

Diagnostic usefulness of sCD163, procalcitonin and neopterin for sepsis risk assessment in critically ill patients

Agnieszka Sapa^{1, A, C-F}, Alina Rak^{1, B-D}, Magdalena Wybieralska^{2, B, C}, Jakub Machoń^{3, B, C, E}, Anna Krzywonos-Zawadzka^{1, B, E}, Kamil Zawadzki^{3, B, C}, Marek Wełna^{3, B}, Mieczysław Woźniak^{1, A, F}

¹ Department of Clinical Chemistry, Wrocław Medical University, Poland

² Ziemo-Vita Public Health Care Laboratory Ltd., Wrocław, Poland

³ Department of Anesthesiology and Intensive Therapy, Wrocław Medical University, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;

D – writing the article; E – critical revision of the article; F – final approval of article

Advances in Clinical and Experimental Medicine, ISSN 1899-5276 (print), ISSN 2451-2680 (online)

Adv Clin Exp Med. 2017;26(1):101–108

Address for correspondence

Agnieszka Sapa

E-mail: agnieszka.sapa@umed.wroc.pl

Funding sources

none declared

Conflict of interest

none declared

Received on October 29, 2015

Revise on May 04, 2016

Accepted on May 19, 2016

Abstract

Background. Sepsis is one of the most common causes of hospitalization and it is characterized by a high mortality rate in spite of the great progress in diagnosis and treatment achieved in recent years. Early diagnosis of sepsis is one of the most important elements of effective treatment. The clinical symptoms are not specific and biomarkers are considered to be useful tools in sepsis diagnostics.

Objectives. The aim of our study was to evaluate the diagnostic value of sCD163 as a marker of sepsis and a comparison of it with procalcitonin and neopterin in ICU patients.

Material and methods. Concentrations of PCT, sCD163 and NPT were measured in 52 serum samples collected from 30 patients of the Department of Anesthesiology and Intensive Therapy of the University Hospital in Wrocław. Venous blood was collected on the 1st and 3rd day of hospitalization. The Human CD163 Quantikine ELISA Kit was used to determine the concentrations of sCD163. Neopterin concentrations were measured by a Neopterin ELISA kit. PCT was measured at the University Center of Laboratory Diagnostics in Wrocław using an automatic VIDAS® B.R.A.H.M.S. PCT assay.

Results. Our study showed that there was a significant difference between the values obtained in the study and the reference group for PCT ($p < 0.0001$), sCD163 ($p = 0.0001$) and NPT ($p = 0.0001$), whereas there was no difference observed between the samples obtained on the 1st and 3rd day ($p = 0.5129$). The area under the ROC curve was 0.847, and was comparable to the AUC of procalcitonin (0.840), and slightly higher than the AUC of neopterin (0.763), although these differences were not significant ($p = 0.2990$ and $p = 0.9329$, respectively).

Conclusions. sCD163 and neopterin are promising parameters in the diagnosis of sepsis, and their value in the diagnosis of sepsis in critically ill patients may be comparable to procalcitonin.

Key words: biomarkers, sepsis, procalcitonin, sCD163, neopterin

DOI

10.17219/acem/63251

Copyright

Copyright by Author(s)

This is an article distributed under the terms of the

Creative Commons Attribution Non-Commercial License

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Sepsis is a serious medical condition characterized by a high mortality rate in spite of the great progress in diagnosis and treatment achieved in recent years.¹ Annual mortality due to sepsis ranges from 30 to 50 cases per 100,000 people and thus sepsis ranks in the top 10 causes of death.^{1,2} The mortality rate corresponds to the severity of the disease and varies from 25–30% in severe sepsis to as high as 40–70% in septic shock.²

Early diagnosis of sepsis is one of the most important elements of effective treatment.³ Traditional clinical signs and symptoms of inflammation and laboratory parameters, i.e. body temperature, leukocyte count, erythrocyte sedimentation rate (ESR) or even C-reactive protein elevation, have been found to have low diagnostic accuracy.^{1,4} Many biomarkers have been introduced in the diagnosis and treatment monitoring of sepsis, but their clinical utility has not yet been clearly determined.^{1,3} Procalcitonin (PCT) has been used commonly, as its diagnostic value is relatively well described, although it is not an ideal sepsis marker.⁵ Another marker of potential value in the diagnosis of infection is neopterin (NPT), however its value in sepsis has not yet been sufficiently evaluated and NPT determination has not been introduced as a routine parameter.⁴ According to the current publications about soluble CD163 (sCD163), one can conclude that it is a marker which correlates with common markers of sepsis. It can be used as an adjunct to the diagnostic process. Some researchers suggest its usefulness as a prognostic factor.^{6–8}

