



LETTER



APRIL and sTACI could be predictors of multiorgan dysfunction syndrome in sepsis

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ABSTRACT

Although the role of B cells in sepsis immunoregulation has become an interesting topic, there is lack of data on the role of B cell function regulators in prediction of multiorgan dysfunction syndrome (MODS). The aim of this study was to evaluate the prognostic value of A Proliferation Inducing Ligand (APRIL) and soluble Transmembrane Activator and CAML Interactor Protein (sTACI), the main B cell function regulators, in prediction of MODS development within the first 48 h after admission to intensive care unit, among septic patients. We included 112 patients with sepsis, treated at Clinic for Infectious Diseases and Emergency Center, Clinical Center of Vojvodina, Novi Sad, Serbia. Plasma concentrations of APRIL and sTACI were determined at the admission and potential development of MODS was confirmed in the first 48 h. Concentrations of APRIL ($p = 0.003$) and sTACI ($p < 0.001$) were higher in patients who developed MODS ($n = 30$). ROC curve analysis showed that AUC for sTACI (AUC = 0.764) was greater than that for procalcitonin (AUC = 0.719) and APRIL (AUC = 0.673) in MODS development prediction. Multivariate regression analysis showed that sTACI, as an anti-inflammatory biomarker stimulating the apoptosis of B cells, was the only independent predictor of MODS, beside SOFA score. Elevated level of sTACI could be the alarm for the increased B cell apoptosis and development of immune paralysis. Including these biomarkers into predictive scores specific for septic patients may potentially improve their sensitivity and specificity. Measurement of their concentrations dynamics could contribute to better assessment of sepsis evolution and timely introduction of immunomodulatory therapy.

ARTICLE HISTORY

Received 30 March 2018
Revised 30 March 2018
Accepted 5 April 2018

KEYWORDS

biomarkers; multiple organ failure; prognosis; sepsis; Transmembrane activator and CAML interactor protein; tumor necrosis factor ligand superfamily member 13

Sepsis is the leading cause of death in intensive care units (ICU). Despite all the medical procedures undertaken, mortality due to sepsis remains high [1,2].

Predicting potential development of multiorgan dysfunction syndrome (MODS) before it becomes clinically manifest is essential for timely initialization of therapy. Therefore, experts in the field continue to investigate the biomarkers predictors of MODS development within the first few hours after admission to the ICU [3,4].

It is known that sepsis pathogenesis implies secretion of large number of pro- and anti-inflammatory mediators, referred to as the cytokine storm. According to the literature, these mediators have different diagnostic and prognostic values [5–7]. Whether pro- or anti-inflammatory cytokines dominate in an individual patient, depends on various factors, including age, comorbidities and

assumably genetic predisposition [6,8]. To the best of our knowledge, prognostic value of cytokines regulating B-cell function, as well as their role in the pathogenesis of sepsis, have not been clearly characterized.

Members of the tumor necrosis factor alpha (TNF- α) superfamily, A Proliferation Inducing Ligand (APRIL) and Transmembrane Activator and CAML Interactor Protein (TACI), have been recognized as the main regulators of B-cell homeostasis [9–11]. Therefore, they have been studied in the autoimmune and malignant diseases [12–14], while there are not much available data on their role in bacterial infections. Roderburg et al. were the first to examine the role of APRIL in sepsis, in the aspect of mortality prediction. However, the role of APRIL in the prediction of early development of MODS has not been evaluated to the date [15]. However, there

is no available data on the concentrations of soluble TACI (sTACI) in septic patients.

APRIL stimulates B-cell proliferation and is thought to be essential in regulating their homeostasis. It is responsible for growth stimulation, differentiation and regulation of apoptosis of B-cells [9,10]. Taken into account the role of humoral immunity in the pathogenesis of sepsis [10], as well as the proven role of APRIL in homeostasis of B-cells [9,11], we hypothesized that the concentration of this biomarker could serve as the valuable predictor of the sepsis course and outcome.

