 (< 53.3)	< 300 (< 40)	< 200 (< 26.7) with respiratory support	< 100 (< 13.3) with respiratory support
Coagulation	Platelets, $\times 10^3$/ µL	≥ 150	< 150	< 100	< 50	< 20
Liver	Bilirubin, (mol/L)	< 20	20–32	33–101	102–204	> 204
Cardiovascular		MAP > 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine (any dose) [a]	Dopamine 5.1–15 or epinephrine < 0.1 or norepinephrine < 0.1 [a]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1 [a]
Central nervous system	Glasgow Coma Scale	15	13–14	10–12	6–9	< 6
Renal	Creatinine (µmol/L)	< 110	110–170	171–299	300–440	> 440
	Diuresis (mL/d)				< 500	< 200

Legend: PaO_2 – Partial pressure of oxygen; FiO_2 – Fraction of inspired oxygen; MAP – Mean arterial pressure; a – Catecholamine doses are given as µg/kg/min for at least 1 hour

The gold standard for the diagnosis of sepsis is a microbiological examination of blood. Whenever possible, two to four sets of blood specimens should be collected from different venipuncture sites. For most bacteria, the median time to positivity of hemoculture is 12 to 36 hours, whereas for certain bacteria and fungi this interval is even longer. When using traditional microbiological methods, further 48 to 72 hours are needed to identify the causative agent of sepsis and define its susceptibility to antimicrobials (14-16).

Treatment of sepsis has to be started early with broad-spectrum antibiotics, which is not only expensive, but also leads to multiple drug-resistant bacteria. Therefore, biomarkers with high predictive value in the diagnosis of sepsis are needed (17). One of the earliest biomarkers used to diagnose infection is C-reactive protein (CRP), so named for its ability to precipitate from serum in the presence of pneumococcal cell wall C-polysaccharide. CRP is an acute-phase reactant found in the blood that is produced by hepatocytes in the setting of infection or tissue injury. CRP production is triggered by cytokines (IL-1, IL-6 and TNF-α). Plasma CRP levels increase within 6–12 hours after an inflammatory stimulus and peak at around 48 h. It has a short half-life (16,18).

Procalcitonin (PCT) is a precursor of the hormone calcitonin, which is produced in the thyroid to regulate serum calcium concentrations. Under normal conditions, the thyroid gland is the only tissue that produces PCT and serum levels are very low (17). During infection, PCT is produced by other cells as well and its plasma levels increase. Although the exact stimuli that mediate PCT secretion are unknown, evidence suggests that early inflammatory signals such as TNF-α, IL-1β and IL-6 are involved (19). Elevations in PCT are generally observed before CRP rises and it peaks within a much shorter time frame. Additionally, when the patient responds to therapy, PCT levels return to normal much faster than CRP (20).

CD64 is a neutrophil cell surface marker also known as FcγR1 (21). It is the first of the three receptors on the neutrophil whose function is to bind the Fc portion of IgG (hence γ) antibodies that facilitate bacterial opsonization and phagocytosis (22). CD64 is constitutively expressed on neutrophils, albeit at low levels, until the immune system encounters an infectious agent whereupon the surface expression of CD64 is highly upregulated (23).

In the absence of stimulating factors, the CD64 expression decreases within 48 hours and normalizes within seven days (24).

We aimed to compare the diagnostic accuracies of different biomarkers, namely C-reactive protein (CRP), procalcitonin (PCT), the neutrophil CD64 index, neutrophil granulocyte count and immature neutrophil count in the diagnosis of sepsis.

2. Methods

We sought to enroll all admissions due to severe infection to the general intensive care unit (ICU) at the University Clinic of Pulmonary and Allergic Diseases Golnik between January 2009 and February 2010. Ten healthy subjects served as controls. The study was approved by the Slovenian Medical Ethics Committee (reference number 63/05/04). All data were anonymized. Blood was collected from patients within six hours of their admission to the unit.

