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Original article

THE SIRS SCORE RELEVANCE FOR ASSESSMENT OF SYSTEMIC INFLAMMATION COMPARED TO C-REACTIVE PROTEIN IN PATIENTS WITH LIVER CIRRHOSIS
РЕЛЕВАНТНОСТА НА SIRS СКОРОТВО ПРОЦЕНКА НА СИСТЕМСКА ИНФЛАМАЦИЈА ВО СПОРЕДБА СО Ц-РЕАКТИВЕН ПРОТЕИН КАЈ ПАЦИЕНТИТЕ СО ЦРНОДРОБНА ЦИРОЗА

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Abstract

Introduction. Systemic inflammation is a key mechanism that determines the natural history and prognosis inpatients with liver disease. The presence of systemic inflammation is usually assessed through the presence of systemic inflammatory response syndrome (SIRS), but due to numerous morphological and hemodynamic abnormalities the application of SIRS criteria in patients with liver cirrhosis is difficult and not entirely relevant. The aim of the study was to determine the SIRS occurrence by applying different diagnostic criteria and to analyze the relevancy of the parameters included in the SCCM/ESICM/ACCP/ATS/SIS score by comparison to CRP cut-off value of 29 mg/L.

Methods. In patients with liver cirrhosis we estimated the occurrence of systemic inflammation by application of three SIRS criteria: the criterion of the International sepsis definitions conference of 2001 (SCCM/ESICM/ ACCP/ATS/SIS), the modified SIRS score and the CRP cut-off value of 29 mg/L. The positive findings of the parameters included in the SIRS score were compared to the CRP cut-off value in order to analyze their relevance in the assessment of SIRS.

Results. Seventy-six patients were enrolled in the study, 60 males and 16 females with a mean age of 57±11 (31-84). The presence of SIRS was registered in 31 patients (40.79%) according to the first SIRS criterion, in 5 (6.58%) patients according to the second SIRS criterion and in 15 (27.63 %) patients according to the third SIRS criterion and the average CRP in the group was 21.61 mg/L±30.98 (0.5-158.90). The percentage difference in SIRS occurrence between the first and third SIRS criterion was statistically significant for $p<0.05$ {Difference test: Difference 21.05%[(6.45-34.49) CI 95%]; Chi-square=7.926;df=1 p=0.0049} in favor of a significantly larger number of patients with SIRS according to the first SIRS criterion and the percentage difference in SIRS occurrence between the second and the third SIRS criterion was statistically significant for $p<0.05$ {Difference test: Difference 13.16%[(2.33-24.12) CI 95%]; Chi-square=5.721; df=1 p=0.0168} in favor of a significantly larger number of patients with SIRS according to the third SIRS criterion. The percentage difference between the occurrence of positive finding of the analyzed parameters included in the SIRS score and the occurrence of positive finding of the same parameter in patients who fulfilled the third SIRS criterion was statistically significant for $p<0.05$for decreased partial pressure of CO2below 32 mmHg {Difference test: Difference 44.73%[(29.49-57.03) CI 95%]; Chi-square=30.98;df=1 p=0.0001}, for elevated respiratory rate above 20/min {Difference test: Difference 35.53% [(22.41-47.35) CI 95%]; Chi-square=25.87; df=1 p=0.0001}, for decreased leukocyte count below 4.000/mm³{Difference test: Difference 18.42%[(8.39-29.03) CI 95%]; Chi-square=12.271; df=1 p=0.0005} and for elevated heart rate above 90/min {Difference test: Difference 11.85%[(-1.71-22.34) CI 95%]; Chi-square=5.336;df=1 p=0.0209}. The percentage difference between the occurrence of positive finding of the analyzed parameters included in the SIRS score and the occurrence of positive finding of the same parameter in patients who fulfilled the third SIRS criterion was not statistically significant for $p>0.05$ for body

temperature abnormalities and for elevated leukocyte count.

Keywords: systemic inflammation, SIRS score, C-reactive protein, liver cirrhosis

Апстракт

Вовед. Системската инфламација претставува клу-чен механизам кој го детерминират екот на црно-дробната болест и прогнозата кај овие пациенти. Нејзиното присуство вообичаено се проценува преку присуството на синдромот на системски инфлама-торен одговор (SIRS), но поради бројните мор-фолошки и хемодинамски нарушувања примената на критериумите за SIRS кај пациените со црно-дробна цироза е отежнато и нецелосно релевантно. Цел на студијата е да се одреди застапеноста на SIRS со примена на различни дијагностички крите-риуми и преку споредба со пресечната вредност на CRP од 29 mg/L да се анализира релевантноста на параметрите кои влегуваат во состав на SCCM/ ESICM/ACCP/ATS/SISскорот во проценка на при-суството на SIRS.