PCT is synthesized by thyroid gland C cells under physiological circumstances, whereas inflammation stimulates other cells to produce this polypeptide. The PCT level starts to rise within 6 h after an inflammation process is initiated, reaches maximum values between 12 and 48 h, and then returns to normal values if the infection agent has been eradicated.⁵ A persisting high or continuously increasing concentration of PCT suggests a systemic inflammatory reaction or septic complication after surgery. PCT concentration remains low in local infections without systemic response. There are many reports indicating that PCT is preferably induced in patients with sepsis of bacterial origin, especially severe sepsis and septic shock. Moreover, PCT concentration often correlates with the severity of the inflammation. One of the limitations of this parameter is the nonspecific increase in many clinical states regardless of sepsis, including surgical procedures, injuries, heat shock, burns, long-lasting cardiogenic shock and severe systemic inflammation process.⁹ Considering these facts as well as the lack of optimal cut-off values for PCT for different groups of patients, results should be interpreted cautiously in a sepsis risk assessment.¹⁰

Neopterin is excreted by monocytes/macrophages mostly in response to interferon gamma stimulation, whereas IL-4 (interleukin – IL), IL-10 and IL-12 inhibit NPT excretion.^{11,12} Neopterin is an early and sensitive marker of cellular response but it lacks specificity. It is considered to be a useful tool in the investigation of

clinical cases in which cellular response is crucial. Elevation of NPT often precedes the clinical manifestation of inflammation or seroconversion.¹³ The correlation between NPT serum level and the risk of septic complications has been described.⁵ Localized infections usually do not increase NPT concentration, whereas the process of persistent inflammation and systemic infection with the activation of cellular response is likely to increase NPT level.¹² Sepsis is the most common cause of NPT elevation; moreover, higher NPT concentrations correlate with poor prognosis for patients.¹⁴

CD163 (cluster of differentiation – CD) is a glycoprotein present only on the cell membrane on the surface of macrophages and monocytes. It is a member of the scavenger receptor cysteine-rich (SRCR) family class B.^{15,16} CD163 is a 130 kDa protein consisting of 9 extracellular SRCR protein domains which are linked to a short transmembrane segment and a short cytoplasmic tail. In vitro tests have revealed that glucocorticoids, IL-10 and IL-6 increase the amount of CD163, while IL-4 and IL-13 do not raise the level of CD163 concentration, and TNF- α (tumor necrosis factor alpha), IFN- γ (interferon gamma) and CXCL4 (CXC chemokine ligand 4) decrease the concentration of CD163. Such variable responses to pro- and anti-inflammatory mediators suggest that CD163 is expressed mostly on M2 macrophages. M2 macrophages participate in tissue and wound repair, angiogenesis and tumor progression. CD163 is not only present as a membrane-bound protein, but also circulates in blood as a soluble CD163 (sCD163) and it is actively released from the cell membrane of monocytes and macrophages.¹⁶ sCD163 is present in serum and other body fluids.¹⁵ In vitro studies have also shown that sCD163 secretion by monocytes and macrophages might be induced by TLR (toll-like receptor) or LPS (lipopolysaccharide). Shedding of sCD163 is equal to TNF- α response to LPS. Oxidative stress also leads to significant shedding of CD163. Even without inflammatory stimulation, small amounts of sCD163 are released to circulation.¹⁶ CD163 has been identified as a hemoglobin scavenger receptor (HbSR). The receptor is capable of capturing haptoglobin-hemoglobin complexes (Hp-Hb) formed during intravascular hemolysis. HbSR and its ligands are directly involved in the inflammatory response.¹⁷

Hemoglobin and free heme play an important role in the occurrence of sepsis. Pathological agents like hemolysis, DIC and ischemic reperfusion, as well as the toxicity and side effects of drugs may lead to a release of hemoglobin and heme. At the same time, oxidation and reduction reactions catalyzed by hydrogen peroxide lead to a release of oxygen free radicals which results in organ damage. It is necessary to remove the hemoglobin and free heme in a short time. Haptoglobin (Hp) takes part in the removal of hemoglobin, and thus it inhibits the reactions of oxidative damage and is involved in anti-inflammatory response. Hemoglobin can be removed by phagocytic cells

Table 1. Patients characteristics, divided into study and reference group according to the diagnosis of sepsis at the moment of sample collection

Characteristics	Reference group – patients without sepsis	Study group – patients with sepsis
Gender f/m	3/11	4/12
Age (years) mean (range)	63.9 (20–85)	66.8 (38–92)
WBC (G/L) mean (range)	12.59 (5.37–23.56)	14.70 (3.83–29.10)
APACHE II mean (range)	17.93 (10–35)	22 (10–41)
CRP (mg/L) mean (range)	87.96 (1.36–197.07)	187.03 (11.27–413.12)
Number of dysfunctional organs median (range)	2 (0–4)	4 (1–6)
Lactate (mmol/L) mean (range)	2.43 (0.80–5.50)	3.48 (0.92–8.71)

only when it is joined in a complex with haptoglobin (Hp-Hb) and through the CD163.¹⁸

sCD163 is a specific biomarker of macrophages used in many clinical conditions such as coronary artery disease, atherosclerosis, rheumatoid arthritis, cancer and multiple sclerosis. It also plays an important role in the detection of inflammation, sepsis, bacteremia, mononucleosis, Crohn's disease, celiac disease, hemophagocytic syndrome, macrophage activation syndrome, acute liver failure, burns, preeclampsia in pregnancy and many other conditions.^{15,16} In numerous of these diseases, patients are exposed to large amounts of free heme due to intravascular hemolysis and tissue damage. CD163 is highly efficient in the removal of potentially toxic free hemoglobin from the circulation and tissues with inflammation, so sCD163 is to be considered a prognostic marker in many diseases, especially inflammatory ones.