Patients were treated according to good clinical practice. Most of the patients received antibiotic therapy before

admission to ICU. On admission, blood was drawn for routine blood tests (CRP, PCT, blood count) and additionally for the neutrophil CD64 index. In the analysis we included only those blood test results which were determined on the same day as the neutrophil CD64 index. Treating physicians were blind to the value of the neutrophil CD64 index.

Patient records were examined to determine the clinical outcomes of hospitalizations and assigned a clinical score denoting the likelihood of sepsis or bacterial infection without sepsis. Thereafter, the patients were assigned either to the sepsis group (positive blood cultures or the diagnosis of sepsis upon discharge from the ICU) or the infection without sepsis group. The CRP concentration was determined using the immunoturbidimetric assay (Roche Diagnostics) on the Hitachi analyzer, and the PCT concentration by the electrochemiluminescence method (Roche Diagnostics). CD64 expression on neutrophils was measured using the flow cytometer FACSCalibur (Becton Dickinson, NY, USA) and the Leuko64 kit (Trillium Diagnostics, LLC, Maine, USA)., This test kit includes fluorescent beads and antibodies to CD64 and CD163. The patient's sample provided both an internal negative control (lymphocytes) and an internal positive control (monocytes). The lymphocyte population was defined by forward and side scatter characteristics, and was distinct from granulocytes. Surface CD163 staining along with forward and side scatter characteristics were used to define the monocyte population. The neutrophil CD64 index was then calculated using the ratio of the mean fluorescent intensity of the cell populations to that of the beads.

Continuous variables are presented as the mean ± SD for normally distributed data or the median (interquartile range (IQR)) for non-normally distributed data. Comparisons of group differences for continuous variables were performed by Mann-Whitney test. The p value of < 0.05 was considered to be statistically significant. Categorical data were presented as the number of patients in each category with corresponding percentages. The significance of differences in proportions was tested by Chi-square test.

The performance of each biomarker for identifying sepsis was assessed as the area under a receiver operating characteristic (ROC) curve (AUC). For each biomarker ROC curves were used to derive cut-offs for sensitivity and specific-

Table 2: Groups of patients.

Patients	Number (women, men)	p	Age (years) median, interquartile range	p	Mortality
Sepsis	21 (11, 10)	NS	70 (55, 76)	*** for healthy group, NS for other	4 (19 %)
Severe infection without sepsis	25 (12, 13)	NS	68 (56, 77)	*** for healthy group, NS for other	7 (28 %)
Healthy controls	11 (5, 6)	NS to other groups	32 (29, 35)	*** for other	0 (0 %)

*Legend: *** – $p < 0.01$; NS – statistically non-significant difference.*

ity to distinguish sepsis from infection without sepsis.

The biomarker was highly discriminatory if the AUC was > 0.90 (25).

The discriminatory value of a biomarker was defined as the value higher than the highest value found in patients with infection without sepsis, and the minimal value as the highest biomarker value still excluding the diagnosis of sepsis.

3. Results

We included 46 patients and 11 healthy controls (Table 2).

In the group of sepsis there were 21 patients (47.6 % of men), the mean age was 70 (55, 76) years. Hemocultures were positive in 13 patients (62 %). The causes of infection were pneumonia in 14 patients (in 11, in 1, in1, unknown in 1 patient), urinary infection in 4 patients (in 3 patients, unknown in 1), endocarditis in 1 patient (, leg ulcer in 1 patient (, infection of the central venous canal in 1 patient (. All patients required inotropic and vasopressor treatment. Seven patients had severe comorbidity (advanced COPB in 2 and heart failure in 5 patients). Four (19 %) patients died.

In the group of severe infection without sepsis there were 25 patients (52 % of men), the mean age was 68 (56, 77) years. The causes of infection were: pneumonia in 13 patients (in 5, in 1, in 1, and unknown cause in 6 patients), acute exacerbation of COPB due to different infections in 5 patients, empyema in 3 patients, tuberculosis in 1, erysipelas in 1, acute bronchitis caused by in 1, and acute worsening of polymyositis due to respiratory infection in 1 patient. In 17 patients severe comorbidities were observed (COPB in 10, lung fibrosis in 2 and heart failure in 5 patients). Seven (28 %) patients died.

