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The significance of sTREM-1 as a diagnostic biomarker of sepsis in the context of Sepsis-3 definition

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ABSTRACT

Aim. Sepsis remains the leading cause of mortality in spite of advanced diagnostics. The aim of the study was to test the diagnostic value of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in the context of a new definition of sepsis.
Methods. The study was conducted on 41 patients who were suspected of having sepsis according to SIRS (Systemic Inflammatory Response Syndrome) criteria or sterile SIRS. 20 healthy volunteer blood donors were the control group (adult patients of both sexes). According to the latest sepsis criteria (Sepsis-3), patients were retrospectively divided into three subgroups: septic patients, patients with SIRS plus infection and patients with sterile SIRS (non-infectious SIRS).
All subjects had concentrations of sTREM-1 determined by the ELISA method (Abcam commercial test, Cambridge, MA, USA). Samples were collected upon admission to hospital and kept at -20°C until laboratory analysis was performed.
Results. Concentrations of sTREM-1 were significantly increased in patients, compared to the healthy population (p=0.021), but there were no significant differences among subgroups of patients (SIRS plus infection vs. sepsis p=0.871, SIRS plus infection vs. sterile SIRS p=0.72, sepsis vs. sterile SIRS p=0.65).
The value of 300pg/mL was determined to be the optimal cut-off. Concentrations of sTREM-1 were significantly higher in septic patients who did not develop Multiple Organ Dysfunction Syndrome (MODS) within the first 48 hours after admission than in those who did.
Conclusion. According to our results, sTREM-1 failed to express significance as a diagnostic biomarker of sepsis, according to the new definition. Also, it seems not to be a valuable marker in differentiation of sepsis and non-infective SIRS.
Key words: sepsis, sTREM-1, SIRS

INTRODUCTION

The definition of sepsis, which was introduced in 2012, was revised and published in February 2016 by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). (1,2) According to this guideline, sepsis is defined as an organ dysfunction due to a dysregulated host response to infection. Sepsis involves early activation of both pro- and anti-inflammatory responses, with major modifications in non-immunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation. Organ dysfunction should be recognized as a change in baseline of the total SOFA (Sequential Organ Failure Assessment) score of 2 points or more. The term ″severe sepsis″ is completely omitted in the renewed definition. ″Septic shock″ is a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality. (2)
Early diagnosis and estimation of possible complications and outcomes are crucial for timely and adequate therapeutic management. Assessment of clinical severity of sepsis is routinely performed using predictive scores: APACHE II (Acute Physiology and Chronic Health Evaluation) and SOFA. (3) Assessment of the severity of septic state based solely on predictive scores is not completely adequate for prediction of potential complications and lethal outcomes. (4) There is a constant search for a marker that is specific and sensitive enough to increase the predictive value of clinical scores or to be more sensitive than these scores. (5) Microbiological testing of the blood is important in diagnostics of sepsis, but the time required for obtaining results ranges from 48 hours to 7 days. Biomarkers of sepsis, however, can be obtained in a much shorter period of time, which makes them superior in diagnosing sepsis and monitoring therapy. (6,7)
Triggering receptor expressed on myeloid cells-1 (TREM-1) is a biomarker discovered in 2000. It is an immunoglobulin family member that can be found on the surface of neutrophils, monocytes, macrophages and endothelial cells, and has a role in response to infection. Bouchon et al. first described how TREM-1 activates the inflammatory reaction, synthesis of inflammatory mediators, and inhibition of anti-inflammatory mediators. (8) TREM-1 enables the synthesis of proinflammatory

cytokines via Toll-like receptor (TLR) and modulates the innate inflammatory response by enhancing the signal pathway mediated by TLR. TREM-1 is a member of the TREM family of receptors, coded by a gene on the human chromosome 6p21.1. The soluble form of TREM-1 is a soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), that is delivered to the circulation after proteolytic unbinding mediated by metalloproteinase. (8-12)

Recent studies have shown that there is an increase in sTREM-1 concentration in body fluids in sepsis, while its concentration in the non-infectious etiology of inflammatory conditions is not increased. Based on this, sTREM-1 is tested as a potential biomarker for differentiation of sterile SIRS (Systemic Inflammatory Response Syndrome) and sepsis. (8-13)

The aim of this study was to determine the significance of sTREM-1 in differentiation of septic patients, from patients with sterile SIRS and patients who had SIRS plus infection but were not septic, according to Sepsis-3 criteria.

