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ASSOCIATION OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME WITH BACTEREMIA IN PATIENTS WITH SEPSIS

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ABSTRACT

The aim of this study was to evaluate the usability of systemic inflammatory response syndrome (SIRS) and commonly used biochemical parameters as predictors for positive blood culture in patients with sepsis. The study included 313 patients aged ≥18 years with severe sepsis and septic shock consecutively admitted in the Intensive Care Unit (ICU) of the University Clinic for Infectious Diseases in Skopje, Republic of North Macedonia. The study took place from January 1, 2011 to December 31, 2017. We recorded demographic variables, common laboratory tests, SIRS parameters, site of infection, comorbidities and Sequential Organ Failure Assessment (SOFA) score. Blood cultures were positive in 65 (20.8%) patients with sepsis. Gram-positive bacteria were isolated from 35 (53.8%) patients. From the evaluated variables in this study, only the presence of four SIRS parameters was associated with bacteremia, finding that will help to predict bacteremia and initiate early appropriate therapy in septic patients.

Keywords: bacteremia, sepsis, severe sepsis, septic shock

INTRODUCTION

Sepsis is a life-threatening medical emergency. It is estimated that sepsis affects more than 30 million people worldwide every year, potentially leading to 6 million deaths [1]. Detection of bacteria in blood culture is valuable for clinicians treating patients with sepsis. Diagnosis of bacteremia helps for timely and appropriate antimicrobial therapy and ultimately helps reduce mortality of sepsis [2]. Standard cultivation methods are time consuming and some studies have attempted to develop models for prediction of bacteremia [3,4,5]. From the 1992 consensus conference, the systemic inflammatory response syndrome (SIRS) becomes integral part of sepsis definitions [6]. Shortly after many realized that too many hospitalized patients with SIRS never developed infection and one in eight patients with infection does not meet the SIRS criteria [7]. The concept of accentuated systemic inflammation as the cause of sepsis manifestation was challenged with findings that parallel to systemic inflammation, there is almost equal anti-inflammatory response in septic patients. The predominant understanding was that sepsis is the result of dysregulated host response to infection. In 2016 the sepsis definition was changed and SIRS was excluded from definitions [8]. SIRS is too sensitive to diagnose sepsis, but still, it is a solid concept to describe systemic innate inflammatory response

to diverse insults. Moreover, the presence of SIRS might be a predictor for bacteremia in patients with sepsis [9,10].

The aim of this study was to evaluate the association of SIRS, and commonly used biochemical parameters, with positive blood culture in patients with sepsis.

MATERIAL AND METHODS

The present study included 313 patients aged ≥18 years consecutively admitted in the Intensive Care Unit (ICU) of the University Clinic for Infectious Diseases in Skopje, Republic of North Macedonia. The study took place from January 1, 2011 to December 31, 2017. We studied patients with severe sepsis and septic shock defined according to the 2012 consensus criteria [11]. Systemic inflammatory response syndrome (SIRS) was defined as 2 or more of the following variables, body temperature >38ºC or <36ºC, heart rate >90 beats/min, respiratory rate >20 breaths/min or PaCO2<32 mmHg, White Blood Cells (WBC) >12 x 109/L or <4 x109/L; sepsis was defined as infection plus at least two systemic inflammatory response syndrome criteria. Severe sepsis was defined by sepsis plus at least one sepsis-induced acute organ dysfunction. Organ dysfunction was defined as follows: cardiovascular system failure was systolic blood pressure <90mmHg or mean arterial blood pressure <70mmHg; renal dysfunction was urinary output ≤0,5 ml/kg/hour or twofold increased serum creatinine above normal value; respiratory dysfunction was PaO2<70 mmHg or mechanical ventilation or PaO2/FiO2 ≤250 (or ≤200 in patients with pneumonia); thrombocytopenia was defined as platelet count < 100.000 x 109/L; hepatic dysfunction was hyperbilirubinemia (plasma total bilirubin >34.2 μmol/L) or a threefold increase in serum aminotransferases; acidosis pH ≤7,3 or base excess ≥5 mmoL/L; central nervous system (CNS) dysfunction was Glasgow coma scale <13. Septic shock was defined, when sepsis resulted in arterial hypotension needing vasopressors, despite initial adequate fluid resuscitation. Hypotension was noted when mean arterial pressure (MAP) was < 70 mmHg or systolic arterial blood pressure < 90 mmHg.