There were no statistically significant differences by the gender ratio and age between the groups. In the group with infection without sepsis there was a significantly higher number ($p < 0.05$) of patients with severe comorbidities. Although more patients died in the group of severe infection without sepsis, the

Table 3: Diagnostic accuracy of measured biomarkers in patients with sepsis compared to patients with infection without sepsis.

Biomarkers	Discriminatory value	Minimum value	Sensitivity	ROC AUC	95 % CI for sensitivity	95 % CI for specificity
CD64	7,54	1,2	14,3 %	0,78	3–36,3 %	86,3–100 %
7.54	1.2	14.3 %	0.78	3 %–36.3 %	86.3 %–100 %	85,8–100 %
CRP	339.6 mg/L	29.2 mg/L	37 %	0.56	11.3 %–52.2 %	85.8 %–100 %
PCT	14.8 µg/L	0.17 µg/L	66.7 %	0.84	30.8 %–78.5 %	76.8 %–100 %
Neutrophil granulocyte count	19.8×10^9/L	1.44×10^9/L	29.4 %	0.69	10.3 %–56.0 %	83.2 %–100 %
Immature neutrophil count	1.18×10^9/L	0.23×10^9/L	53.3 %	0.91	26.6 %–78.8 %	71.5 %–100 %

Legend: Discriminatory value – value higher than the highest value found in patients with infection without sepsis; Minimal value – the highest biomarker value still excluding sepsis diagnosis in this study; Sensitivity – proportion of patients with sepsis with a biomarker above discriminatory value; ROC AUC – area under the ROC curve; 95 % CI – 95 % confidence interval.