Методи. Кај пациенти со црнодробна цироза беше одредувана застапеноста на системска инфламаци-ја преку примена на три критериуми за SIRS: кри-териумот на интернационалната конференцијата за дефиниција на сепса од 2001 година (SCCM/ESICM/ ACCP/ATS/SIS), модифицираниот SIRS скор и пре-сечната вредност за серумскиот CRP од 29mg/L. Застапеноста на позитивен наод на критериоумте кои влегуваат во состав на SIRS скорот беше компари-рана со пресечната вредност на CRP за да се анали-зира нивната релевантност во проценката на SIRS.

Резултати. Во студијата учествуваа 76 пациени (60 мажи и 16 жени) со средна возраст од 57±11год (31-84). SIRS беше присутен кај 31 пациент (40.79%) според првиот, кај 5 пациенти (6.58%) според вто-риот и кај 15 пациенти (27.63%) според третиот критериум а средната вредност на серумскиот CRP во рамки на групата изнесуваше 21.61 mg/L±30.98 (0.5-158.90). Процентуалната разлика помеѓу заста-пеноста на позитивен наод при примененапрвиот и третиот SIRS критериум е статистички сигнифи-кантна за p<0.05{Difference test: Difference 21.05% [(6.45-34.49) CI 95%]; Chi-square=7.926; df=1 p=0.0049} во прилог на значајно поголем број на позитивни наоди при примена на првиот SIRSкритериум, а процентуалната разлика помеѓу застапеноста на позитивен наод при примена на вториот и третиот SIRSкритериум е статистички сигнификантна за p<0.05{Difference test: Difference 13.16%[(2.33-24.12) CI 95%]; Chi-square=5.721;df=1 p=0.0168} во прилог на значајно поголем број на позитивни наоди при примена на третиот SIRS критериум. Процентуал-ната разлика помеѓу застапеноста на позитивен наод на анализираните параметри кои влегуваат во состав на SIRSскорот и застапеноста на позитивен наод на истите параметри кај пациентите кои го исполнија третиот SIRS критериум е статистички сигнификантна за p<0.05 за намален парцијален притисок на CO2 под 32 mmHg {Difference test: Diffe-rence 44.73% [(29.49-57.03) CI 95%]; Chi-square= 30.98; df=1 p=0.0001}, за покачена респираторна фрекфенција над 20/мин {Difference test: Difference 35.53% [(22.41-47.35) CI 95%]; Chi-square=25.87; df=1 p=0.0001}, за намален концентрација на леукоцити под 4.000/mm³ {Difference test: Difference 18.42% [(8.39-29.03) CI 95%]; Chi-square=12.271; df=1 p=0.0005} и за покачена срцева фрекфенција над 90/min {Difference test: Difference 11.85% [(-1.71-22.34) CI 95%]; Chi-square=5.336; df=1 p=0.0.0209}. Процен-туалната разлика помеѓу застапеноста на позити-вен наод на анализираните параметри кои влегуваат во состав на SIRS скорот и застапеноста на позитивен наод на истите параметри кај пациентите кои го исполнија третиот SIRS критериум не е статис-тички сигнификантна за p>0.05 за отстапувањата во телесната температура и за покачената концен-трација на леукоцити над 12.000/mm³.

Заклучок. Во споредба со пресечната вредност на CRP од 29mg/L, кај пациентите со црнодробна ци-роза намалениотпарцијален притисок на CO2под 32 mmHg, покачената респираторна фрекфенција над 20/мин, покачената срцева фрекфенција над 90/мин и намалената концентрација на леукоцити под 4.000/mm³ не се релевантни индикатори на SIRS што укажува на тоа дека SCCM/ESICM/ACCP/ ATS/SIS критеиумите не се соодветни и погодни за проценка на присуството на SIRS кај овие пациенти.