We recorded demographic data, common laboratory tests, SIRS parameters, source of infection, comorbidities and sequential organ failure assessment (SOFA) scores [12]. At admission, all patients had two sets of blood cultures drawn from separate venipuncture sites. Bacteremia was defined as identical organisms isolated from two sets of blood cultures. If only one set of blood cultures was positive for pathogenic organism (such as Streptococcus pneumonia or Gram-negative bacilli) that could account for the clinical presentation, then the culture was considered positive. A blood culture contamination was considered if coagulase-negative Staphylococci, diphtheroids, Bacillus spp., Propionibacterium acnes, Corynebacterium spp., were detected from one blood culture. However, determining these organisms in both blood cultures in appropriate clinical contexts was considered as a true-positive [13,14].

The Kolmogoroff-Smirnov test was used to verify the normality of distribution of continuous variables. Normally, distributed variables are presented as mean (SD) and non-normally distributed variables as median and range. Difference testing between groups was performed using the Student's t-test, when data were normally distributed. When normality was rejected, nonparametric Mann-Whitney U-test was used for independent groups. Categorical variables were expressed as numbers and percentages and analyzed using the chi-square and Fisher exact test when necessary. All statistics were two-tailed, and a $P < 0.05$ was considered to be significant. Data were analyzed with SPSS 23.0 software (SPSS, Chicago, IL).

RESULTS

A total of 313 patients met inclusion criteria and were stratified in two groups consisting of bacteremic and non-bacteremic patients.

The patients mean age was 58.1 years (SD 16.1), 193 (61.7%) were male and 28-day mortality was 49.2%. The most frequent comorbidities were chronic heart failure, diabetes mellitus and cerebrovascular diseases. Even though SOFA scores and overall mortality were higher in the bacteremic group, there were no statistically significant differences between the two groups (Table 1).

Table 1. *Basic characteristics of patients with sepsis stratified by bacteremia*

Variable	All patients (n=313)	Non-bacteremic (n=248)	Bacteremic (n=65)	P value
Age (years, mean± SD)	58.1±16.1	57.6±16.4	59.5±15.1	0.377
Male, n (%) Female, n (%)	193 (61.7) 120 (38.3)	148 (76.7) 100 (83.3)	45 (23.3) 20 (16.7)	0.159
ICU stay (days, mean± SD)	14.6±12.9	14.6±12.6	15.0±14.1	0.813
Comorbidities, n (%) Congestive heart failure Diabetes mellitus Cerebrovascular disease COPD Chronic alcoholism Metastatic cancer Chronic kidney disease Chronic liver disease AIDS/HIV infection	 83 (26.5) 68 (21.7) 48 (15.3) 30 (9.6) 13 (4.2) 31 (9.9) 19 (6.1) 11 (3.5) 4 (1.3)	 65 (26.2) 49 (19.8) 33 (13.3) 27 (10.9) 10 (4.0) 27 (10.9) 12 (4.8) 8 (3.2) 2 (0.8)	 18 (27.7) 19 (29.2) 15 (23.1) 3 (4.6) 3 (4.6) 4 (6.2) 7 (10.8) 3 (4.6) 2 (3.1)	 0.810 0.099 0.052 0.126 0.834 0.255 0.075 0.588 0.194
Overall mortality, n (%)	172 (55.0)	130 (52.4)	42 (64.6)	0.079
28-day mortality, n (%)	154 (49.2)	117 (47.2)	37 (56.9)	0.162
SOFA score (mean±SD)	7.8±3.3	7.7±3.4	8.4±3.2	0.124

SD: standard deviation; SOFA: sequential organ failure assessment;