TACI receptor is expressed in all developmental stages of B-cells after leaving the bone marrow. The highest level of expression is found on so-called mature innate-like B-cells: marginal zone B-lymphocytes [9,16] and B1-lymphocytes [10], that implies their essential role in the immune response to T-cell independent antigens. Mutations in the gene for TACI receptor have been identified in the patients with different types of immunodeficiency [17]. In addition to its transmembrane form, TACI receptor circulates as a soluble form, playing the same role in the circulation. Prior research has shown that concentrations of sTACI receptor strongly correlate to the concentrations of transmembrane form of the receptor [18]. Since the concentrations of the soluble form of the receptor are easily determined using ELISA (enzyme-linked immunosorbent assay) test, this biomarker could become important in everyday clinical practice.

The aim of this study is to determine the prognostic value of APRIL and sTACI receptors in the prediction of MODS development, within the first 48 hours after the admission to the ICU.

In this study we included 140 patients admitted to the Clinic for Infectious Diseases and Department for Anaesthesiology and Reanimation of the Clinical Center of Vojvodina, with diagnosis of sepsis, defined according to the criteria of The Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) [50]. According to Sepsis-3 definition, criteria for diagnosis of sepsis are acute increase of SOFA score for 2 or more points, caused by infection. SOFA score represents numerical scoring system used for the assessment of the function of six organ systems- central nervous, cardiovascular, respiratory, renal, liver and coagulation- by scoring from 0 to 4 (0 is given for preserved function, 1 is minor organ impairment, while 2 or more points mean the dysfunction of an organ system). MODS is defined as the dysfunction of at least two organ systems that were given scores 2 or more using SOFA scoring system.

Initially, all the patients with SOFA score 2 and higher were included in the study ($n = 140$). Patients with signs of MODS development present at the admission were excluded from further analysis ($n = 28$). The

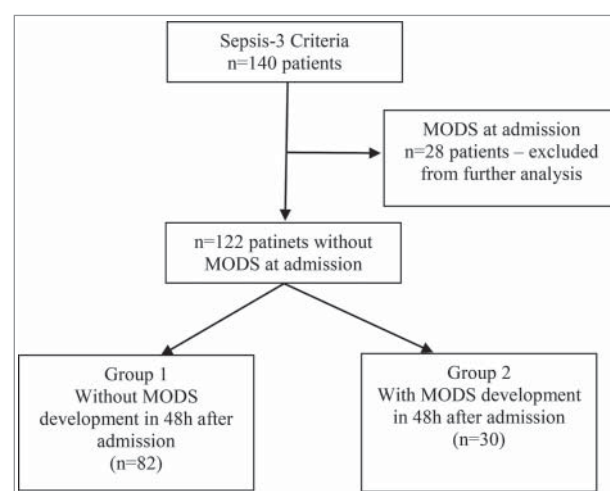


Figure 1. Patients selection criteria.

development of MODS was monitored in the rest of 112 patients (Figure 1).

One hundred- fourty patients presented with the diagnosis of sepsis and had routine laboratory parameters determined within the first hour after admission (complete blood count (CBC), glucose, urea, creatinine, electrolyte levels, bilirubin level and concentrations of C reactive protein (CRP) and procalcitonin (PCT)), as well as predictive APACHE II (Acute Physiology and Chronic Health Evaluation II) and SOFA score (Sequential Organ Failure Assessment). Concentrations of C-reactive protein (CRP) were determined using immunoturbidimetric assay (ABX Micros) and expressed in mg/L. Concentrations of procalcitonin (PCT) were determined using automatic analysed (mini Vidas), the lower limit of detection was set at 0.05 ng/L.

Twenty-eight patients presented with dysfunction of two or more organs at the admission (in two or more organ systems, SOFA score was equal to or higher than 2) so these patients were excluded from the study.

Plasma samples of the rest 112 patients were frozen on -70°C and concentration of APRIL and sTACI were determined later, using ELISA tests, by commercially available R&D Systems kits (Human APRIL/TNFSF13 DuoSet ELISA R&D and Human TACI/TNFRSF13B DuoSet ELISA R&D), according to the technical guide of the producer. Concentrations of APRIL were expressed in ng/ml, and BAFF and sTACI in pg/ml. Tests we used were sandwich enzyme immunoassays for the quantitative measurement of APRIL and sTACI in human serum, plasma or cell supernatants, with detection limits of 0.94–60.0 ng/ml for APRIL and 93.6–6000.0 pg/ml for sTACI.