Taking into consideration the advantages and limitations of PCT and NPT, we decided to determine the clinical value of serum measurements of sCD163, PCT and NPT as indicators of sepsis in critically-ill patients, that are at extreme risk of sepsis. Furthermore, the aim of the study was to compare their usefulness using ROC (receiver operator characteristic) curve analysis in this specific group of patients and to calculate cut-off values, exceeding which indicates elevated risk of sepsis.

Material and methods

Patients

Fifty-four vein blood samples were drawn from 30 patients of the Anesthesiology and Intensive Care Unit (AICU) of the Wroclaw Medical University Hospital. Samples were collected twice from each of 24 patients, on the 1st and 3rd day of hospitalization in the AICU. Only one sample was collected from 6 patients, because 4 patients died within 3 days and the remaining 2 were transferred to another hospital. Patient characteristics are presented in Table 1. All patients were divided into 2 groups – a study and a reference group. The study group consisted of 16 patients with an established diagnosis of sepsis at the time of sample collection. The reference group

consisted of patients in a severe general condition, who didn't meet the diagnostic criteria of sepsis at the moment of material collection. This group included 14 patients.

Material

As material for this study we used serum remaining from samples collected for routine laboratory tests from patients of the AICU. All serum samples were frozen at –20°C and were stored at this temperature until the assay except for PCT which was performed immediately as a routine test. Use of this material was approved by the Bioethics Committee of Wroclaw Medical University.

Measurement of sCD163 concentration

The CD163 Quantikine ELISA Kit (R & D Systems, Minneapolis, USA) was used to measure the concentration of sCD163 in serum. The procedure was performed according to the manufacturer's instructions and the samples were diluted 10-fold according to the manufacturer's recommendations.

Measurement of neopterin concentration

A Neopterin ELISA kit (IBL International GMBH, Hamburg, Germany) was used to measure the concentration of neopterin in serum. The procedure was performed according to the manufacturer's instructions.

Procalcitonin concentration

The concentration of PCT in the serum samples was determined as a routine test in all patients by the University Center of Laboratory Diagnostics in Wroclaw. The measurements were performed via the automatic VIDAS® B.R.A.H.M.S. PCT assay (BioMérieux, Marcy l'Etoile, France).

Statistical analysis

MedCalc v.14.12.0 (Ostend, Belgium) was used for the statistical calculations. The data was described with mean, highest and lowest value, standard deviation, me-

dian and D'Agostino-Pearson test for normal distribution. A Mann-Whitney rank-sum test for independent samples was used for the comparison between groups divided by the presence or absence of sepsis. A Wilcoxon test for paired samples was used to compare the values obtained on the 1st and 3rd day. A p value < 0.05 was considered statistically significant. The ROC curves were prepared for PCT, sCD163 and NPT and the areas under curves were compared using the method of DeLong et al. available in the MedCalc software.

Results

Table 2 shows the summarized results for the serum procalcitonin, sCD163 and neopterin measurements in patients, including the division into two groups.

Comparison of results between groups

We divided the results of the PCT, sCD163 and NPT measurements into two groups depending on the day of material collection (1st and 3rd day of hospitalization) and according to the clinical condition of the patients (with or without diagnosis of sepsis at the moment of sample collection – study and reference groups). Using the Wilcoxon test, we found that the differences between the 1st and 3rd day of material collection for PCT ($p = 0.1005$), sCD163 ($p = 0.5129$) and NPT ($p = 0.4576$) were not statistically significant. In contrast, there were statistically significant differences in PCT ($p < 0.0001$), sCD163

($p = 0.0001$) and NPT ($p = 0.0001$) concentration between the study and reference groups, which was confirmed by a Mann-Whitney test. In Figs. 1, 2, 3, we show a graphical comparison between the study and reference groups including all the results obtained, regardless of the day of sample collection.