The source of infections was classified as follows: lower respiratory tract (n=181, 57.8%), central nervous system (n=58, 18.5%), soft tissue (n=26, 8.3%), urinary tract (n=17, 5.4%), abdomen (n=9, 2.9%), endocarditis (n=6, 1.9%) and other/unknown (n=16, 5.1%). Among patients with positive blood cultures, 18 (27.7%) had pneumonia, soft tissue infection (n=16, 24.6%), meningitis (n=14, 21.5%), urinary tract infection (n=8, 12.3%), endocarditis (n=3, 4.6%), abdominal infection (n=3, 4.6%) and other/unknown (n=3, 4.6%). We did not find significant statistical association between sites of infections and bacteremia.

Blood cultures were positive in 81 (25.8%) patients, but as true positives were acknowledged 65 (20.8%) patients with positive cultures. Gram-positive bacteria were isolated from 35 (53.8%) patients. The most common isolates were Escherichia coli (n=13, 20%), Staphylococcus aureus (n=11, 16.9%), Pseudomonas aeruginosa (n=7, 10.8%), Enterococcus spp. (n=6, 9.2%), Streptococcus pneumoniae (n=5, 7.7%), MRSA (n=5, 7.7%), Listeria monocytogenes (n=4, 6.2%), Proteus mirabilis (n=3, 4.6%), Klebsiella pneumoniae (n=2, 3.1%), Streptococcus pyogenes (n=2, 3.1%), Acinetobacter baumanii (n=2, 3.1%), coagulase-negative staphylococci (n=1, 1.5%), Enterobacter spp. (n=1, 1.5%), Morganella morganii (n=1, 1.5%), Salmonella enteritidis (n=1, 1.5%) and Streptococcus agalactiae (n=1, 1.5%).

There was not association with bacteremia in septic patients with two and three SIRS parameters, only patients with four SIRS criteria present were significantly associated with positive blood cultures (Table 2). Examined laboratory tests were not statistically different between studied groups (Table 3).

Table 2. *SIRS of patients with sepsis stratified by bacteremia*

Variable	All patients (n=313)	Non-bacteremic (n=248)	Bacteremic (n=65)	P value
SIRS criteria Body temperature > 38 or <36ºC Heart rate > 90beats/min Respiratory rate > 20breaths/min WBC >12 or <4 x10^9/L	 165 (52.7) 279 (89.1) 267 (85.3) 224 (71.6)	 125 (50.4) 219 (88.3) 215 (86.7) 175 (70.6)	 40 (61.5) 60 (92.3) 52 (80.0) 49 (75.4)	 0.109 0.356 0.175 0.443
No. of SIRS criteria, n (%) 2 3 4	 67 (21.4) 143 (45.7) 103 (32.9)	 57 (23.0) 117 (47.2) 74 (29.8)	 10 (15.4) 26 (40.0) 29 (44.6)	 0.184 0.301 0.024

Variable	All patients (n=313)	Non-bacteremic (n=248)	Bacteremic (n=65)	P value
ESR (mm/h, mean ± SD)	57.1±29.9	56.3±29.8	60.0±30.2	0.462
Hemoglobin (g/L, mean ± SD)	112.2±18.1	113.4±23.6	107.3±24.7	0.073
Platelets (x 10^9/L, mean ± SD)	174.3±123.7	178.2±123.9	159.6±123.1	0.283
Glycemia (mmol/L, mean ± SD)	9.5±5.5	9.4±5.6	9.8±5.1	0.629
Urea (mmol/L, mean ± SD)	18.1±11.6	17.5±11.4	20.0±11.8	0.132
Creatinine (µmol/L, mean ± SD)	171.5±157.1	170.9±162.1	174.1±137.8	0.889
CRP (mg/L, mean±SD)	223.5±132.7	208.7±121.6	240.1±147.7	0.158

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

DISCUSSION

Systemic inflammatory response syndrome (SIRS) is a combination of physiological reactions to various nonspecific, infectious or noninfectious insults. For many years SIRS was a basis for understanding and defining sepsis and some studies find it predictive of bacteremia [15,16]. The main finding of this study is that SIRS number, namely the four SIRS criteria in septic patients are predictive of bacteremia. Studies have examined the relationship between

fever and bacteremia and showed that fever had no predictive value for bacteremia [17,18]. We observed a higher percentage of abnormal body temperature in the bacteremic group, but with no statistical difference. This may be explained by the influence of older patients who have weak response to pyrogens and lower baseline body temperature [19].