In the following period we monitored the state of patients and confirmed the development of MODS in the first 48 hours after the admission. MODS was defined as the development of two or more organs dysfunction

(acute increase of ≥ 2 SOFA points per each organ system) in the first 48 h of the admission to the ICU.

Source and cause of infection were confirmed by isolation from body fluid culture (blood culture, urine, sputum culture derived from forced sputum production, tracheal aspiration, bronchoalveolar lavage, cerebrospinal fluid culture) or using SEPTIFAST method or radiology methods (Chest rail or CT scan).

Exclusion criteria were: patients with systemic inflammation caused by some other condition like burns or pancreatitis, polytraumatized patients, patients in haemorrhagic shock, patients with malignancy, autoimmune disorder, liver or cardiac failure, pregnant women, patients younger than 18 and patients who have not signed informed consent.

The study was approved by ethical committee of the Clinical Center of Vojvodina. All the participants have signed the informed consent (the patient himself, or the family)

Data were analyzed using SPSS v. 21.0 software. Categorical variables were expressed numerically and as a percentage, while mean values of continuous variables were given as arithmetic means and standard deviations or median and interquartile range, as appropriate according to the distribution. Non-parametric approaches were used, since most continuous variables were skewed. Differences between groups were evaluated using Mann-Whitney U test for continuous variables and using χ^2 test for categorical variables. For all the variables that were statistically significant, we constructed Receiver Operating Characteristic (ROC) curves and measured areas under curve (AUC). For the purpose of defining independent predictors of MODS development, we performed multivariate regression analysis using binary logistic regression model. We constructed regression model with the inclusion of the MODS development in the first 48 hours after admission as the dependent variable. For the independent variables we picked those parameters that showed predictive value using univariate analysis. In the case of multicollinearity between parameters, we included in the model the parameter that showed greater predictive value using univariate analysis. Significance (p) was set at the value of 0.05.

We included overall of 112 patients diagnosed with sepsis in the study, hospitalized in the Clinic for Infectious Diseases and Department for Anaesthesiology and Reanimation, Clinical Center of Vojvodina. The state of each patient was monitored and eventual development of MODS was proven within the first 48 hours after the admission.

In 30 (26.8%) patients we confirmed MODS development, while in 82 (73.2%) patients there were no signs of MODS in the first 48 hours after admission to intensive

care unit. Demographic and clinical data on the patients are summarized in Table 1. Among patients who developed MODS within 48 hours, 14 of them had 2-organ failure, 11 of them had 3-organ failure, and 5 of them had 4-organ failure. Structure of the organ failure among patients who developed MODS 48 h after admission was following: kidney (creatinin $>170 \mu\text{mol/l}$) – 22 patients, liver (bilirubin $>32 \mu\text{mol/l}$) – 13 patients, coagulation (platelets $<100 \times 10^6/\text{L}$) – 12 patients, cardiovascular system (Dopamin or Dobutamin therapy) – 10 patients, central nervous system (GCS < 13) – 19 patients, respiratory insufficiency ($\text{pO}_2/\text{FiO}_2 < 300 \text{ mmHg}$) – 5 patients.

Observed groups of patients (MODS development present or absent) showed no statistically significant difference in age and gender.

Baseline APACHE II and SOFA scores were significantly higher in patients who developed MODS, compared to those who did not develop MODS within the first 48 hours after admission.

The cause of infection was confirmed by blood culture or SEPTIFAST method in 30 (26.8%) patients. Data on the isolated pathogens are summarized in Table 1.

Baseline levels of relevant laboratory parameters obtained at the admission are shown in Table 2. Among routine laboratory parameters procalcitonin (PCT) was

Table 1. Demographic and clinical features of patients.

