

Comparison of serum biomarkers for the early diagnosis of patients with liver cirrhosis and systemic inflammatory response syndrome

Danhong Yang (✉ ydh-11@163.com)

Zhejiang Provincial People's Hospital <https://orcid.org/0000-0002-1235-942X>

Yuanjun Xie

Zhejiang Chinese Medical University

Qiang Zhang

Bengbu Medical College

Yicheng Huang

Zhejiang Provincial People's Hospital

Yining Dai

Zhejiang Provincial People's Hospital

Wei Yu

Zhejiang Provincial People's Hospital

Hongying Pan

Zhejiang Provincial People's Hospital

Research article

Keywords: Liver Cirrhosis(LC),Systemic inflammatory response syndrome (SIRS) , Soluble triggering receptor expressed on myeloid cells-1(sTREM-1),Cytokines,Early identification

Posted Date: June 5th, 2019

DOI: <https://doi.org/10.21203/rs.2.10101/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Systemic inflammatory response syndrome (SIRS) can cause serious negative effects among patients with liver cirrhosis (LC). . It is very important to finding methods for early diagnose and intervene early in these patients. This study was to assess the accuracy of early diagnostic value of serum biomarkers in patients with LC and SIRS. Methods A total of 123 LC patients were enrolled, 64 of whom were diagnosed with SIRS and 59 patients without SIRS. Various biomarkers and cytokines were measured in two groups of patients: LC+SIRS and LC-SIRS. Receiver operating characteristic curves (ROCs) were used to assess the ability of tested biomarkers to diagnose LC with SIRS. Results White blood cell (WBC) count, neutrophil percentage (N%), as well as levels of C-reactive protein (CRP), procalcitonin (PCT), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), interleukin (IL)-6, IL-10 and tumor necrosis factor (TNF)- α , were significantly higher in the LC+SIRS group than in the LC-SIRS group. But only sTREM-1 had high accuracy of the early diagnosis for LC+SIRS. The WBC count, N% as well as levels of CRP, PCT, IL-6, and TNF- α had moderate diagnostic value, and IL-10 had low diagnostic value. The cutoff value of sTREM-1 was 179.23 pg/mL and showed 84.4% sensitivity and 93.2% specificity. The AUC of sTREM-1 was 0.904 (95% CI 0.899–0.982) and higher than that of the WBC count as well as levels of CRP, PCT, IL-6, IL-10 and TNF- α . In addition, 24 (37.50%) LC+SIRS cases died during 90-day follow-up. Neutrophil percentage as well as levels of CRP, PCT, sTREM-1, IL-6 and TNF- α were significantly higher those who died than in those who survived. Conclusion The WBC count, N% and levels of CRP, PCT, sTREM-1, IL-6, IL-10 and TNF- α are helpful for the early diagnosis of LC+SIRS. Serum sTREM-1 cut-off levels provide better accuracy than customary levels for cirrhosis with SIRS and appears to be a useful early marker to discriminate between SIRS and no-SIRS. It may also be helpful for implications in the prevention and treatment of cirrhosis and SIRS/sepsis.

Background

Patients with liver cirrhosis (LC) have an altered defense against bacteria. This reduced bacterial clearance in LC can contribute to a high risk of systemic inflammatory response syndrome (SIRS) [1]. The latter is a common and serious burden among LC patients because it can cause liver function to deteriorate further, and has serious negative effects on the disease course [2,3]. Some evidence suggests that systemic inflammation in LC patients maximizes the risk of complications (e.g., portal hypertensive bleeding, hepatic encephalopathy, acute-on-chronic liver failure) and increases the mortality risk due to acute renal insults [3]. About 30% of LC patients die within 1 month of infection and another 30% die within 1 year. We have reported that 90-day mortality in LC patients with SIRS can be up to 38% [4]. Therefore, finding methods to diagnose and intervene early in these patients is very important.