ROC curves

Considering that there were no differences found in PCT, sCD163 and NPT concentrations between the groups divided on the basis of the day of hospitalization and the total group of patients was relatively small, the

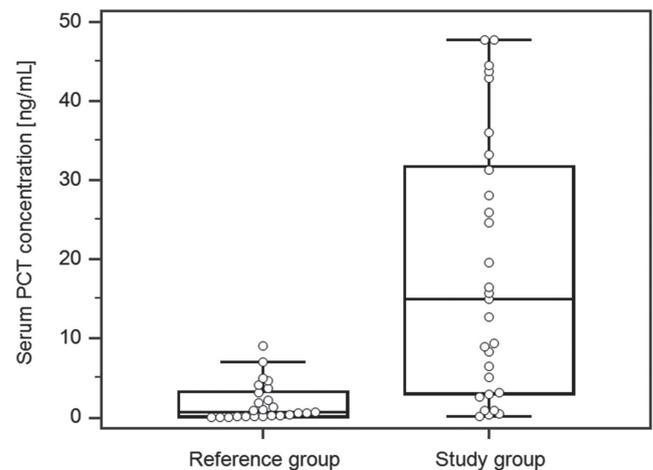


Fig. 1. Comparison of PCT concentration between reference and study groups. Boxes show the median and interquartile range, whiskers show 10–90th percentiles. Mann-Whitney test between PCT results in septic and non-septic group regardless of the day of sample collection

Table 2. PCT, sCD163 and NPT concentration in all patients, study and reference group

Statistical parameter	All patients (n = 30)	Study group (n = 16)	Reference group (n = 14)
Procalcitonin (ng/mL)			
Number of measurements	54	29	25
Mean (range)	10.75 (0.05–47.77)	18.42 (0.09–47.77)	1.86 (0.05–9.08)
Median	3.39	14.95	0.61
Distribution normality	no ($p = 0.0004$)	yes ($p = 0.0667$)	no ($p = 0.0013$)
sCD163 (mg/L)			
Number of measurements	54	29	25
Mean (range)	0.933 (0.295–1.391)	1.109 (0.295–1.391)	0.673 (0.327–1.290)
Median	1.082	1.257	0.586
Distribution normality	no $p < 0.0001$	no $p = 0.0023$	yes $p = 0.1430$
Neopterin (nmol/L)			
Number of measurements	54	29	25
Mean (range)	93.35 (5.59–577.82)	138.85 (25.47–577.82)	40.56 (5.59–189.81)
Median	51.49	68.14	16.15
Distribution normality	no ($p < 0.0001$)	yes ($p = 0.0010$)	no ($p = 0.0002$)

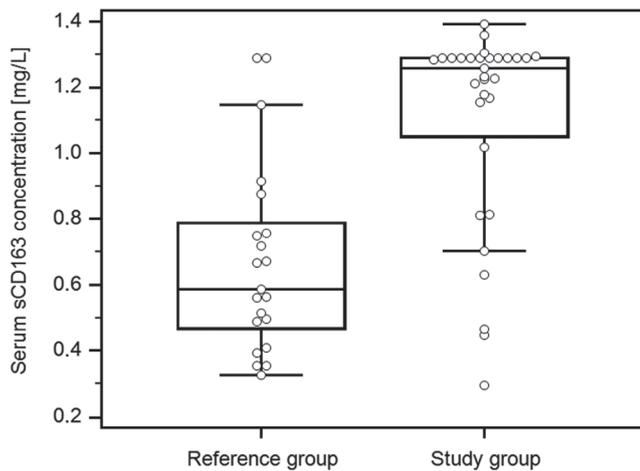


Fig. 2. Comparison of sCD163 concentration between reference and study groups. Boxes show the median and interquartile range, whiskers show 10–90th percentiles. Mann-Whitney test between sCD163 results in septic and non-septic group regardless of the day of sample collection

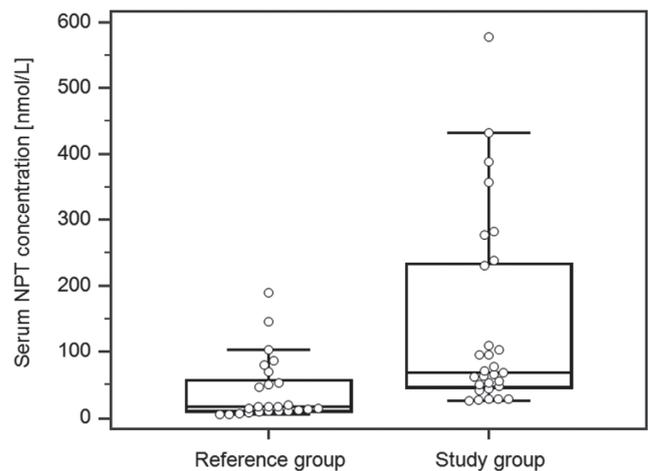


Fig. 3. Comparison of NPT concentration between reference and study groups. Boxes show the median and interquartile range, whiskers show 10–90th percentiles. Mann-Whitney test between NPT results in septic and non-septic group regardless of the day of sample collection

ROC curves were prepared on the basis of all obtained results, taking into account the established diagnosis of sepsis at the moment of sample collection. ROC curves for PCT, sCD163 and NPT are showed in Fig. 3.

Comparison of the areas under the curves (AUC) for PCT, sCD163 and NPT revealed that there was no statistically significant difference, so it could be assumed that the PCT, sCD163 and NPT have similar diagnostic value in assessing the risk of sepsis development in ICU patients. The parameters describing the ROC curves and AUC comparison data are shown in Tables 3 and 4.