Клучни зборови: системската инфламација, системски инфламаторен одговор (SIRS), C-реактивен протеин, црнодробна цироза

Introduction

A large amount of evidence suggests that systemic inflammation (SI) is common in patients with advanced liver cirrhosis and portal hypertension and that SI is the key mechanism that determines the liver disease course and the prognosis in these patients [1-6]. SI develops as a result of a persistent inadequate stimulation of the immune system and it is manifested by the presence of activated immune cells and elevated levels of inflammatory cytokines [7]. SI is usually a consequence of underlying bacterial infection, but in patients with liver cirrhosis SI can also exist independently of an infection and

can still persist after the infection re-solves [8]. The presence of SI is usually assessed through the presence of systemic inflammatory response syndrome (SIRS) which is confirmed by fulfilling certain diagnostic criteria.

The causes of SI in liver cirrhosis are different in different stage of the disease. In early, compensated cirrhosis there is a release of ligands from the necrotic hepatocytes known as damage-associated molecular patterns (DAMPs) that cause so called "sterile inflammation" [9]. This inflammation follows the inflammation caused by a primary etiological agent (alcohol, virus, etc.) that leads to liver architectonics impairment and consecutive liver dysfunction. It is assumed that in more severe inflammation these particles can spill into the systemic circulation and cause immunological activation [7]. In advanced, decompensated cirrhosis, the leading mechanism that causes SI is the intestinal translocation of bacteria and bacterial products (lipopolysaccharides, lipopeptides, glycopolymers, methylated-DNA) into the systemic/splanchnic circulation called pathogen-associated molecular patterns (PAMPs) [7, 10-17]. These patterns stimulate leukocyte activation and secretion of inflammatory cytokines, continuously activate the immune system and worsen the SI [7,18-21].
Not only that SI is involved in the pathogenesis of most manifestations and complications of liver cirrhosis and portal hypertension, but SI is also related to bacterial infection, hemodynamic derangement and inflammatory organ damage [7]. The activation of the intestinal immune system causes local release of NO and other vasodilators, leading to development of hyperdynamic circulation and consecutive rennin-angiotensin system activation, which consequently results in ascites formation [15,17]. The inflammatory brain signaling and the migration of activated immune cells in the brain tissue activate the brain macrophages towards TNF-α production, modify the brain function and contribute to development of encephalopathy [22-24]. According to some studies, the renal damage in these patients is also mediated by specific inflammatory cytokines, PAMPs and DAMPs, which reduce the glomerular filtration rate and damage the tubular epithelium [25-27]. One study that analyzed the prognostic value of SI in patients with liver cirrhosis and acute renal failure, established that in these patients SI is a prognostic factor independent of the presence of infection [28].
Considering that in patients with liver cirrhosis the score calculation and the SIRS assessment can be quite difficult, the value of some biological variables that are considered surrogate markers of inflammatory stress is increasingly recognized. These include: CRP, pro-calcitonin, ferritin, serum free cortisol, copeptin, von-Willebrand factor, etc. [29]. Cervoni *et al.* evaluated the value of CRP as a surrogate marker of systemic inflammation and suggested that in patients with liver cirrhosis CRP can be more relevant SIRS indicator than the commonly used SIRS scores, especially when previously defined cut-off values are used [1].
The aim of the study was to determine the SIRS occurrence by applying different diagnostic criteria and to analyze the relevance of the parameters included in the SCCM/ESICM/ACCP/ATS/SIS score by comparison to CRP cut-off value of 29 mg/L.

Materials and methods

Patients
In this cross-sectional study we enrolled outpatients and hospitalized patients with liver cirrhosis without other significant comorbidities. Inclusion criteria were: histologically proven liver cirrhosis or liver cirrhosis diagnosed based on clear clinical, morphological and biochemical parameters. Exclusion criteria were: age below 18 years, pregnancy, hepatocellular carcinoma or other extrahepatic neoplasm, significant organ insufficiency (cardiac, respiratory, renal), diabetes, active alcohol consumption (for one month or less), recent gastrointestinal bleeding (in less than a month), active infection. Prior to enrolment all patients signed the informed consent for participation in the study. The research and the study protocol were in line with the ethical principles of the Declaration of Helsinki.

Data collection and evaluation of participants
At enrolment in every patient we performed complete blood count, biochemical analysis of blood and urine sample, leukocyte count and biochemical analysis of ascites (in patients with ascites); we measured vital parameters (blood pressure, heart rate, respiratory rate, blood

oxygen saturation), daily urine output, gas analysis from capillary blood sample. When there was a suspicion for a bacterial infection additional investigations were performed in order to confirm or exclude its presence. Finally we calculated the CTP and MELD score and we registered the presence of acute decompensation.