Studies have shown that the pathophysiologic background of SIRS and septic complications such as hypercytokinemia, if prolonged, can cause multiple organ dysfunction syndrome (MODS) [5]. Cytokines such as interleukin (IL)-6 are thought to be key mediators in the acute response to SIRS and MOF development [6,7]. Cytokines are involved in injury to and cirrhosis of the liver. Clinical research has shown the prominent role of T helper cell type 1 (Th1) cells, Th2 cells, pro-inflammatory or anti-

inflammatory cytokines in LC pathogenesis [8]. LC patients with SIRS can have acute and extrahepatic manifestations. Cytokines are secreted by immune-system cells and play an important part in infection control, inflammation, regeneration and fibrosis [9]. In recent years, there has been considerable interest in the search for possible immunologic markers for the diagnosis and progression of SIRS/sepsis [10,11]. Knowing the cutoff values for cytokines to predict early SIRS in LC patients would be extremely helpful, but little work has been done in this area. We don't know which is more predictable between levels of serum cytokines and some traditional inflammatory markers such as C-reactive protein (CRP) and procalcitonin(PCT) in early recognition of cirrhosis with SIRS.

Triggering receptor expressed on myeloid cells-1 (TREM-1) is a cell-surface receptor on blood neutrophils and mature monocytes/macrophages [12]. TREM-1 is a 30-kDa glycoprotein of the immunoglobulin superfamily [12]. *In vitro* and *in vivo* studies have shown that TREM-1 expression is upregulated strongly by extracellular bacteria (particularly their cell-wall components) and by fungi [13]. TREM-1 expression can be induced by bacterial products such as lipopolysaccharides and lipoteichoic acid. Recently it is reported that TREM-1 is a potent amplifier of the inflammatory response to invading pathogens because activation of its receptors during infection results in enhanced production of pro-inflammatory cytokines [14]. Hence, TREM-1 has attracted attention as a diagnostic/prognostic biomarker for SIRS/sepsis [14]. A soluble form of TREM-1 (sTREM-1) is released from activated phagocytes and can be found in serum [15]. The plasma level of sTREM-1 appears to be a reliable parameter in differentiating patients with sepsis from those with SIRS [16,17]. However, application of sTREM-1 for the early diagnosis of LC patients with SIRS has not been done.

In the present study, comparison of the white blood cell (WBC) count, neutrophil percentage, as well as levels of CRP, PCT, sTREM-1 and cytokines was done. We wish to find out a effective and sensitive biomarker as a strategy for the early diagnosis of LC patients with SIRS.

Methods

Ethical approval of the study protocol

The study protocol was approved by the Bioethics Committee of Zhejiang Provincial People's Hospital (EC/2014/002, KY2018011; Hangzhou, China). Written informed consent was obtained from all patients or their relatives. The study protocol was in agreement with the Declaration of Helsinki.

Definitions and criteria

A patient was considered to have SIRS if he/she fulfilled at least two of the following criteria: (i) body temperature $<36^{\circ}\text{C}$ or $>38^{\circ}\text{C}$; (ii) heart rate >90 bpm; (iii) tachypnea (>20 breaths/min) or partial pressure of carbon dioxide <4.3 kPa; (iv) WBC count >12.0 or $<4 \times 10^9/\text{L}$, or neutrophil percentage $>10\%$. Exclusion criteria were: age <18 years and >80 years; disseminated and concomitant malignant disease; pregnancy; treatment for acquired immune deficiency syndrome or immunosuppression; severe cardiopulmonary

disorders; patients on steroids or other immunosuppressive therapy; patients with certain autoimmune disorders and collagen disease such as hyperthyroidism, systemic lupus erythematosus (SLE), dermatomyositis, scleroderma, and so on; life expectancy < 24 h;

Study cohort

One hundred and twenty-three LC patients were admitted consecutively to Zhejiang Provincial People's Hospital between February 2015 and October 2017. They were evaluated within 12 h for SIRS according to the criteria of the American College of Clinical Pharmacy/Society of Critical Care Medicine Consensus Conference [18]. The final diagnosis was based on other clinical data, including diagnostic imaging and microbiological results.