The second aim of this study was to determine the significance of sTREM-1 in the differentiation of patients who developed Multiple Organ Dysfunction Syndrome (MODS), within the first 48 hours of hospital admission, from patients who did not develop MODS.

MATERIALS AND METHODS

This cohort study included 41 patients hospitalized at the Clinic for Infectious Diseases and Department of Anesthesia and Reanimation, Clinical Center of Vojvodina, and 20 healthy volunteer blood donors that constituted the control group. Data were analyzed retrospectively. All consecutively admitted patients who were treated at the Clinic for Infectious Diseases or Department of Anesthesia and Reanimation a the Clinical Center of Vojvodina, from July 1st until December 31st 2015, who were suspected of having sepsis, according to SIRS criteria, were eligible for inclusion. (1) Also, patients with development of sterile SIRS due to pancreatitis or burns were also eligible for inclusion in the study. Following the latest criteria for sepsis, patients were retrospectively divided into three subgroups according to the clinical condition: septic patients (formerly severe sepsis), patients with SIRS plus infection (formerly septic patients) and patients with sterile SIRS (non-infectious SIRS). (2) Exclusion criteria were: age under 18 and patients that did not meet the requirements for diagnosis of sepsis according to SIRS criteria or presence of non-infectious SIRS. (1)

The study was approved by the relevant ethical committee of Clinical Centre of Vojvodina and Medical Faculty of Novi Sad and informed consent was obtained from patients or authorized persons.

All patients included in the study had demographic and clinical data documented. According to the routine diagnostic protocol, all patients had laboratory analyses performed on admission: complete blood count, creatinine concentration, concentrations of electrolytes, bilirubin, blood gas analysis, concentrations of inflammatory parameters (C reactive protein-CRP, procalcitonin PCT) as well as prothrombin time (PT), a parameter of hemostasis. Concentrations of sTREM-1 were determined using commercially available sandwich ELISA testing kits (Abcam commercial test, Cambridge, MA, USA) on admission. Extinction was analyzed automatically on spectrophotometer (Chemwell, USA). Samples were collected upon admission to hospital when sepsis was suspected, and kept at -20°C until laboratory analysis was performed.

According to the manufacturer's guidelines, concentrations of 500-32000 pg/ml are recommended for the highest standard. Since there are no referent values for the healthy population, nor available results on these biomarkers' concentrations in septic patients, we constructed a standard curve based on higher numbers of measurements than recommended. For the highest standard we set a non-diluted standard solution with concentration of 320 ng/ml, followed by diluted solutions (first dilution 1:10 and successive 7 dilutions 1:2) until we reached a minimal concentration of 500 pg/ml.

The origin of sepsis was identified using laboratory analyses, radiological procedures and physical examination, while body fluid cultures obtained on admission to hospital were used for microbiological evaluation. In the first 24 hours we calculated predictive APACHE II and SOFA scores for all patients. (3) Early prediction of MODS is of utmost importance for routine clinical practice , so we tested the predictive value of this biomarker in MODS development.

For the purpose of determination of sensitivity and specificity of sTREM-1-a for the diagnosis of sepsis, as well as to determine cut-off values for sepsis, we constructed a Receiver Operating Curve (ROC) and determined the Areas Under the Curve (AUC).

To assess the development of complications and also the outcome of the disease, we monitored patients for 28 days from the day of sepsis development.