Systemic inflammation

The presence of SI was determined by using three SIRS criteria. The first SIRS criterion was the criterion of the International sepsis definitions conference (2001 SCCM/ESICM/ACCP/ATS/SIS) [30] and the second criterion was a modification of the same SIRS score [31]. The presence of SIRS according to the first SIRS criterion was defined by the presence of two and according to the second by the presence of three of the same four parameters included in both SIRS scores:

1. body temperature> 38°C or < 36°C;
2. heart rate> 90 beats/minute;
3. respiratory rate (RR) >20 respirations/minute or partial pressure of CO2 (Pa CO2) <32 mmHg or application of mechanical ventilation because of acute respiratory process;
4. leukocyte count >12.000/mm³ or <4.000/mm³ or presence of immature neutrophils >10%.

The third SIRS criterion was the presence of elevated CRP above 29 mg/L in three consecutive measurements within two weeks since enrolment, a value for which Cervoni *et al.* established that is a relevant SIRS indicator in patients with liver cirrhosis and discriminates patients with SIRS from patients without SIRS [1]. By using the three SIRS criteria we determined and compared the occurrence of SIRS. In order to determine the pertinence of the separate parameters in the SIRS assessment in comparison to the CRP cut-off value, we calculated the percentage difference between the occurrence of positive finding of the parameters included in the SCCM/ESICM/ACCP/ATS/SIS score and the third SIRS criterion.

Results

Patients

Seventy-six patients were enrolled in the study, 60 males and 16 females. The mean age of patients was 57±11 (31-84). According to the CTP classification, 20 patients were in class A, 27 patients in class B and 29 patients in class C (mean CTP score 9). The mean MELD score was 19±9 (6-37) and acute decompensation was registered in 34 patients (44.74%). Regarding the etiology, 37 patients were diagnosed with alcoholic liver disease, 13 patients had chronic hepatitis B, 6 patients had chronic hepatitis C, 1 patient was diagnosed with primary biliary cholangitis, 6 patients with autoimmune hepatitis, 1 patient with non-alcoholic fatty liver disease and in 12 patients the liver cirrhosis was cryptogenic. Thirty-seven patients were hospitalized and 39 patients were enrolled during the outpatient follow-up. Eleven patients were hospitalized because of hepatic encephalopathy, 10 because of refractory ascites, 7 because of profound peripheral edemas, 6 because of hepatic failure, 3 because of jaundice and 2 patients because of impaired renal function.

Systemic inflammation and systemic inflammatory response syndrome

The presence of SIRS was registered in 31 (40.79%) patients according to the first SIRS criterion, in 5 (6.58%) patients according to the second SIRS criterion and in 15 (27.63 %) patients according to the third SIRS criterion. The average CRP in the group was 21.61 mg/L ± 30.98 (0.5-158.90). The percentage difference in SIRS occurrence between the first and third SIRS criterion was statistically significant for $p<0.05$ {Difference test: Difference 21.05% [(6.45-34.49) CI 95%]; Chi-square=7.926; df=1 p=0.0049} in favor of a significantly larger number of patients with SIRS according to the first SIRS criterion. The percentage difference in SIRS occurrence between the second and the third SIRS criterion was statistically significant for $p<0.05$ {Difference test: Difference 13.16% [(2.33-24.12) CI 95%]; Chi-square=5.721; df=1 p=0,0168} in favor of a significantly larger number of patients with SIRS according to the third SIRS criterion.

Diagnostic parameters included in SCCM/ESICM/ACCP/ATS/SIS score

We analyzed the occurrence of all parameters included in the first and second SIRS criterion. Elevated body temperature above 38˚C was registered in 2 patients, decreased body temperature below 36˚C in 6, leukocyte count