Among these 123 LC patients, 64 had at least two criteria of SIRS upon hospital admission and were diagnosed as such; the other 59 LC patients did not and were excluded from the diagnosis of SIRS. The association of SIRS with or without sepsis was assessed by microbiologic cultures. Patients with bacterial infection were treated with antibiotics. Two groups were created: LC+SIRS, and LC-SIRS.

Follow-up

Survival data were obtained by telephone contact to patients or their family. All patients in the cohort were studied for 90 days or until death.

Laboratory examination

Routine microbiology examination for SIRS patients involved more than one pair of blood cultures. Analyses of urine, sputum, bronchoalveolar lavage fluid, cerebrospinal fluid, abscesses and closed wounds were undertaken. Blood was drawn immediately after presentation to the Emergency Department of Zhejiang Provincial People's Hospital and analyzed in the laboratory within 24 h for measurement of WBC counts, neutrophil percentage, CRP level, procalcitonin level, and blood chemistry.

A particle-enhanced immunoturbidimetric method for quantitative determination of whole-range CRP was used employing a kit from Shanghai Upper Biotech Pharma (Shanghai, China). Procalcitonin levels were measured using a Cobas E601 chemiluminescence analyzer (8000 series; Roche, Basel, Switzerland). Additional serum samples were collected, aliquots were prepared, and samples frozen at -80°C until analyses of sTREM-1 and cytokines. sTREM-1 levels were determined in duplicate using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) (Quantikine[®] Human TREM-1 Immunoassay kit; R&D Systems, Minneapolis, MN, USA). Serum levels of IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17 and tumor necrosis factor (TNF)- α were measured *via* a multiplex analyte detection system based on a fluorescent bead immunoassay (eBioscience, San Diego, CA, USA) and a BD FACS Canto™ II system (BD Biosciences, Sparks, MD, USA).

Statistical analyses

Descriptive data are the mean \pm standard deviation or number (percentage). Comparison of continuous variables was carried out using the Student's *t*-test. Skewness distribution data are the median with range (25–75 interquartile range) and were analyzed using the Mann–Whitney *U*-test. Categorical variables were analyzed using Fisher's exact test or Pearson's χ^2 -test. Evaluation of the early diagnostic performance of CRP, procalcitonin, sTREM-1, and cytokines was done using receiver operating characteristic curves (ROCs). The latter were compared using a non-parametric method. The cutoff value, which was the maximum area under the ROC curve (AUC), and accuracies were calculated with 95% confidence intervals. $P < 0.05$ was considered significant. SPSS v17.0 (IBM, Armonk, NY, USA) was used for all analyses.

Results

Patient characteristics

Detailed characterization of the 123 patients is shown in Table 1. More patients had a “mixed” etiology (alcohol + hepatitis-B virus (HBV)) in the LC+SIRS group compared with the LC–SIRS group (20.31% [13/64] vs. 5.08% [3/59]) ($P = 0.015$). There was no significant difference between the LC+SIRS group and LC–SIRS group in terms of age ($P = 0.224$), sex ratio ($P = 0.907$), alanine transaminase level ($P = 0.899$) or the proportion of people with Child–Pugh class-B disease ($P = 0.247$). Patients in the LC+SIRS group had significantly higher total prothrombin ($P < 0.001$), prothrombin time ($P < 0.001$), creatinine ($P < 0.001$), proportion of people with Child–Pugh class-C disease ($P < 0.001$), proportion of people with Child–Pugh score ($P < 0.001$), as well as a lower albumin level ($P < 0.001$), platelet count ($P < 0.001$), and proportion of people with Child–Pugh class-A disease ($P < 0.001$), compared with the LC–SIRS group. Mortality prevalence at 90 days was 1.69% (1/59) for the LC–SIRS group and 37.50% (24/64) for the LC+SIRS group ($P < 0.001$). In addition, the prevalence of infection was significantly higher in the LC+SIRS group compared with the LC–SIRS group (95.31% [61/64] vs. 3.39% [2/59]) ($P < 0.001$) (Table 1).