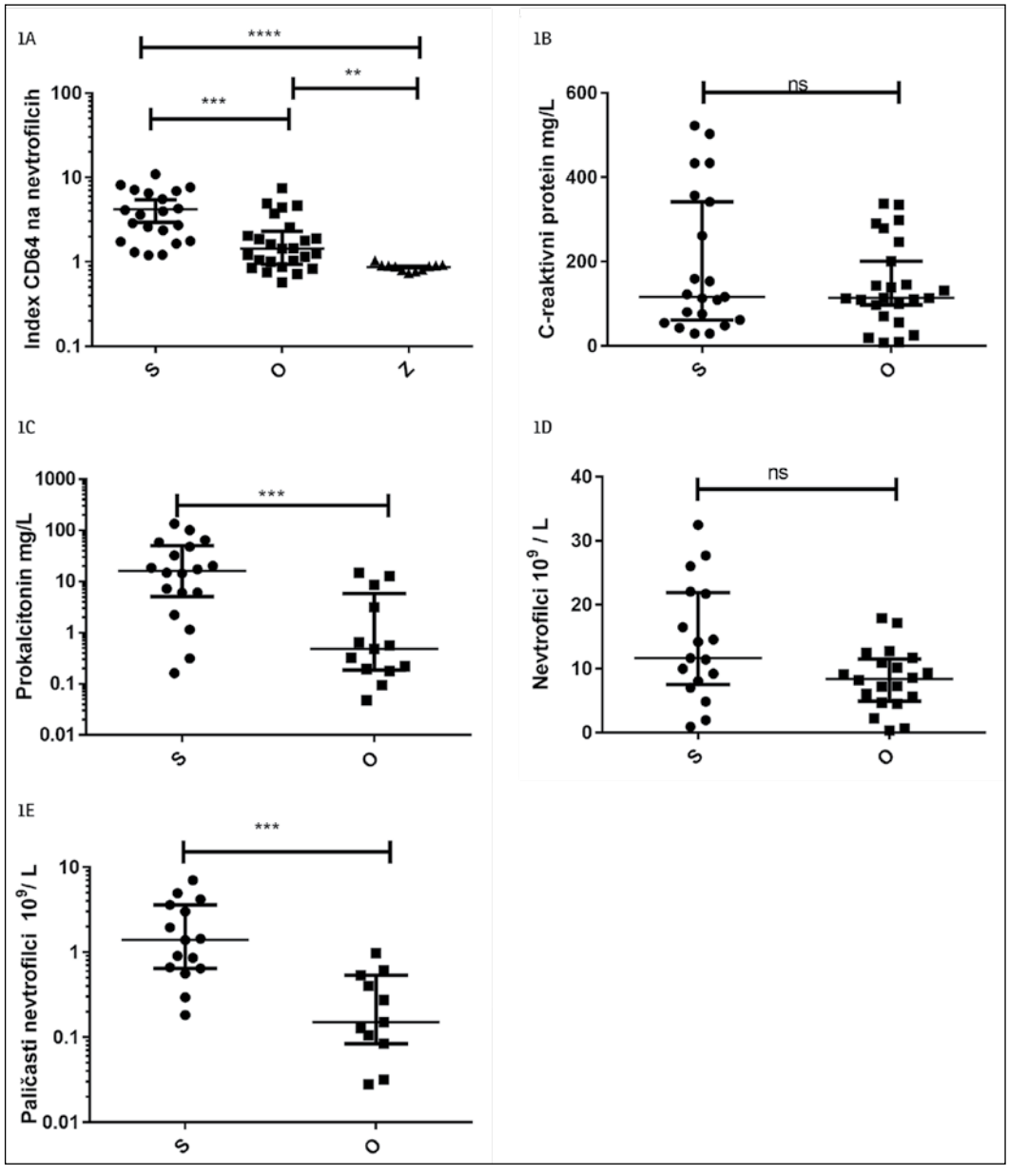

Figure 1A–E: Sepsis biomarkers in patients with sepsis (S) and in patients with infection without sepsis (O) (healthy controls (Z) used only for neutrophil CD64 index).
*Legend: Longer line shows the median, shorter line shows the interquartile range; ns – statistically non-significant difference, **** – p < 0.01; *** – p < 0.05.*

difference was not statistically significant.

The group of 11 healthy controls (55 % of men), was significantly younger compared to both groups of patients (mean age 32 (29, 35) years).

The values of biomarkers in all three groups are shown in Figures 1A-E.

Diagnostic accuracies of the measured biomarkers are shown in Table 3.

The biomarkers above the discriminatory value in the patients with sepsis are shown in Table 4.

In 13 of the 21 patients, at least one biomarker was above the discriminatory value. In 10 patients more markers

were above the discriminatory value at the same time, whereas in three patients only one marker was above the discriminatory value. Some patients did not have all markers determined on the same day as the CD64 index; those were excluded from the analysis. The combination of biomarkers was more likely to distinguish sepsis from infection without sepsis than a single marker.

4. Discussion

In this study we compared the diagnostic value of some biomarkers of inflammation to establish the diagnosis of sepsis. We were particularly interested in the diagnostic accuracy of the neutrophil CD64 index, which has been considerably studied in the diagnosis of sepsis in children (23,26) and in distinguishing diseases that are clinically dif-

Table 4: Biomarkers above discriminatory value in patients with sepsis.

Patient	CD64 Index > 7.54	CRP > 339.6 mg/L	Procalcitonin > 14.8 µg/L	Neutrophil granulocyte count > 19.8 × 10^9/L	Immature neutrophil count > 1.18 × 10^9/L
1	*	*	*	*	*
2		*	*	*	*
3	*	*	nm		
4		*	*		*
5		*	*		
6		*	*		
7	*		*	*	*
8			nm	*	*
9			*	*	*
10			*		*
11					*
12			*		nm
13			*	nm	nm
14			nm		nm
15					nm
16				nm	nm
17				nm	nm
18				nm	nm
19					
20					
21					

*Legend: * – Biomarker above discriminatory value; nm – Not measured; Empty field – Biomarker below discriminatory value.*

ficult to distinguish between themselves, for example, sepsis from severe infection without sepsis. Therefore, we also divided the patients into two groups based on the clinical picture and the course of disease, the laboratory and the microbiological findings, into a group of sepsis and a group of infection without sepsis.