The most sensitive parameter was the NPT (100%), but at the same time it had the lowest diagnostic specificity (58.3%). PCT is more specific but less sensitive than NPT, whereas sCD163 is characterized by the highest diagnostic sensitivity and specificity in our study group.

Discussion

Early diagnosis of sepsis enables appropriate treatment and it is essential in emergency and intensive care units. Biomarkers are considered to be useful tools in sepsis diagnostics as they make it possible to differentiate the infection etiology and assess the severity of the inflammation process.³ Many studies have proved that procalcitonin is the most valuable biomarker, characterized by relatively high diagnostic accuracy, but one must remember the numerous limitations of this parameter as a sepsis marker.¹⁰ Another parameter is neopterin, which is a marker of cellular activation in inflammation and its concentration is related to the risk of sepsis.⁵ In spite of many clinical studies performed on NPT's diagnostic value, including as a predictor of mortality in sepsis, it still has not been determined what the total benefit is of NPT determination for patients and health care units. For these reasons, NPT is not a routinely used parameter. Over the last several

Table 3. ROC curve data for PCT, sCD163 and NPT

Marker	AUC	Sensitivity (%)	Specificity (%)	Standard error	95% CI	Cut-off value
PCT	0.840	71.4	87.5	0.0542	0.712–0.927	4.58 ng/mL
sCD163	0.847	82.1	91.7	0.0599	0.720–0.932	1.146 mg/L
NPT	0.763	100.0	58.3	0.0708	0.625–0.870	16.4 nmol/L

Table 4. Comparison of ROC curves

	sCD163 vs. NPT	sCD163 vs. PCT	PCT vs. NPT
Difference between areas	0.0833	0.00670	0.0766
Standard error	0.0802	0.0796	0.0704
95% confidence interval	-0.0739 to 0.241	-0.149 to 0.163	-0.0613 to 0.215
z statistic	1.039	0.0842	1.089
Significance level	p = 0.2990	p = 0.9329	p = 0.2761

years, soluble CD163 has been studied by many groups of scientists as a potential marker for the diagnosis of sepsis. sCD163 concentration is not routinely measured in patients with suspicion of sepsis and there is still a need for a determination of its clinical utility.

The aim of our study was the evaluation of the clinical value of sCD163 as a marker of sepsis and a comparison of it with procalcitonin and neopterin in a very specific group of ICU patients using a comparison of ROC curves and the determination of optimal cut-off values. To reliably evaluate the diagnostic value of sCD163 in the diagnosis of sepsis, the study group consisted of patients with similar clinical conditions and demographics factors to the reference group. Patients in both groups were in severe general condition, although the reference group did not meet the criteria of sepsis at the moment of sample collection.

An elevated concentration of all markers was observed in both groups in comparison to the cut-off values suggested by the manufacturers of the tests. Yet there was a significant difference between the study and reference groups for PCT, sCD163 and NPT, which is shown in Figs. 1, 2, 3 (sCD163 median in the reference group was 0.586 mg/L vs. 1.257 mg/L in the study group, $p = 0.0001$; for PCT 0.61 vs. 14.95 $\mu\text{g/L}$, respectively, $p < 0.0001$; for NPT 16.15 nmoL/L vs. 68.14 nmoL/L, respectively, $p = 0.0001$).

There were similar observations made of PCT by Meisner et al. Their results confirmed the elevation of PCT in multi-organ dysfunction syndrome (MODS) and sepsis. They observed a correlation with the SOFA scale, and usually a higher concentrations of PCT in patients that died due to MODS or sepsis than in survivors.¹⁹ Also, Sudhir et al. have confirmed the increase of the SOFA result with increasing PCT concentration, but their study revealed no correlation between PCT and the severity of sepsis or mortality rate.²⁰

Neopterin's usefulness in sepsis was evaluated by Ploder et al. in a study that included patients after severe trauma and patients with sepsis, and they confirmed the elevation of NPT levels in these patients.²¹ In a retrospective study by Fisgin et al., NPT was assessed as a marker of mortality in patients with sepsis. Their results confirmed significantly higher concentrations of NPT in patients that died of sepsis (median 15 ng/mL) than in survivors (median 5 ng/mL, $p = 0.03$).²² Also, other clinical studies performed in ICU patients with sepsis, septic shock, MODS or infection have revealed that NPT makes it possible to distinguish between patients with confirmed infection and those without septic complications.^{11,23}

Our results also show that the concentration of sCD163 was higher in the study than in the reference group. Median concentration in the study group was 1.257 mg/L and it was 2 times higher compared to the reference group (0.586 mg/L). The AUC value for sCD163 was 0.847. Based on a ROC curve analysis, the cut-off value

was 1.146 mg/L with a diagnostic sensitivity of 82.1% and specificity 91.7%. Despite the relatively small group of patients, our results suggest a potential high diagnostic value of sCD163 measurements in sepsis diagnosis.