Variable	MODS development in first 48 h		p
	Present n = 30	Absent n = 82	
Age (x \pm SD) (Min-max)	65.47 \pm 12.26 (35–87)	59.35 \pm 16.54 (18–85)	0.068 *
Gender – n (%)			
male	17 (56.7%)	46 (56.1%)	0.957**
Female	13 (43.3%)	36 (43.9%)	
APACHEII (x \pm SD)	18.30 \pm 3.40	11.90 \pm 5.18	<0.001**
SOFA (x \pm SD)	7.33 \pm 1.97	3.95 \pm 1.79	<0.001*
Bloodstream infection (Blood culture or SEPTIFAST confirmed)	8/30 (26.7%)	22/82 (26.8%)	
S. aureus	1	3	
S. pneumoniae	2	4	
Coagulasa negative Staphylococcus	0	2	
Enterococcus spp.	0	1	
Enterobacter spp.	1	0	
N. meningitidis	0	3	
K. pneumoniae	1	3	
Acinetobacter	2	1	
E. coli	1	5	
SEPSIS SOURCE			
Lungs	5	14	
Urinary tract	9	27	
Abdomen	11	15	
Central nervous system	3	10	
Soft tissue	1	12	
Other	1	4	

*p values calculated using unpaired t test (normal distribution).

**p values calculated using chi-square test.

Table 2. Baseline levels of laboratory parameters.

Variable	MODS development in first 48 h		p*
	Present n = 30	Absent n = 82	
WBC [$\times 10^9/L$]	11.0 (8.4–16.2)	15.3 (8.1–20.5)	0.267
CRP [mg/L]	205.8 (126.7–284.0)	232.6 (179.6–281.4)	0.289
PCT [ng/L]	73.4 (14.9–146.9)	12.0 (3.4–29.1)	<0.001
Fibrinogen [g/L]	4.8 (3.9–5.7)	5.5 (4.5–6.3)	0.069
Plt [$\times 10^9/L$]	141.5 (106.0–192.0)	188.0 (118.0–273.0)	0.067
INR	1.3 (1.1–2.1)	1.3 (1.1–1.6)	0.392
APRIL [ng/mL]	10.0 (7.0–13.5)	6.5 (4.7–10.0)	0.005
sTACI [pg/mL]	887.5 (600.0–1425.0)	275.0 (150.0–700.0)	<0.001

*p values calculated using Mann-Whitney U test (skewed distribution), data presented as median (IQR).

shown to be important predictor of MODS development, while white blood cell (WBC) count, CRP concentration, fibrinogen, platelet count and INR failed to predict MODS development (Table 2). In addition to PCT, APRIL and sTACI were significant predictors of MODS development (Table 2 and Figure 2).

For the purpose of quantification and comparison of the discriminative value of separate parameters in prediction of MODS development within the first 48 hours after admission to the ICU, we constructed ROC curves for parameters that were classified as significant predictors of MODS development (Table 3 and Figure 3). The most valuable in the prediction of MODS development within the first 48 hours after the admission to the ICU, were APACHE II (AUC = 0.869, $p < 0.001$) and SOFA scores (AUC = 0.888, $p < 0.001$). Although there were no significant differences among individual biomarkers, the highest predictive value was observed with sTACI (AUC = 0.764, $p < 0.001$), that had higher predictive value than routinely used CRP and PCT. An important marker, in addition to sTACI, was APRIL (AUC = 0.673, $p < 0.001$), which was somewhat less significant than procalcitonin (AUC = 0.719, $p < 0.001$) (Table 3 and Figure 3). When comparing significance between AUC ROC of observed variables, both scores showed significantly higher AUC than any other single biomarker (AUC_{SOFA} vs AUC_{PCT} $p = 0.004$, AUC_{SOFA} vs

AUC_{APRIL} $p < 0.001$, AUC_{SOFA} vs AUC_{sTACI} $p = 0.04$, AUC_{APACHEII} vs AUC_{PCT} $p = 0.012$, AUC_{APACHEII} vs AUC_{APRIL} $p = 0.002$). However, AUC_{APACHEII} was not significantly higher than AUC_{sTACI} ($p = 0.07$). There was no significant difference among AUC ROC value of separate biomarkers unlike (AUC_{sTACI} vs AUC_{APRIL} $p = 0.178$, AUC_{sTACI} vs AUC_{PCT} $p = 0.618$, AUC_{APRIL} vs AUC_{PCT} $p = 0.554$).