In the sepsis group, similarly to other studies (22,27,28), we included patients with positive hemoculture and those with a proven infection, who were diagnosed with sepsis by a physician, and patients who needed inotropic and vasopressor support. Patients with severe infection without sepsis were predominantly the patients with advanced lung and heart disease in whom the infection further impaired the functioning of these organs. The incidence of significant comorbidities was statistically higher in this group compared to the group of patients with sepsis. In the group of patients without sepsis, pneumonia was frequently caused by an influenza virus causing a severe course and high mor-

Table 5: Summary of studies on diagnostic values of neutrophil CD64 index for sepsis amongst adults (21).

Study (publication year)	Number of patients	Patients	Compared group	Sensitivity / Specificity	ROC AUC
Davis (2005)	160	Random patients with SIRS, infection or sepsis	Patients with severe tissue damage	94 %/85 %	-
Davis (2006)	100	Random patients with SIRS, infection or sepsis	Healthy	88 %/77 %	-
Livaditi (2006)	47	Sepsis, severe sepsis, septic shock	None	-	-
Cardelli (2008)	112	Sepsis proven by positive blood culture, suspected sepsis, negative blood culture	Healthy	96 %/95 %	0.97
Danikas (2008)	32	Severe sepsis, septic shock	Healthy	60 %/100 %	0.892
Lobreglio (2008)	30	Sepsis proven by positive blood culture	Patients without infection	92 %/100 %	-
Hsu (2011)	66	Severe sepsis, septic shock, SIRS with acute respiratory insufficiency	SIRS with acute respiratory insufficiency	89 %/96 %	0.928
Gamez-Dias (2011)	361	Patients in emergency department suspected to have sepsis (infection, fever, delirium, hypotension)	Patients without sepsis proven later	66 %/65 %	0.706
Gerrits (2013)	75	Sepsis	SIRS after surgery, healthy	100 %/95 %	
Icardi (2009)	119	Patients with infection	Patients without infection	95 %/89 %	
Žargaj	46	sepsa s pozitivno hemokulturo ali dokazana okužba, s strani zdravnika postavljena diagnoza sepse in potreba po inotropni podpori.	huda okužba brez sepse	14,3 %/40 %	0,78
(2016)	46	Sepsis proven by positive blood culture or patients with infection, doctor's diagnosis of sepsis and a need for inotropic support	Patients with severe infection	14.3 %/40 %	0.78

tality. This can explain high mortality in patients with infection without sepsis.

In our study, the serum CRP concentration in the patients with sepsis was not significantly higher than in the patients with infection without sepsis. The AUC was 0.56 in the patients with sepsis compared to the patients with infection without sepsis, which means that the test had a little diagnostic value to discriminate between both conditions. Most studies have proved that PCT is a better test for sepsis than CRP (29). Patil noted that serum procalcitonin concentrations in adult patients with positive hemoculture were higher (8.66 ng/mL) than in patients with negative hemoculture (1.03 ng/mL) ($p < 0.001$) (30). Llewelyn summed up that the procalcitonin values were higher in severe infections, such as sepsis, than in patients with SIRS (3.1 ng/mL [0.8–3.9] versus 0.2 ng/mL [0.1–0.8] ($p < 0.001$) (18). In the analysis of patients in the intensive care unit, Gibot found that PCT distinguished patients with sepsis from those admitted to the intensive care unit ($p > 0.001$) with a diagnostic AUC of 0.91 (31).

On the other hand, PCT did not distinguish sepsis from SIRS and other diseases in the study by Tanga and coworkers (32). Gibot also concluded that the concentration of PCT was higher in patients infected with Gram-negative 30.09 ng/ml (4.55–76.01) than in those infected with Gram-positive organisms 1.33 ng/ml (1.04–4.98) ($p < 0.0001$) (31).