above 12.000/mm³ in 4, leukocytes count below 4.000/mm³ in 16, heart rate above 90/min in 13, RR above 20/min in 32 and PaCO2below 32 mmHg in 59 patients. Ten patients fulfilled none of the four parameters included in the first and second SIRS scores, 35 patients fulfilled only one, 26 fulfilled two, 5 ful-filled three and not a single patient fulfilled all four criteria included in the first and second SIRS score. The percentage difference between the occurrence of decreased PaCO2 below 32 mmHg and decreased PaCO2 below 32 mmHg in patients who fulfilled the third SIRS criterion was statistically significant for $p<0.05$ {Difference test: Difference 44.73%[(29.49-57.03) CI 95%]; Chi-square=30.98;df=1 p=0.0001}in favor of a significantly larger number of patients with decreased PaCO2 below 32 mmHg. The percentage difference between the occurrence of elevated RR above 20/min and elevated RR above 20/min in patients who fulfilled the third SIRS criterion was statistically significant for $p<0.05$ {Difference test: Difference 35.53% [(22.41-47.35) CI 95%]; Chi-square=25.87; df=1 p=0.0001} in favor of a significantly larger number of patients with elevated RR above 20/min. The percentage difference between the occurrence of decreased leukocyte count below 4.000/mm³ and decreased leukocyte count below 4.000/mm³ in patients who fulfilled the third SIRS criterion was statistically significant for $p<0.05$ {Difference test: Difference 18.42% [(8.39-29.03) CI 95%]; Chi-square=12.271; df=1 p=0.0005} in favor of a significantly larger number of patients with leukocyte count below 4.000/mm³. The percentage difference between the occurrence of elevated heart rate above 90/min and elevated heart rate above 90/min in patients who fulfilled the third SIRS criterion was statistically significant for $p<0.05$ {Difference test: Difference 11.85% [(-1.71-22.34) CI 95%]; Chi-square =5.336;df=1 p=0.0209} in favor of a significantly larger number of patients with elevated heart rate above 90/min. The percentage difference between the occurrence of elevated body temperature above 38°C and elevated body temperature above 38°C in patients who fulfilled the third SIRS criterion was not statistically significant for $p>0.05$ {Difference test: Difference 1.31%[(-4.77-7.86) CI 95%]; Chi-square=0.335; df=1 p=0.5629}. The percentage difference between the occurrence of decreased body temperature below 36°C and decreased body temperature below 36°C in patients who fulfilled the third SIRS criterion was not statistically significant for $p>0.05$ {Difference test: Difference 3.94% [(-4.26-12.61) CI 95%]; Chi-square=1.052; df=1 p=0.3050}. The percentage difference between the occurrence of elevated leukocyte count above 12.000/ mm³and elevated leukocyte count above 12.000/mm³ in patients who fulfilled the third SIRS criterion was not statistically significant for $p>0.05${Difference test: Difference 1.31%[(-6.41-9.25) CI 95%]; Chi-square= 0.147;df=1 p=0.7010}.

Discussion

The results obtained in our study have shown that the SIRS occurrence significantly differs and depends on the applied criterion and that small change in the definition of SIRS results in a significant difference in the SIRS occurrence. Also, there was a statistically significant difference between the elevated CRP above the cut-off value and the abnormalities in the respire-tory function parameters, heart rate and low leukocyte count which indicates that these parameters are not relevant SIRS indicators when compared to the CRP cut-off value. Considering the fact that three out of four criteria included in the SIRS score are not reliable SIRS indicators, we can conclude that SCCM/ESICM/ ACCP/ATS/SIS score is also not appropriate for assessment of SIRS occurrence and that it should not be used in the assessment of SI in patients with liver cirrhosis.

The diagnostic criteria for SIRS were initially defined in 1992 by the American college of chest physicians and the Society of critical care medicine (ACCP/SCCM) [30]. Since these criteria were relatively poorly accepted by the clinicians, in 2001 the International Sepsis Definitions Conference (SCCM/ESICM/ACCP/ATS/SIS) performed a revision of the ACCP/SCCM criteria. Although they were evaluated as oversensitive and insufficiently specific, still they did not suffer a significant change [32]. Klouwenberg*et al.* analyzed the value of different diagnostic criteria and the SIRS incidence varied between 49% and 99% depending on the applied criterion. They concluded that small variations in the cut-off for different diagnostic criteria had a huge influence on the incidence of SIRS and sepsis, that the

ACCP/SCCM criteria were overly sensitive, insufficiently specific and not particularly useful for clinical diagnosis of sepsis in the intensive care units [33]. Considering the fact that many studies estimated the ACCP/SCCM criteria as too liberal, Bernard in his study PROWESS applied a modification of the ACCP/SCCM criteria and defined the SIRS occurrence by the presence of three instead of two out of four criteria [34]. Although most studies doubt their relevancy due to their oversensitivity and low specificity, ACCP/ SCCM criteria are still widely used especially as inclusion criteria mainly in a population of critically ill patients in the intensive care units