In order to assess the predictive role of all the observed parameters we performed multivariate analysis using binary logistic regression model. In the model we included parameters that showed the greatest predictive value using previously described methods. Taken into account high correlation between APACHE II and SOFA scores (Spearman $\rho = 0.811$), we could not include both scores in the regression model, so we picked SOFA score, due to its higher predictive value. Along with the SOFA score, we included PCT, sTACI and APRIL as independent variables.

Model was statistically significant χ^2 (4, N = 112) = 62.252, $p < 0.001$. It successfully differentiated patients that developed MODS from those who did not. Model explained 42.6–62.0% of variance in the means of MODS development and classified correctly 84.8% of cases. Introducing the observed parameters in the regression model, only two independent variables (SOFA score $p < 0.001$ and sTACI $p = 0.004$) gave the unique contribution to the model. The most important predictor remained SOFA score, which significance ratio was 2.247, compared to sTACI's significance ratio of 1.001 (Table 4).

The significant predictors of MODS development in our study were APACHE II and SOFA scores, as well as PCT and concentrations of APRIL and sTACI receptor. According to the AUC analysis, the most significant predictors of MODS development within the first 48 hours after admission to the ICU were predictive APACHE II (AUC = 0.869) and SOFA scores (AUC = 0.888).

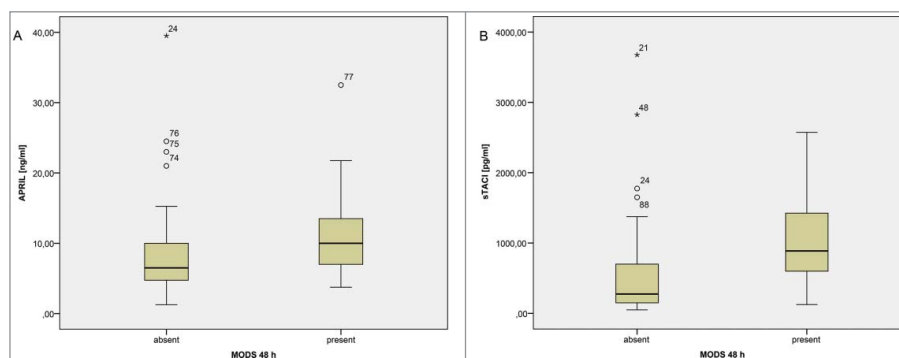


Figure 2. APRIL (a) and sTACI (b) concentrations in the means of MODS development within the first 48 h after admission. Abbreviations: APRIL – A Proliferation Inducing Ligand; sTACI – Soluble Transmembrane Activator and CAML Interactor Protein; MODS – Multiorgan Dysfunction Syndrome.

Table 3. ROC curve analysis.

	AUC	SE	95% CI	p	Cut-off	Sens	Spec
APACHE II	0.869	0.0329	0.792–0.925	<0.001	14	90.00%	75.61%
SOFA	0.888	0.0323	0.815–0.940	<0.001	5	76.67%	80.49%
PCT	0.719	0.0552	0.630–0.803	<0.001	34.6	70.00%	79.27%
APRIL	0.673	0.0572	0.580–0.761	<0.001	8.25	66.7%	67.07%
sTACI	0.764	0.0501	0.674–0.839	<0.001	550	76.67%	67.07%

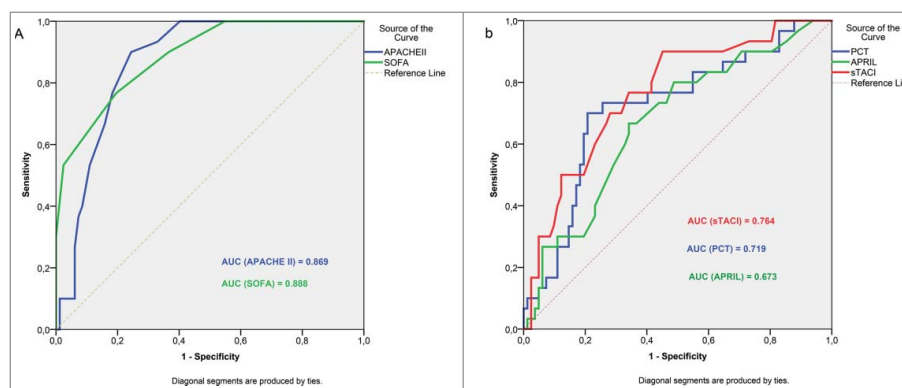


Figure 3. ROC curve analysis comparing the prognostic values of APACHE II and SOFA scores for prediction of MODS development (a), and ROC curve analysis comparing the prognostic values of APRIL, sTACI and procalcitonin for prediction of MODS development (b). Abbreviations: APRIL – A Proliferation Inducing Ligand; sTACI – Soluble Transmembrane Activator and CAML Interactor Protein; MODS – Multiorgan Dysfunction Syndrome; PCT – procalcitonin; AUC – Area Under the Curve.