Feng et al. achieved similar results while measuring the concentration of sCD163 in the serum of 102 patients with sepsis and 30 patients with SIRS without infection in the aim of sepsis diagnosis, evaluation its severity and further prognosis. On the first day of hospitalization, the concentration of sCD163 in the septic patients was 2.51 times higher than in the patients with SIRS ($p = 0.001$). The authors noticed the maximum concentration on the third day of hospitalization, then a slow reduction in the following days. According to the authors, if the concentration doesn't decrease it means a worse prognosis for the patient. In our study there was no significant difference in concentration between the first and the third day of hospitalization, which could be the consequence of stabilizing the patients' condition. The ROC curve analysis by Feng et al. for the ability to discriminate between SIRS and sepsis showed that the area under the curve of sCD163 was 0.856. The cut-off value was 1.49 mg/L with a sensitivity of 74% and a specificity of 93.33%. In the present study we obtained higher diagnostic sensitivity but slightly less diagnostic specificity for a similar cut-off value. The authors also evaluated the usefulness of sCD163 concentration for the diagnosis and prognosis of sepsis. Their results suggest that sCD163 has clinical value for the recognition and prognosis of sepsis. The researchers also showed that on the first day of hospitalization the concentration of sCD163 in the serum of septic patients was significantly higher than in the patients with SIRS; additionally it better indicates sepsis diagnosis than the routinely-used PCT and CRP. sCD163 could be a valuable parameter as a specific and sensitive marker of infection. sCD163 is also a good indicator of the severity of sepsis and its monitoring.⁶

Also, a similar level of increase of the concentration of sCD163 as in this study was observed by Møller et al., who assessed the value of this parameter in patients with pneumococcal bacteremia (positive blood cultures for the presence of *Streptococcus pneumoniae*). They received 1.7 times higher concentrations of sCD163 in the study group compared to healthy subjects ($p < 0.0001$). The concentration of sCD163 was significantly increased in septic patients (median 4.6 mg/L) compared to healthy persons (median 2.7 mg/L). The study also showed that there is no difference in the concentrations of sCD163 depending on gender. However there is an age-related difference because the concentrations of sCD163 in older patients was lower. This observation may be one of the reasons for the relatively lower concentrations of sCD163 obtained in this study, but due to the small size of the group, the analysis in the age subgroups was not credible. The ROC curve for predicting the risk of death made by Møller et al. was characterized by the AUC = 0.82 with sensitivity 82% and

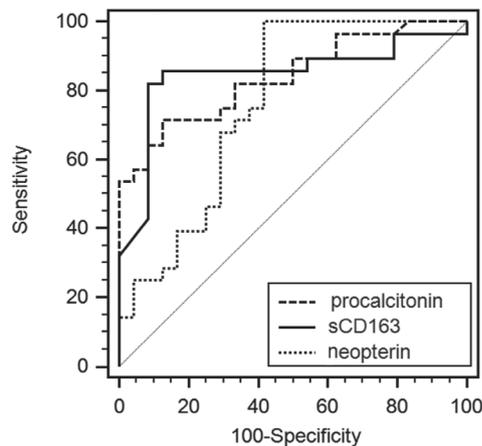


Fig. 4. PCT, sCD163 and NPT ROC curves

specificity 79% and it indicated a high diagnostic value for this parameter in the assessment of the risk of death.²⁴

Slightly less diagnostic value than in this study was found by Su et al. who, in their work, defined the diagnostic value of sCD163 based on research carried out in the ICU in 100 septic patients and 30 patients with SIRS. These authors obtained an AUC for sCD163 of 0.696. The concentration of sCD163 in the septic patients was significantly higher (2.52 times) than in the patients with SIRS ($p < 0.001$). Based on the ROC curve analysis, the specified cut-off value was 2.84 mg/L with a sensitivity of 53.5% and specificity of 78.9%. This cut-off value is higher than in our study, but it should be taken into consideration that the values obtained in ELISA are affected not only by the composition of the study group but also by assay characteristics i.e. antibodies specificity, linearity, limit of quantification, precision and accuracy. Moreover, Su et al. observed that the median of the concentrations of sCD163 increased during hospitalization in patients who did not survive, while in survivors there was a decreasing tendency. According to the authors, the concentration of sCD163 has a positive diagnostic value for the prognosis and assessment of the disease dynamics.⁷

Definitely a higher level of increase of the concentration of sCD163 was found by Kjærsgaard et al., who observed changes in the concentration of sCD163 during a 4-day stay in a hospital ward in 21 septic patients compared to 15 patients without sepsis and a control group (healthy people). During the 4 days, the concentrations of sCD163 were higher (3.44 times) in patients with sepsis than in those without sepsis ($p < 0.001$). The AUC of the ROC curve prepared by the authors to distinguish sepsis was 0.95. The cut-off value was 1.74 mg/L with a high sensitivity and specificity, both equaled 93%. The results reported by Kjærsgaard et al. showed the high diagnostic value of sCD163. In this study we also demonstrated statistically significant differences between the concentrations of sCD163 in the study group (patients with sepsis) and the reference group (patients without sepsis, in severe condi-

tion), but the AUC (0.847), sensitivity and specificity was lower than in the Kjærsgaard et al. publication.²⁵