Statistical analysis was performed using IBM SPSS Statistics 20.0. Statistical significance for categorical variables was determined using $\chi 2$ test. Continuous variables were presented as a mean and standard deviation (SD), if normally distributed. If variables did not follow normal distribution, they were presented as a median (interquartile range). Since we confirmed that continuous variables for the majority of parameters were not normally distributed and that variances were not homogenous, we used non-parametric tests for testing the differences among groups: Mann-Whitney U and Kruskal-Wallis test. Statistical significance was set at $p<0.05$. For variables that were normally distributed, we used ANOVA test with post hoc Tukey HSD test for pairwise comparisons.

RESULTS

Forty-one patients were included, according to the inclusion criteria, and were not excluded, according to exclusion criteria. The majority of patients, 21 (51.21%), fulfilled the criteria for diagnosis of sepsis according to Sepsis-3 definition, while there was an equal number of patients with sterile SIRS, 10 (24.39%), and SIRS plus infection, 10 (24.39%). The mean age of patients was 58±20.7 years (range 20-85). There was no significant difference in sex ($\chi 2=0.024$; $p=0.87$).

The urinary tract was the most common origin of sepsis - 11(35.48%) - followed by the respiratory tract, 8 (25.8%), while sepsis related to use of central venous catheters was not frequent, 1 (3.22%).

Seventeen patients (41.46%) developed MODS within the first 48 hours after hospital admission. Results obtained by $\chi 2$ square test show that the difference in MODS development is trending towards significance ($p=0.054$) when all subgroups of patients are compared (table 1).

MODS was less common in patients with SIRS plus infection than in the other two groups: SIRS plus infection vs. sepsis ($p=0.041$), SIRS plus infection vs. sterile SIRS ($p=0.019$), sterile SIRS vs. sepsis ($p=0.519$).

In our study 28 (68.29%) patients survived, while 13 (31.71%) had a lethal outcome. Statistical significance was obtained among the three subgroups according to outcome, with a significantly higher lethal outcome in patients with sterile SIRS than in the other two groups: sepsis vs. sterile

SIRS (70% vs. 23.8%, p=0.014), SIRS plus infection vs. sterile SIRS (70% vs. 10%, p=0.006). There was no statistical significance between SIRS plus infection and sepsis groups (23.8% vs 10%, p=0.363).

We tested routine predictive scores (APACHE II and SOFA) as potential predictors of clinical severity. Post hoc analysis showed that the difference in APACHE II score was derived from the difference between groups of patients with SIRS plus infection and sepsis (p=0.002) and between groups of SIRS plus infection and sterile SIRS (p=0.001). APACHE II score was significantly lower in patients with SIRS plus infection compared to the other two groups, while groups with sepsis and sterile SIRS did not differ significantly according to APACHE II score (p=0.578) (table 2).

Post hoc analysis for SOFA score showed that the difference confirmed by ANOVA came from significantly lower SOFA scores in patients with SIRS plus infection than in septic patients (p=0.001). Groups of patients with sterile SIRS and sepsis did not differ significantly according to SOFA score (p=0.372), similarly to the groups of SIRS plus infection and sterile SIRS (p=0.099). There was no significant difference in routine laboratory parameters among the three subgroups of patients (table 3).

Concentrations of sTREM-1 were significantly increased in all three groups of patients compared to healthy subjects (p=0.021) (table 3), but concentrations did not vary significantly in the observed groups of patients (SIRS plus infection vs. sepsis p=0.871, SIRS plus infection vs. sterile SIRS p=0.72, sepsis vs. sterile SIRS p=0.65).

Although the small number of patients is a limiting factor for proper analysis of ROC, for the purpose of determination of sensitivity and specificity of sTREM-1-a in diagnosing sepsis, as well as for determining cut-off values for sepsis in our sample of patients, we constructed ROC curves and determined areas under the curve (AUC) (table 4).