Comparison of tested biomarkers between the two groups

The WBC count, neutrophil percentage, as well as levels of procalcitonin, CRP, and sTREM-1 were significantly higher in the LC+SIRS group than those in the LC–SIRS group ($P < 0.001$). Levels of IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17A and TNF- α could be measured. Of these cytokines, levels of IL-6, IL-10 and TNF- α in LC+SIRS patients were significantly higher than those of LC–SIRSpatients ($P < 0.001$, 0.002 and < 0.001 , respectively). There was no significant difference in levels of IL-11 β , IL-2, IL-4, IL-8, IL-12 or IL-17A in the serum of patients in the LC+SIRS group and LC–SIRS group ($P = 0.140$, 0.678, 0.625, 0.140, 0.515, and 0.907, respectively)(Table 2).

Discriminative power of test biomarkers for the early diagnosis of LC+SIRS patients upon hospital admission

Figure 1 shows the ROC curves for the WBC count, neutrophil percentage as well as levels of CRP, procalcitonin, sTREM-1, IL-6, IL-10 and TNF- α for the early diagnosis of LC+SIRS patients. Values for the AUC, cutoff value, sensitivity, specificity, Youden Index and accuracy are listed in Table 3.

We compared the pairwise AUCs of test biomarkers. sTREM-1 had higher AUCs than the WBC count ($P = 0.008$), neutrophil percentage (1.102) as well as levels of CRP (<0.001), procalcitonin (<0.001), IL-6 (0.006), IL-10 (0.008) and TNF- α (0.007). The neutrophil percentage had higher AUCs than CRP ($P = 0.013$), procalcitonin (0.009) and IL-10 (0.003) (Figure 1).

Discussion

SIRS can occur in patients with liver cirrhosis of various etiology. We found significant differences in levels of ALB, TB, PT, Cr, PLT count, Child–Pugh class C ratio, Child score, infection ratio and 90-day mortality between patients with and without SIRS. LC with SIRS patients were in critical condition and with a poor in-hospital outcome, especially in patients with Child–Pugh class C and their lower immunity may be responsible for the high incidence of SIRS. SIRS appears to have important prognostic relevance and increases the risk of encephalopathy, renal failure, infection and death during acute or chronic liver failure [19,20]. Unfortunately, predicting SIRS early in LC patients is difficult. Serum levels of CRP and procalcitonin have been suggested to be early markers for the diagnosis of SIRS as well as for the diagnosis and prediction of bacterial infection in LC [21,22]. The CRP concentration is closely related to the increasing speed, amplitude, duration, and severity of inflammation.

Previously, we found that CRP >25 mg/L is associated significantly with 90-day mortality in LC+SIRS patients [4]. Procalcitonin is a sensitive and specific serologic marker, and its level increases at the early stage of LC with serious bacterial infection, and so has value for early diagnosis [23]. However, our data showed that levels of CRP and procalcitonin in LC+SIRS patients did not increase significantly (Table 2), even though they were significantly different between the LC+SIRS group and LC–SIRS group. Procalcitonin is derived mostly from the liver. Liver failure may lead to the formation of a network of monocytes to reduce the concentration of acute-phase proteins (APPs) [24]. The more severe the underlying liver dysfunction, the lower the CRP response to bacteremia [25].

Similarly, the reason why the WBC count and neutrophil percentage were not high may have been related to hypersplenism and decompensated LC. We showed the WBC count was in the normal range even if it was significantly different between LC+SIRS patients and LC–SIRS patients. However, the WBC count was not significantly different in patients who died and those who survived. Some new biomarkers of SIRS would be particularly useful for the early diagnosis in this population.