In our study, the serum PCT concentration was statistically significantly higher in the group of sepsis compared to the patients with infection without sepsis. PCT (AUC 0.84) proved to be a better biomarker than CRP (AUC 0.56) in the diagnosis of sepsis, similarly to other studies (29-31). Also, PCT had a better diagnostic value for sepsis compared to the neutrophil CD64 index (AUC 0.78) and neutrophil count (AUC 0.69). The neutrophil CD64 index was expected to be significantly higher in both groups of patients compared to healthy controls, and was higher in the patients with sepsis compared to the patients with infection without sepsis, but in our patients its diagnostic accuracy was low (AUC 0.78).

Although some publications have reported a high diagnostic value of this index (33,34), many other studies, such as ours, have not confirmed it (35,36). One of the reasons for contradicting conclusions is the choice of patients in compared groups (Table 5).

Our patients in the infection without sepsis group were internal medicine patients with severe comorbidities, clinically difficult to distinguish from sepsis. A similar result was obtained by Gamez-Diaz, who also included critically ill patients requiring intensive care, and during hospitalization differentiated between critically ill patients with sepsis from those without sepsis (35). The studies that found a good diagnostic value of the neutrophil CD64 index included healthy subjects or patients after surgery without infection in control groups (22,28,33).

The CD64 test was expected to be the most discriminative (AUC was 1.0) when comparing the patients to healthy individuals. Certainly, to distinguish patients with sepsis from healthy subjects we do not need laboratory tests. In clinical practice, however, it is necessary to distinguish among different diseases.

The cut-off value where the test reliably distinguished the patients with sepsis from the patients with infection without sepsis was 7.5, a high value, and many patients with sepsis had significantly lower values. However, the neutrophil CD64 index had a good negative predictive value, since no patient with

sepsis had this index below 1.2; the index of less than 1.2 certainly excluded sepsis in our study.

In our study we did not confirm differences in neutrophil granulocyte count among the groups, whereas the concentration of immature neutrophil count was significantly higher in the patients with sepsis than in the patients with infection without sepsis. We found that the neutrophil CD64 index had a better diagnostic value than neutrophil granulocyte count in the patients with sepsis compared to the patients with infection without sepsis. The highest diagnostic values were found for the immature neutrophil count (AUC 0.91).

So far, we have not found a biomarker with sufficient (> 0.9) sensitivity and specificity to diagnose sepsis. However, an increasing number of studies (31,35) have indicated that combinations of various biomarkers are a useful approach to improving the accuracy of diagnosing sepsis. In our study, at least one marker (CRP, PCT, neutrophil CD64 index, neutrophil granulocyte count or neutrophil granulocyte count) was above the discriminatory value in 62 % of patients for distinguishing the patients with sepsis from those with infection without sepsis. A large majority of patients with sepsis were detected using only two markers, namely immature neutrophil count and PCT.

The limitation of our study is heterogeneity of the group of patients with infection without sepsis. Another limitation is that we assessed the performance of biomarkers in identifying sepsis and infection without sepsis only at the time of sampling. Thus, we cannot draw conclusions about the predictive value of the investigated biomarkers for the potential later development of sepsis, or assess the impact of serial measurements.

5. Conclusions

The neutrophil CD64 index has proved to be one of the least discriminative biomarkers to distinguish sepsis from severe infection without sepsis in patients in the intensive care unit. The highest diagnostic values were provided by the immature neutrophil count (AUC 0.91) and PCT (AUC 0.84). A combination of biomarkers has been shown to have similar predictive values as the immature neutrophil count and PCT. However, the neutrophil CD64 index has proved to be useful regarding the negative predictive value, since none of the patients with sepsis had the index below 1.2. The combination of biomarkers had better diagnostic accuracy compared to a single biomarker, whereas the most accurate biomarkers were the immature neutrophil count and PCT.

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