Abdelrahman et al. likewise analyzed the concentrations of sCD163 in ICU patients, which were divided into a study group (patients with sepsis) and a reference group (patients with SIRS). Based on the results obtained, the authors checked the diagnostic value of sCD163 in the diagnosis of sepsis and in the assessment of its severity. The researchers received a similar level of increase of sCD163 concentration as in this study. The septic patients had an average of 2.9 times higher concentrations of sCD163 than the patients with SIRS ($p < 0.001$). The cut-off value obtained from the ROC curve analysis was 5.36 mg/L with a sensitivity of 93.5% and specificity of 90.2%, which confirmed the high diagnostic value of this parameter in sepsis diagnosis. The authors didn't specify the AUC value in their publication.⁸

A lower diagnostic value was found by Ingels et al., who determined the concentrations of sCD163 in seriously ill patients. They obtained 1.65 times higher values in comparison with healthy people ($p < 0.0001$). The authors observed a relationship between the presence of sepsis and the concentration of sCD163; patients with sepsis recognized at the moment of admission to the hospital had 1.29 times higher concentrations than patients without sepsis ($p < 0.0001$). The researchers didn't show in their work on the ROC curve for the differentiation of sepsis, only for predicting mortality (AUC = 0.68).²⁶

Definitely different results were found by Găini et al. who, in 2006, assessed the concentrations of sCD163 in patients with a community-acquired infection. The reference group consisted of healthy people, and the median concentration of sCD163 in this group was 1.9 mg/L (range: 0.4–4.7 mg/L). The ROC curve analysis showed that the AUC was low, equal to 0.58, and there weren't statistically significant differences between the studied groups of patients. The authors concluded that the concentrations of sCD163 did not differentiate patients with the infection from those without the infection.²⁶ In 2008, Găini et al. determined the concentrations of sCD163 in patients with sepsis and SIRS. In septic patients, the concentrations were higher than in the control group ($p < 0.0001$), however there wasn't a statistically-significant difference between patients with sepsis and SIRS.²⁸

In the publications mentioned above, the authors determined the concentrations of sCD163 in serum samples, but this parameter is also very efficient when measured in urine. The study by Su et al. revealed that in septic patients the concentration was 2.34 times higher than in patients with SIRS ($p < 0.001$). In the reference group, the concentration was undetectable. The AUC of ROC prepared to distinguish SIRS from sepsis was 0.83 with a sensitivity of 82.5% and specificity of 75%, and the cut-off value was equal to 0.043 mg/L. Moreover, the results correlated with the concentrations of sCD163 in serum ($r = 0.511$; $p < 0.001$).¹⁸

In conclusion, the assumptions of this study were confirmed by the results obtained. Based on the above-mentioned publications and the results received, sCD163 is a promising parameter, however its clinical utility has not yet been adequately determined. Similarly, neopterin, despite a relatively high sensitivity, hasn't been introduced as a routine laboratory parameter. In some cases, measurement of the concentration of NPT and in particular sCD163 provides valuable information for diagnosis, as shown in the above-mentioned reports, so there is a necessity to investigate these parameters and specifically determine their diagnostic usefulness. Both markers could be an additional parameters to PCT in order to make diagnosis easier and accelerate therapeutic decisions.