TREM-1 is expressed on neutrophils and monocytes. It is implicated in the development and amplification of the early inflammatory response to infection and injury. sTREM-1 is the soluble form of this receptor and is released into body fluids when TREM-1 expression is upregulated [26]. As reported by Jedynak and colleagues, the serum level of sTREM-1 measured within the first 24 h of treatment in the intensive care unit is a useful prognostic biomarker for patients with sepsis, severe sepsis or septic shock [27]. sTREM-1 expression is upregulated in the presence of bacteria and fungi, whereas it is expressed only weakly in noninfectious disorders such as vasculitis or psoriasis.

Various studies have suggested that the sTREM-1 concentration in different biologic fluids is significantly higher in patients with bacterial infection than in those with a non-microbial inflammatory process [28–29]. sTREM-1 is the best biomarker evaluated for the diagnosis and prognosis of sepsis to date [30]. Furthermore, the serum level of sTREM-1 reflects the severity of sepsis more accurately than that of CRP and procalcitonin, and is more sensitive for dynamic evaluation of the sepsis prognosis.[31] The serum concentration of sTREM-1 can early predict the 28-day sepsis mortality [32].

We revealed that LC+SIRS patients had a significantly increased serum level of sTREM-1, the highest AUC (0.940), sensitivity of 0.844, and specificity of 0.942 at a cutoff value of 179.230 ng/mL. Serum levels of sTREM-1 could be used to predict the early diagnosis of LC+SIRS compared with the WBC count, neutrophil percentage or levels of CRP, procalcitonin, IL-6, TNF- α or IL-10 (Table 3, Figure 1). Even in the LC+SIRS group, levels of CRP and procalcitonin were more meaningful in the non-survival group than in the survival group. We demonstrated that the serum level of sTREM-1 was a suitable biomarker for identification of LC patients with SIRS. Moreover, the serum level of sTREM-1 may be an outcome predictor in LC patients with SIRS, and could act as an indicator for starting early therapeutic interventions.

Recently some data demonstrate that the TREM-1 pathway on Kupffer cells plays an essential role in hepatic inflammation and fibrogenesis in a mouse model of fibrosis. TREM-1 controls the mobilization of inflammatory cells in response to injury and consequently enhances liver damage[33]. Maybe we will study the relationship between TREM-1 and severity of liver inflammation in the future.

Cytokines are key mediators of pro- and anti-inflammatory processes. LC is associated with impairment of detoxification, synthetic processes, metabolic processes, and alterations (and even increased synthesis) of some pro-inflammatory molecules. The role of the liver as one of the major sites of cytokine production has been acknowledged widely[34]. A severe inflammatory response on the basis of LC can impact directly on circulating levels of cytokines and growth factors and, ultimately, affect immune-system functions [35,36]. Studies have shown that SIRS/sepsis leads to the release of some cytokines, among which IL-6 and TNF- α are important. In addition, levels of IL-4, IL-8, IL-10, IL-12 and interferon- γ are also increased [37,38].

IL-6 release is induced by lipopolysaccharides, viral infections, or products released by necrotic cells. Several scholars have investigated the correlation between levels of IL-6 and TNF- α and pathologic states based on inflammatory processes [39,40]. Increased plasma levels of TNF- α have been reported after

endotoxin stimulation in healthy volunteers and septic-shock patients with Gram-positive and Gram-negative bacteremia. The blood concentration of IL-6 and TNF- α is positively correlated with the severity of infection and inflammation, and is used as a sensitive indicator to judge disease severity and the prognosis [41]. We observed meaningful differences in the concentrations of the pro-inflammatory cytokines IL-6 and TNF- α , as well as the anti-inflammatory cytokine IL-10, in LC+SIRS patients. However, there were no significant differences in the concentrations of the pro-inflammatory cytokines IL-1 β , IL-2, IL-8, IL-12 or IL-17A, or the anti-inflammatory cytokine, IL-4 (Table 2). IL-6 and TNF- α were representative cytokines produced in LC and showed significantly high expression in the early phase of LC+SIRS. However, their specificity was relatively low for LC+SIRS patients, and their diagnostic ability inferior to that of sTREM-1.