When discussing the applicability of the SIRS criteria on a specific population of patients with liver cirrhosis, then the restrain related to their relevance is even more justified. Namely, liver cirrhosis is associated with many complex structural, hemodynamic and neurohumoral abnormalities that clearly interfere with the pathophysiological mechanisms of the systemic inflammatory response, which leads to inappropriate interpretation of the parameters that are considered SIRS representatives. This is the reason why many researchers focused on identifying some biological variable that would be more precise SIRS indicator and indicate towards SIRS more precisely. Studies that have evaluated CRP value in this context established that the CRP level reflects the degree of SI regardless of the reason that led to it, that is, irrespectively of whether SIRS is caused by a bacterial infection or not [29]. Actually, the elevated CRP level can also persist after a resolution of an infection indicating that SI can become a persistent condition and act as an autonomic state [8]. It has been established that in patients with liver cirrhosis CRP is a precise marker of SIRS, it can predict six-month mortality [1] and that high CRP values are strongly associated with organ failure and lethal outcome, even in patients in whom a bacterial infection has not been established [35]. Cervoni*et al*. among others established that in patients with liver cirrhosis SI is a predictor of short-term mortality independent of age, MELD score and existing comorbidities and that the presence of CRP above 29 mg/L measured 15 days after the basic values is an indicator of prolonged SI that persists after the resolution of bacterial infection [1]. This is the reason why we decided to apply their cut-off value as our third SIRS criterion and to compare the positive findings of the separate criteria included in the SCCM/ESICM/ACCP/ ATS/SIS score to the CRP cut-off value in order to analyze their relevancy as SIRS indicators.

The abnormalities in the respiratory function parameters were the most frequent positive findings among other criteria within the SIRS score, but our analysis showed that they were also the least reliable ones. Decreased PaCO2 below 32 mmHg was present in 49 patients (64.47%) and elevated RR above 20/min was registered in 32 patients (42.11%). However, when we compared the positive finding of these parameters to the presence of the CRP cut-off value, we discovered that the percentage difference between both, the elevated respiratory rate and the decreased PaCO2 in patients that fulfilled the third SIRS criterion was statisticaly significant for both parameters{Difference test: Difference 44.73% [(29.49-57.03) CI 95%]; Chi-square=30.98; df=1 p=0.0.0001} for PaCO2 below 32 mm Hg and {Difference test: Difference 35.53% [(22.41-47.35) CI 95%]; Chi-square=25.87; df=1 p=0.0001 for RR above 20/min}. This indicates that in a substantial number of cirrhotic patients there is an abnormality in the respiratory function parameters that is not in line with the presence of systemic inflammation and the CRP rise. Also, in a large number of patients the respiratory function criterion within the SIRS criterion, especially the decreased PaCO2 below 32 mmHg, was falsely positive, mainly as a consequence of the present hepatic encephalopathy [38], which was the cause for increased RR and decreased PaCO2.

Not only the leukocyte elevation, but the decreased leukocyte count below 4.000/mm³ is also considered a SIRS indicator. However, low leukocyte count below 4.000/mm³is a common finding in patients with liver cirrhosis and portal hypertension due to the coexisting enlarged spleen and hypersplenism. In our study a leukocyte count below 4.000/mm³ was registered in 16 patients (14.93%) and also, all 16 patients had a significantly enlarged spleen. This means that in all cirrhotic patients with enlarged spleen and consecutive low leukocyte count this criterion would be falsely positive. In patients with low leukocyte count a potential leukocyte rise in terms of systemic inflammation

could result in a leukocyte count that would remain within the normal range resulting in a falsely negative criterion. This explains why in this population of patients the leukocyte count below 4.000/mm³ is not a SIRS representative which was also confirmed by the percentage difference between the occurrence of positive finding of this criterion and the occurrence of positive finding of the same criterion in our patients who fulfilled the third SIRS criterion {Difference test: Difference 18.42% [(8.39-29.03) CI 95%]; Chi-square=12.271; df=1 p=0.0005}.

The elevation of NO and other vasodilatatory molecules in cirrhotic patients lead to splanchnic arterial vasodilatation and consecutive hyperdynamic circulation, which is related to low mean arterial pressure and elevated heart rate. On the other hand, the frequent usage of non-selective beta blockers in patients with gastro-esophageal varices reduces the heart rate and in certain way moderates the hemodynamic reaction to inflammatory stress. Our study has shown a statistically significant difference between the occurrence of positive finding of elevated heart rate and the occurrence of positive finding of the same criterion in patients who fulfilled the third SIRS criterion {Difference test: Difference 11.85% [(-1.71-22.34) CI 95%]; Chi-square=5.336; df=1 p=0.0209}, which suggest that the coexisting hyper-dynamic circulation disables the elevated heart rate to be observed as a relevant SIRS indicator.