References

- Riedel S. Procalcitonin and the role of biomarkers in the diagnosis and management of sepsis. *Diagn Microbiol Infect Dis.* 2012;73:221–227.
- Lever A, Mackenzie I. Sepsis: Definition, epidemiology, and diagnosis. *BMJ.* 2007;335:879–883.
- Pierrakos C, Vincent J-L. Sepsis biomarkers: A review. *Crit Care.* 2010;14:R15.
- Hryckiewicz K, Juszczak J, Samet A, Arlukowicz E, Śledzińska A, Bolewska B. Procalcitonin jako marker diagnostyczny zespołu uogólnionej reakcji zapalnej (SIRS) i posocznicy. *Przegl Epidemiol.* 2006;60:7–15.
- Pourakbari B, Mamishi S, Zafari J, et al. Evaluation of procalcitonin and neopterin level in serum of patients with acute bacterial infection. *Braz J Infect Dis.* 2010;14:252–255.
- Feng L, Zhou X, Su LX, Feng D, Jia YH, Xie LX. Clinical significance of soluble hemoglobin scavenger receptor CD163 (sCD163) in sepsis, a prospective study. *PLoS One.* 2012;7(7):e38400. doi: 10.1371/journal.pone.0038400.
- Su L, Feng L, Song Q, et al. Diagnostic value of dynamics serum sCD163, sTREM-1, PCT, and CRP in differentiating sepsis, severity assessment, and prognostic prediction. *Mediators Inflamm.* 2013. Internet: <http://dx.doi.org/10.1155/2013/969875> (accessed 26 June 2015).
- Abdelrahman RS, Wagih AA, Elbarbary AH. The diagnostic value of serum level of soluble hemoglobin scavenger receptor CD163 for sepsis in the ICU. *Tanta Med J.* 2015;43:9–15.
- Meisner M. Pathobiochemistry and clinical use of procalcitonin. *Clin Chim Acta.* 2002;323:17–29.
- Dorizzi R, Polati E, Sette P, Ferrari A, Rizzotti P, Luzzani A. Procalcitonin in the diagnosis of inflammation in intensive care units. *Clin Biochem.* 2006;39:1138–1143.
- Sheldon J, Riches P, Soni N, et al. Plasma neopterin as an adjunct to C-reactive protein in assessment of infection. *Clin Chem.* 1991;37:2038–2042.
- Mierzwa G, Parzęcka M, Szaflarska-Popławska A, Stefańska A, Odrowąż-Sypniewska G. Ocena przydatności klinicznej oznaczania neopteryny u dzieci i młodzieży z przewlekłym zapaleniem błony śluzowej żołądka i/lub dwunastnicy z zakażeniem i bez zakażenia *Helicobacter pylori*. *Prz Gastroenterol.* 2009;4:83–87.
- Shameem Banu A, Latha P, Kaveri K, Jayakumar S. Serum neopterin estimation as an indicator for safe blood transfusion. *J Clin Diagn Res.* 2011;5:1555–1558.
- Kozłowska-Murawska J, Obuchowicz A. Przydatność kliniczna oznaczania stężenia neopteryny. *Wiad Lek.* 2008;61:269–271.
- Onofre G, Koláčková M, Jankovičová K, Krejssek J. Scavenger receptor CD163 and its biological functions. *Acta Medica.* 2009;52:57–61.
- Møller H. Soluble CD163. *Scand J Clin Lab Invest.* 2012;72:1–13.
- Møller HJ, Peterslund NA, Graversen JH, Moestrup SK. Identification of the hemoglobin scavenger receptor/CD163 as a natural soluble protein in plasma. *Blood.* 2002;99:378–380.
- Su L, Feng L, Liu C, et al. Diagnostic value of urine sCD163 levels for sepsis and relevant acute kidney injury: A prospective study. *BMC Nephrol.* 2012;13:123. doi: 10.1186/1471-2369-13-123.
- Meisner M, Tschaikowsky K, Palmaers T, Schmidt J. Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. *Crit Care.* 1999;3:45–50.
- Sudhir U, Venkatachalaiah R, Kumar T, Rao M, Kempgowda P. Significance of serum procalcitonin in sepsis. *Indian J Crit Care Med.* 2011;15:1–5. <http://dx.doi.org/10.4103%2F0972-5229.78214> (accessed 10 July 2015).
- Ploder M, Neurauter G, Spittler A, Schroecksnadel K, Roth E, Fuchs D. Serum phenylalanine in patients post trauma and with sepsis correlate to neopterin concentrations. *Amino Acids.* 2008;35:303–307.
- Fisgin N, Aliyazicioglu Y, Tanyel E, et al. The value of neopterin and procalcitonin in patients with sepsis. *South Med J.* 2010;103:216–219.
- Girgin G, Sahin T, Fuchs D, et al. Tryptophan degradation and serum neopterin concentrations in intensive care unit patients. *Toxicol Mech Methods.* 2011;21:231–235.
- Møller HJ, Moestrup SK, Weis C, et al. Macrophage serum markers in pneumococcal bacteremia: Prediction of survival by soluble CD163. *Crit Care Med.* 2006;34:2561–2566.
- Kjærgaard AG, Rødgaard-Hansen S, Dige A, Krog J, Møller HJ, Tønnesen E. Monocyte expression and soluble levels of the haemoglobin receptor (CD163/sCD163) and the mannose receptor (MR/sMR) in septic and critically ill non-septic ICU patients. *PLoS One.* 2014;9(3):e92331. doi: 10.1371/journal.pone.0092331.
- Ingels C, Møller HJ, Hansen TK, Wouters PJ, Vanhorebeek I, Van den Berghe G. Circulating levels of the shed scavenger receptor sCD163 and association with outcome of critically ill patients. *J Clin Immunol.* 2013;33:619–629.
- Gaiñi S, Koldkjær OG, Pedersen SS, Pedersen C, Moestrup SK, Møller HJ. Soluble haemoglobin scavenger receptor (sCD163) in patients with suspected community-acquired infections. *PMIS.* 2006;114:103–111.
- Gaiñi S, Pedersen SS, Koldkaer OG, Pedersen C, Moestrup SK, Møller HJ. New immunological serum markers in bacteraemia: Anti-inflammatory soluble CD163, but not proinflammatory high mobility group-box 1 protein, is related to prognosis. *Clin Exp Immunol.* 2008;151:423–431.