Almost 90% of analyzed patients had tachycardia, but with no relationship regarding bacteremia. Nevertheless, some studies find tachycardia as a factor associated with positive blood cultures [20].

High respiratory rate is a prominent sign of serious illness, particularly respiratory tract infections [21]. The majority of our patients had tachypnea, but we did not find any association with bacteremia.

Leukocytosis was consistently reported to be associated with bacteremia [22]. White blood cell count in our study was not associated to bacteremia, finding that is in concordance with other authors [23].

In our study we did not find any association of age and comorbidities with positive blood culture, as noted in some reports [16].

Bacteremia has previously been associated with disease severity and organ failure but, as in other studies, we find no difference in overall and 28-day mortality between patients with bacteremia and without bacteremia [24,25].

The degree of organ dysfunctions measured with SOFA scores was higher in bacteremic patients, but with no statistical difference between groups. Opposed to other reports, we did not find that SOFA score is associated with bacteremia in septic patients [26].

Anemia is frequently described and explained with various pathophysiologic mechanisms in patients with sepsis [27]. In our study, the hemoglobin concentration was lower in the bacteremic group, but with no statistical significance. In this cohort low platelet count was not associated with bacteremia. Some studies associated thrombocytopenia with the incidence of bacteremia in patients with sepsis [28]. CRP is a useful adjunctive biomarker of inflammation and sepsis, but, as in other studies, CRP was not prognostic of bacteremia [29]. The concentration of CRP above 170 mg/L in a multivariate model was predictive of bacteremia in patients with pneumonia [30].

CONCLUSION

Regardless of the exclusion of systemic inflammatory response syndrome from sepsis, definitions and tendency on focusing on organ dysfunctions, our opinion is that SIRS is still an important part of sepsis.

In this study, we found that the presence of four parameters of systemic inflammatory response syndrome in patients with sepsis is associated with positive blood cultures. These easy and familiar variables will help clinicians suspect bacteremia in septic patients and urgently begin the appropriate therapy and ultimately contribute to reduce morbidity and mortality.

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Резиме

ПОВРЗАНОСТ НА СИНДРОМОТ НА СИСТЕМСКИ ИНФЛАМАТОРЕН ОДГОВОР СО БАКТЕРИЕМИЈА КАЈ ПАЦИЕНТИ СО СЕПСА

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Целта на студијата е да се процени употребливоста на синдромот на системски инфламаторен одговор и вообичаено користените биохемиски анализи во предвидување на бактериемијата кај пациенти со сепса. Во студијата беа вклучени 313 возрасни пациенти со тешка сепса и септичен шок лекувани во Единицата за интензивна нега на Универзитетската клиника за инфективни болести и фебрилни состојби од јануари 2011 до декември 2017 година. Анализирани беа демографските варијабли, вообичаено користените лабораториски тестови, параметрите на системскиот инфламаторен одговор, локализацијата на инфекцијата, коморбидностите и секвенционалниот индекс за процена на нарушената функција на органите. Крвните култури беа позитивни кај 65 (20,8 %) од болните со сепса, од кои 35 (53,8 %) беа Грам-позитивни бактерии. Од сите анализирани варијабли, само присуството на четири параметри на синдромот на системска инфламација беа асоцирани со позитивна хемокултура. Идентификацијата на лесно достапните параметри на системска инфламација кај пациентите со сепса ќе придонесе за брза клиничка суспекција на присуство на бактериемија и рана и соодветна терапија.

Клучни зборови: бактериемија, сепса, тешка сепса, септичен шок