The study has several limitations. The small sample size might interfere with the data interpretation. Also, the measurement of the vital parameters was not fully standardized. In some patients the measurements were performed by the cardiorespiratory monitor, while in stabile patients the measurements were mainly performed manually. In most patientsthe measurements were performed at one time, i.e. we did not take into account the multiple daily variations. The level of the PaCO2 within the SIRS criteria refers to the value measured in the arterial blood. However, in our study the PaCO2 was measured in the arterialized capillary blood. This was justified by the results from meta-analysis and many studies that compared the values of the gas ana-lyses in the arterial blood to those in the arterialized capillary blood. The results have proved a high level of similarity between both values suggesting that for the pH and PaCO2 the value obtained in the capillary blood from earlobe is an appropriate alternative to the value obtained in the arterial blood [37].

Conclusion

In conclusion, when compared to the CRP cut-off value, the respiratory function abnormalities, elevated HR and low leukocyte count are not reliable SIRS indicators which suggest that the SCCM/ESICM/ACCP/ ATS/SIS criteria are not appropriate for SIRS assessment in patients with liver cirrhosis. Additional research is needed in order to create diagnostic criteria for SIRS that would be appropriate for usage in this population of patients and to define new biological variables that could be applied as surrogate markers of inflammatory stress.

Conflict of interest statement. None declared.

References:

1. Cervoni JP, Thevenot T, Weil D, *et al*. C-reactive protein predicts short-term mortality in patients with cirrhosis. *J Hepatol* 2012; 56: 1299-1304.

2. Dirchwolf M, Ruf AE. Role of systemic inflammation in cirrhosis: From pathogenesis to prognosis. *World J Hepatol* 2015; 7(16): 1974-1981.

3. Keeffe EB, Iwarson S, McMahon BJ, *et al*. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. *Hepatology* 1998; 27: 881-886.

4. Jenne CN, Kubes P. Immune surveillance by the liver. *Nat Immunol* 2013; 14: 996-1006.

5. Thomson AW, Knolle PA. Antigen-presenting cell function in the tolerogenic liver environment. *Nat Rev Immunol* 2010; 10: 753-766.

6. Racanelli V, Rehermann B. The liver as an immunological organ. *Hepatology* 2006; 43: S54-S62.

7. Albillos A, Lario M, Alvarez-Mon M. Cirrhosis-associated immune dysfunction: Distinct features and clinical relevance. *J Hepatol* 2014; 61: 1385-1396.

8. Malik R, Mookerjee RP, Jalan R. Infection and inflammation in liver failure: two sides of the same coin. *J Hepatol* 2009; 51: 426-429.