The value of 300 pg/mL is determined to be the optimal cut-off, since higher concentrations indicate systemic inflammation, irrespectively of the presence of organ dysfunction and whether inflammation was caused by infectious or non-infectious agents (Table 4).

Concentrations of sTREM-1 were significantly higher in septic patients who did not develop MODS within the first 48 hours from admission than in those who did (p=0.016). However, this does not apply

Table 1. Development of MODS within the first 48 hours of hospital admission

MODS 48h	SIRS + infection	SEPSIS	Sterile SIRS	p*
N	10	21	10	0.054*
Yes	1(10.0%)	10(47.6%)	6(60.0%)	
No	9(90.0%)	11(52.4%)	4(40.0%)	

*$\chi 2$ square test
MODS, Multiorgan dysfunction syndrome.

Table 2. APACHE II and SOFA score results

SCORE	SIRS plus infection	SEPSIS	Sterile SIRS	p*
N	10	21	10	
APACHE II	6.00±4.42	17.14±8.57	20.20±9.43	0.001
SOFA	1.60±0.84	6.10±3.73	4.50±2.80	0.002

* ANOVA
APACHE, Acute Physiology and Chronic Health Evaluation; SOFA - Sequentional Organ Failure Assessment.

Table 3. Routine laboratory parameters and sTREM-1 concentrations.

Laboratory parameter	SIRS plus infection	SEPSIS	Sterile SIRS	p*
Leukocytes	12.02±5.35	14.07±8.40	18.31±6.73	0.161
Neutrophils/lymphocytes	11.5(5.5-13.5)	10(4-14.5)	12.5(8.5-26.5)	0.533
Thrombocytes	197.5(157.0-220.0)	168(133.0-285.0)	222(174.0-230.0)	0.631
C-reactive protein (mg/L)	248.2(185.0-327.0)	174.6(143.0-229.4)	158.0(113.0-213.8)	0.085
Procalcitonin (ng/mL)	6.0(1.6-29.5)	12.0(6.0-19.5)	3.0(1.1-6.0)	0.587
Prothrombin time (R)	1.025(1.000-1.520)	1.000(1.000-1.100)	1.000(1.000-1.115)	0.328
Bilirubin (μmol/l)	8.9(8.0-11.4)	12.9(6.0-19.0)	12.0(11.4-17.0)	0.394
Creatinine (μmol/l)	79.0(61.0-98.0)	87.0(61.0-207.0)	110.5(53.0-173.0)	0.471
sTREM-1 (pg/mL)	400(200-700)	400(100-1700)	550(100-4000)	0.021

* Kruskal-Wallis test.
SIRS, Systemic inflammatory response syndrome; sTREM - Solubile triggering receptor expressed on myeloid cells-1.

Table 4. Analysis of optimal cut off values, sensitivity and specificity of sTREM-1-a in diagnosis of sepsis compared to healthy controls.

	AUC	Cut-off values sTREM	Sensitivity	Specificity	p
Controls vs. sepsis	0.750	300	71.4%	73.7%	0.015
Controls vs. SIRS plus infection	0.753	300	62%	68.4%	0.041
Controls vs. sterile SIRS	0.752	300	71.4%	73.7%	0.053

AUC, area under the curve; SIRS, Systemic inflammatory response syndrome; sTREM, Solubile triggering receptor expressed on myeloid cells-1.

when all patients are taken into account. Also, sTREM-1 did not prove itself to be a significant biomarker for differentiation of patients who had a lethal outcome from the survivors- not in the whole sample of patients, neither in the subgroup of septic patients (table 5).

Table 5. Predictive value of sTREM-1 in the development of MODS within the first 48 hours of admission and in prediction of outcome.