Table 4. Binary logistic regression model for the prediction of MODS development within first 48 h after admission.

Variable	B	S.E.	Wald	df	Sig.	Exp(B)
Step 1 ^a						
SOFA	0.809	0.170	22.566	1	<0.001	2.247
APRIL	0.030	0.058	0.273	1	0.601	1.031
sTACI	0.001	<0.001	8.178	1	0.004	1.001
PCT	0.004	0.003	1.643	1	0.201	1.004
Constant	-7.192	1.344	28.623	1	<0.001	0.001

^aVariables entered on step 1: SOFA, APRIL, TACI, PCT.

Among the individual biomarkers, the most valuable predictor was sTACI with AUC = 0.764, while areas under curves for APRIL (AUC = 0.673) and PCT (AUC = 0.719) were smaller. Using multivariate regression analysis, sTACI was the only independent predictor of MODS development within the first 48 hours after admission to the ICU, in addition to the SOFA score.

Although several studies presented CRP as the predictor of MODS development [19] and lethal outcome, majority of the studies [20–23], as well as review articles [24] are concordant with our results, that did not confirm prognostic relevance of baseline levels of CRP in sepsis [20–24].

New definition of sepsis puts the development of organ failure as the parameter for establishment of diagnosis into focus. Theories connected with the organ failure development are various, with leading role attributed to the hypoperfusion and conversion to anaerobic

metabolism. The level of lactates is thus one of the major indicators of tissue damage [25,26]. However, recent studies point to the multifactorial etiology of organ failure development in sepsis, with important role being attributed to the interaction of immune-inflammatory, nervous, endocrine system, as well as behavioral and emotional status. Many authors have emphasized the unregulated immune response as dominant cause of MODS development [27,28]. Inflammatory immune reaction can provoke direct tissue toxicity and contribute to the organ failure. Activating intrinsically inflammatory cells in distant organs, different than the primary organ affected, leads to the development of multiorgan dysfunction and formation of positive interreaction (inflammatory mediators released into the circulation cause cytokine storm and further organ failure) [27,28]. Research on the single organ dysfunction are concordant with abovementioned pathophysiological theories of sepsis-induced organ failure. Namely, Gomez and Kellum reported the dominant role of inflammation per se in the sepsis induced acute kidney injury, more than hypoperfusion itself [29]. In addition, sepsis-induced brain dysfunction is described as the consequence of hypoperfusion and neuroinflammation [30,31]. In addition to the hypoperfusion in the liver dysfunction, the role of inflammatory response and metabolic changes that decrease the potency of biotransformation processes has

been described [32]. Therefore, it comes as no surprise that markers of immune response represent important predictive factors in MODS development in septic patients – APRIL, secreted by the antigen presenting cells in the first line of defense, and its soluble receptor, TACI.

Although the role of APRIL in bacterial infections has not been cleared to the date, our results are not surprising, since it plays the key role in B-cell regulation [10,11] while B-cells have an important role in immune response to bacterial infections [33–36]. In the research on APRIL concentrations in autoimmune and malignant diseases increased concentrations of this biomarker are shown to correlate with the degree of B-cell activation [14,37–39]. Studies showed that the main role of APRIL is in induction of B-cell proliferation and regulation of the B-cells apoptosis [9,11]. This feature is used for the synthesis of new drugs in the treatment of autoimmune diseases and lymphomas, which block the function of APRIL, induce the apoptosis of B-cells and that way decrease the number of circulating B-cells [9,40]. APRIL is secreted by antigen-presenting cells that are the first line defence from infection. Recent study of Roderburg et al. showed that APRIL may serve as a valuable predictor of sepsis outcome, defined as survival or lethal [15]. Concentrations of this molecule seem to increase during bacterial infections and may serve as a useful biomarker of MODS development, since those concentrations indirectly determine the degree of initial activation of innate immunity and further coordination of innate and adaptive immunity. To the date, there are no published data on the role of APRIL in MODS development prediction.