9. Kubes P, Mehal WZ. Sterile inflammation in the liver. *Gastroenterology* 2012; 143: 1158-1172.
10. Albillos A, de la Hera A, Gonzalez M, *et al*. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. *Hepatology* 2003; 37: 208-217.
11. Guarner C, Soriano G, Tomas A, *et al*. Increased serum nitrite and fnitrate levels in patients with cirrhosis: relation-ship to endotoxemia. *Hepatology* 1993; 18: 1139-1143.
12. Campillo B, Bories PN, Benvenuti C, Dupeyron C. Serum and urinary nitrate levels in liver cirrhosis: endotoxemia,
renal function and hyperdynamic circulation. *J Hepatol* 1996; 25: 707-714.
13. Lin RS, Lee FY, Lee SD, *et al*. Endotoxemia in patients with chronic liver diseases: relationship to severity of liver diseases, presence of esophageal varices, and hyperdynamic circulation. *J Hepatol* 1995; 22: 165-172.
14. Gonzalez-Navajas JM, Bellot P, Frances R, *et al*. Presence of bacterial-DNA in cirrhosis identifies a subgroup of patients with marked inflammatory response not related to endotoxin. *J Hepatol* 2008; 48: 61-67.
15. Arroyo V, García-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol* 2014; 61: 396-407. [PMID: 24751830 DOI: 10.1016/j.jhep. 2014.04.012].
16. Bruns T, Zimmermann HW, Stallmach A. Risk factors and outcome of bacterial infections in cirrhosis. *World J Gastroenterol* 2014; 20: 2542-2554. [PMID: 24627590 DOI: 10.3748/wjg.v20. i10.2542]
17. Jalan R, Fernandez J, Wiest R, *et al*. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol* 2014; 60: 1310-1324. [PMID: 24530646 DOI: 10.1016/ j.jhep.2014.01.024]
18. Fukui H. Gut-liver axis in liver cirrhosis: How to manage leaky gut and endotoxemia. *World J Hepatol* 2015; 7: 425-442. [PMID: 25848468 DOI: 10.4254/wjh.v7.i3.425]
19. Ilan Y. Leaky gut and the liver: a role for bacterial translo-cation in nonalcoholic steatohepatitis. *World J Gastroenterol* 2012; 18: 2609-2618. [PMID: 22690069 DOI: 10.3748/wjg.v18. i21.2609].
20. Lutz P, Nischalke HD, Strassburg CP, Spengler U. Spontaneous bacterial peritonitis: The clinical challenge of a leaky gut and a cirrhotic liver. *World J Hepatol* 2015; 7: 304-314. [PMID: 25848460 DOI: 10.4254/wjh.v7.i3.304].
21. Seo YS, Shah VH. The role of gut-liver axis in the pathogenesis of liver cirrhosis and portal hypertension. *Clin Mol Hepatol* 2012; 18: 337-346. [PMID: 23323248 DOI: 10.3350/cmh.2012.18.4.337].
22. Wright G, Davies NA, Shawcross DL, *et al*. Endotoxemia produces coma and brain swelling in bile duct ligated rats. *Hepatology* 2007; 45: 1517-1526.
23. Jover R, Rodrigo R, Felipo V, *et al*. Brain edema and inflammatory activation in bile duct ligated rats with diet-induced hyperammonemia: a model of hepatic encephalo-pathy in cirrhosis. *Hepatology* 2006; 43: 1257-1266.
24. Kerfoot SM, D'Mello C, Nguyen H, *et al*. TNF- alpha-secreting monocytes are recruited into the brain of cho-lestatic mice. *Hepatology* 2006; 43: 154-162.
25. Moreau R, Arroyo V. Acute-on-chronic liver failure: a new clinical entity. *ClinGastroenterolHepatol* 2015; 13: 836-841. [PMID: 24583872 DOI: 10.1016/j.cgh.2014.02.027].
26. Arroyo V, Moreau R, Jalan R, Ginès P. Acute-on-chronic liver failure: A new syndrome that will re-classify cirrhosis. *J Hepatol* 2015; 62: S131-S143. [PMID: 25920082 DOI: 10.1016/j.jhep.2014.11.045].
27. Shah N, Dhar D, El Zahraa Mohammed F, *et al*. Preven-tion of acute kidney injury in a rodent model of cirrhosis following selective gut decontamination is associated with reduced renal TLR4 expression. *J Hepatol* 2012; 56: 1047-1053. [PMID: 22266601 DOI: 10.1016/j.jhep.2011.11.024].
28. Thabut D, Massard J, Gangloff A, *et al*. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology* 2007; 46: 1872-1882. [PMID: 17972337 DOI: 10.1002/hep.21920].
29. Di Martino V, Weil D, Cervoni JP, Thevenot T. New prognostic markers in liver cirrhosis. *World J Hepatol* 2015; 7(9): 1244-1250. doi: 10.4254/wjh.v7.i9.1244

30. Bone RC, Balk RA, Cerra FB, *et al*. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101: 1644-1655.

31. D'Amico G, Pasta L, Morabito A, *et al*. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. *Aliment PharmacolTher* 2014; 39(10): 1180-1193. doi: 10.1111/apt.12721. Epub 2014 Mar 24.

32. Levy MM, Fink MP, Marshall JC, *et al*. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis defini-tions conference. *Crit Care Med* 2003; 31: 1250-1255.

33. Klouwenberg Klein PM, Ong DS, Bonten MJ, Cremer OL. Classification of sepsis, severe sepsis and septic shock: the impact of minor variations in data capture and definition of SIRS criteria. *Intensive Care Med* 2012; 38(5): 811-819. doi: 10.1007/s00134-012-2549-5.

34. Bernard GR, Vincent JL, Laterre PF, *et al*. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344: 699-709.

35. Cervoni JP, Amoros A, Moreau R, *et al*. Prognostic value of C-reactive protein in patients with cirrhosis: external validation from the CANONIC cohort. *Hepatology* 2014; 60 (Suppl): 495A.

36. Fernandez J, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol* 2012; 56(Suppl 1): S1-S12.

37. Higgins C. Capillary-blood gases: To arterialize or not. Available from: www.acutecaretesting.org.