	MODS			**Outcome**		
	Yes	No	p*	Survival	Lethal	p*
Whole sample(n) Median(IQR)	n=17 200 (100-700)	n=24 700 (300-2050)	0.061	n=28 700 (100-1700)	n=13 400 (200-700)	0.384
SIRS+inf(n) Median(IQR)	n=1	n=9 400(200-700)	NA	n=9 550 (200-700)	n=1	NA
Sepsis(n) Median(IQR)	n=10 200 (100-400)	n=11 1700 (550-2400)	0.016	n=16 700 (100-2050)	n=5 200 (200-400)	0.266
Sterile SIRS(n) Median(IQR)	n=6 450 (100-1700)	n=4 2200 (250-4280)	NA	n=3 4000 (2050-4280)	n=7 400 (150-1200)	NA

* $\chi 2$ test.
NA, not applicable due to small number of patients
MODS, Multiorgan dysfunction syndrome; SIRS, Systemic inflammatory response syndrome; sTREM, Solubile triggering receptor expressed on myeloid cells-1.

DISCUSSION

Every disease that causes damage to tissue can lead to MODS development, mainly sepsis, trauma, burns and pancreatitis. (14) Based on our results, the development of MODS within the first 48 hours after hospital admission, in the whole study population, was only trending towards significance. Nevertheless, if pairwise comparisons between groups are performed, we observe that MODS development in patients with SIRS plus infection is less frequent than in the other two groups. This supports the fact that when the new sepsis definition is used, patients with a more severe clinical course of disease are recognized on time. (2) Johnson et al. observed that around 60% of patients with severe pancreatitis presented with MODS or developed MODS within the first 72 hours after the onset of symptoms. (15)

Even when therapy is adequate, mortality from sepsis remains over 10%, and from septic shock over 40%. (2) There was a significant difference in disease outcome among the three observed groups, with a more frequent lethal outcome in patients with sterile SIRS than in the other two groups. There is increasing evidence that in the early phase of acute pancreatitis, excessive leukocyte activation and inflammatory cytokine bursts are critical for development of early organ failure and increased risk of MODS, which implies that non-infectious systemic inflammation can be as severe as sepsis. (16,17)

In our study, APACHE II score was significantly lower in the group of patients with SIRS plus infection than in the other two groups. We noticed that in this group MODS was less frequent than in the other two groups, which makes APACHE II score a good predictor of clinical severity.

The SOFA score showed significantly lower values in patients with SIRS plus infection compared to the other two groups and compared to APACHE II score. Recent studies have brought attention to the SOFA score as a useful diagnostic tool for identification of patients with sepsis. (18) Kenzaka et al. have pointed out that SOFA scores in patients with sepsis, severe sepsis and septic shock are directly proportional to the severity of clinical state. (19) Researchers from Turkey have found significantly higher SOFA scores in patients with sepsis compared to patients with sterile SIRS. (20)

There were no significant differences among the three groups of patients concerning routine laboratory parameters. CRP is an important diagnostic marker of inflammatory states, including infections, which was confirmed in our study also, since the level of CRP did not differ among groups. (21) In our study, PCT was the highest in septic patients but it did not differ significantly among groups. Studies have confirmed that the PCT level correlates with the severity of disease. Endo et al. showed higher PCT levels (an important marker in differential diagnosis of sepsis and sterile SIRS) in septic patients. (22) These results are probably the result of the smaller sample of patients in our study, compared to other studies.

In the last couple of years, attention has been focused on the earliest possible diagnosis of sepsis and search for adequate markers for the differential diagnoses of sepsis and sterile SIRS. Among them, the most important are clinical scores and immunological markers, with PCT and sTREM-1 having a leading role. (23,24)