Nevertheless, concentrations of soluble TACI receptor have shown better predictive capacity than APRIL, as well as the other evaluated sepsis predictors. Pathophysiological basis of obtained results is partly explained by the fact that TACI is the receptor that binds APRIL with the highest affinity [41]. After binding with transmembrane form of TACI receptor, APRIL expresses its protective role on B-cells, preventing their apoptosis. Soluble TACI receptor in blood has the same function as transmembrane form. Binding circulating APRIL before it binds to transmembrane receptor, sTACI is considered to be the main negative regulator of B-cell count [10,18,42]. Our results show that the concentrations of sTACI are better predictor of negative course of the sepsis than APRIL concentrations, and indirectly point to the potential development of depletion of the circulating B-cell count and entering the “state of immune paralysis”, that leads to the lethal outcome. Earlier post mortem studies on patients who died of sepsis, showed an important depletion of all the lines of white cells, first of all

lymphocytes that are more important for the development of immune paralysis than apoptosis of neutrophils and other immune cells [43]. In addition, it is shown that treatment modalities preventing apoptosis of all the white cell lines, including B-cells, increase the survival rate [33,43–45]. Apoptosis of the cells is recognized as one of the basic processes in MODS development in sepsis. Patients with increased apoptosis at the admission, presented with greater chances for later development of MODS [46–48]. Our results show that sTACI concentration is the most important individual predictor of the negative outcome, which confirms the urge for development of therapeutic modalities that would block the process of B-cell apoptosis and contribute to the improvement of sepsis outcome. We assume that monitoring of APRIL and sTACI concentrations dynamic would be of an even higher significance, because it would enable individualization of the sepsis treatment. Additionally, identifying the state of immune paralysis versus proinflammatory response in a single patient could contribute to clinical decision on introducing immunomodulatory therapy [49]. Future research on the role of sTACI as the biomarker in MODS development is necessary, since there are indices that it may be more confident in prediction than PCT, the only biomarker routinely used nowadays.

Actual scoring systems do not have the satisfactory predictive value, bearing in mind specificity of the septic patients’ population in the ICU or triage dispensaries, as well as the complex pathogenesis of sepsis [24]. In order to assess the risk accurately, we are in demand for further research that would introduce new variables, and thus enable construction and validation of the new specific scoring system for septic patients. In the light of new theories about sepsis pathogenesis, that accentuate the dominance of anti-inflammatory response in patients with worse prognosis, construction of the new scoring system could contribute to better assessment of clinical course of sepsis and making on time clinical decision to introduce immunomodulators in addition to antibiotics and supportive therapy. In addition, commercializing the test might be a reasonable option, if further research confirm it to be more indicative of MODS development than procalcitonin.

Abbreviations

APACHE II	Acute Physiology and Chronic Health Evaluation II
APRIL	A Proliferation Inducing Ligand
AUC	area under curve
CNS	central nervous system

CRP	C-reactive protein
ICU	intensive care units
ELISA	enzyme-linked immunosorbent assay
INR	International Normalised Ratio
MODS	multiorgan dysfunction syndrome
PCT	procalcitonin
Plt	Platelets
ROC	Receiver Operating Characteristic curve
SOFA	Sequential Organ Failure Assessment
sTACI	soluble Transmembrane Activator and CAML Interactor Protein
TACI	Transmembrane Activator and CAML Interactor Protein
TNF- α	tumor necrosis factor alfa
WBC	white blood cell

Conflict of interests

All the authors listed deny any financial or non-financial conflict of interests.



Acknowledgments

Funding for the work was received from the project: Non-invasive markers in diagnosis and prognosis of critical illness, Provincial secretariat for science and technological development, Republic of Serbia, Autonomous province of Vojvodina, grant number 114-451-745/2015-01.

Funding

This work was supported by the Provincial Secretariat for Science and Technological Development (114-451-745/2015-01).

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