In our study, concentrations of sTREM-1 were significantly higher in all three groups of patients compared to healthy subjects, but concentrations did not differ significantly among the three subgroups. Gibot et al. tested both PCT and sTREM-1 in the diagnoses of sepsis and showed that both markers were significantly higher in septic patients. (25) Other studies also showed that sTREM is a sensitive marker for establishing the diagnosis of sepsis. (11, 26) In the study that also tested the diagnostic value of sTREM-1 in patients with sepsis and sterile SIRS, concentrations of this biomarker were significantly higher in septic patients than in patients with sterile SIRS. (27) A meta-analysis, that included 11 studies and 1795 patients, found that sTREM had a sensitivity and specificity of 79% and 80% (respectively) in differentiation of sepsis from sterile SIRS. However, it is not considered a unique biomarker that is sufficient for diagnosing sepsis. (28) A Turkish study reported a sensitivity and specificity of 81.8% and 73.2% in differentiation of sepsis and sterile SIRS. (20) Gibs et al. found it superior to PCT and CRP (28) while other studies showed that it was inferior for diagnosing sepsis. (29-31)

A study published in 2013, that tested the dynamics of sCD163, sTREM-1-a, PCT and CRP in 30 patients with SIRS and 100 patients with sepsis, showed that these biomarkers were significantly higher in septic patients and that the diagnostic value of sTREM-1-a was significantly higher than sCD163, PCT and CRP, which implies that it can be considered a better marker of sepsis. (32)

Our study showed that sTREM-1 is not a valuable marker for sepsis in the light of the new definition. Recent studies have shown that concentrations of serum sTREM-1 can be increased in all inflammatory conditions, including SIRS. (33)

For determination of these biomarkers' concentrations in body fluids, there are

several ELISA tests with different detectability ranges, used only for research. A recommended reference range for the healthy population does not exist, so we measured sTREM-1 concentration in 20 healthy subjects.

The value of 300 pg/mL was determined to be the optimal cut-off, since higher concentrations indicate systemic inflammation, irrespectively of the development of organ dysfunction and whether inflammation was caused by infective or non-infective agents. The mean value of sTREM-1 in the study by Bayram et al. in septic patients was 398.97 pg/mL. (20)

In the group of septic patients who did not develop MODS within the first 48 hours, sTREM-1 was significantly higher than in those who did. For the other groups this conclusion was not confirmed. A potential explanation for these results might be in the more intensive immunological response in patients with septic shock in comparison to patients with less severe conditions. A possible explanation for lower concentrations in patients with multiorgan dysfunction can be in the exhaustion of the homeostatic reserve and the state of anergy. Results of the study reported by Su et al. showed a similar correlation of sTREM-1 concentration with the severity of clinical condition. (34)

These results are controversial at first glance because sTREM-1 is an indicator of synthesis of proinflammatory cytokines. It would be expected that there is a correlation between sTREM-1 concentrations and MODS development. The absence of this correlation can be explained by the great individual variability in response to pathogens that lies mostly in genetic predisposition.

Studies conducted in various centers reported that concentrations of sTREM-1-a were higher in patients with a lethal outcome due to sepsis than in survivors. (24) In the study by Gibot et al., sTREM-1 was reported as a good prognostic marker especially in the long-term follow up. (25) In our study, although there were no significant differences, concentrations of sTREM-1 were higher in survivors than in patients with a lethal outcome in the overall population and in septic patients. According to our results, sTREM-1 was not a reliable biomarker of lethal outcome.

Study limitations

There were several limitations in the current analysis. The sample size in our study is not adequate for all statistical analyses (especially for subgroups). Also, the small number of patients is a limiting factor for proper analysis of ROC. Further trials with larger sample sizes are needed to identify the optimal cut-off value and to establish diagnostic accuracy. It is necessary to continue studying the prognostic potential of sTREM-1 as a predictor of course of sepsis.

CONCLUSIONS

Our results indicate that sTREM-1 is not a reliable marker in the diagnosis of sepsis in the light of the new definition, neither in the differential diagnosis of sepsis nor of sterile SIRS. Furthermore, sTREM-1 is not a reliable biomarker of MODS development within the first 48 hours of admission in patients with systemic inflammation. The significance of sTREM-1 as a diagnostic and prognostic marker in sepsis is yet to be defined and determined in future research.

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