Our study had two main limitations. First, our study cohort was relatively small. Further validation of a larger dataset is required. Second, the serum concentrations of test markers according to the severity of LC with SIRS/sepsis should have been studied. The definition comprises four clinical entities, SIRS, sepsis, severe sepsis and MODS, which may have different early-diagnosis markers and models for prediction of LC [42,43].

Conclusions

The WBC count, neutrophil percentage and levels of CRP, procalcitonin, sTREM-1, IL-6, IL-10 and TNF- α are helpful for the early diagnosis of LC+SIRS, and the serum level of sTREM-1 is a novel biomarker for these patients. Serum sTREM-1 cut-off levels provide better accuracy than customary levels for cirrhosis with SIRS and appears to be a useful early marker to discriminate between LC patients with SIRS and LC patients without SIRS. It may also be helpful for implications in the prevention and treatment of cirrhosis and SIRS/sepsis.

Acknowledgment

We thank Arshad Makhdam, PhD, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Funding: This work was supported by the Medical and Health Science and Technology Project of Zhejiang Province (2014KYA022) and Public Welfare Science and Technology Project of Zhejiang Province (2015C33165).

References

- 1 Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the national hospital discharge survey. *Chest* 2003; 124(3): 1016–1020 [PMID:12970032]
- 2 Bruns T, Zimmermann HW, Stallmach A. Risk factors and outcome of bacterial infections in cirrhosis. *World J Gastroenterol* 2014; 20(10): 2542–2554. [PMID:24627590]

- 3 Cazzaniga M, Dionigi E, Gobbo G, Fioretti A, Monti V, Salerno F . The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. *J Hepatol* 2009; 51: 475–482 [PMID:19560225]
- 4 Yang DH, Xie YJ, Pan HY, Huang YC, Dai YN, Tong YX, Chen MJ. Clinical characteristics and prognostic factors of liver cirrhosis patients with systemic inflammatory response syndrome. *Hepatology Research* 2017 ;47(11):1174-1185 [PMID: 28249358]
- 5 Herzum I, Renz H. Inflammatory Markers in SIRS, Sepsis and Septic Shock. *Current Medicinal Chemistry* 2008; 15(6), 581-7 [PMID:18336272]
- 6 Watanabe E, Hirasawa H, Oda S, SHIGA H, MATSUDA K, NAKAMURA M, ABE R, NAKADA T. Cytokine-Related genotypic differences in peak interleukin-6 blood levels of patients with SIRS and Septic complications. *J Trauma* 2005;59:1181–1190 [PMID:16385298]
- 7 Giannoudis PV, Harwood PJ, Loughenbury P, Van Griensven M, Krettek C, Pape HC. Correlation between IL-6 levels and the systemic inflammatory response score: can an IL-6 cutoff predict a SIRS state? *The Journal of Trauma* 2008 ;65(3):646-652 [PMID:18784579]
- 8 Simpson KJ, Lukacs NW, Colletti L, Strieter RM, Kunkel SL. Cytokines and the liver. *J Hepatol* 1997;27:1120-1132 [PMID:9453442]
- 9 Li W, Li N, Wang R, Li Q, Wu H. Interferon gamma, interleukin-6, and -17a levels were correlated with minimal hepatic encephalopathy in HBV patients. *Hepatol Int* 2015; 9(2):218–23 [PMID:25794550]
- 10 Michelena J, Altamirano J, Abalde JG, Affò S, Morales-Ibanez O, Sancho-Bru P, Dominguez M, García-Pagán JC, Fernández J, Arroyo V, Ginès P, Louvet A, Mathurin P, Mehal WZ, Caballería J, Bataller R. Systemic Inflammatory Response and Serum Lipopolysaccharide Levels Predict Multiple Organ Failure and Death in Alcoholic Hepatitis. *Hepatology* 2015;62(3):762-772 [PMID:25761863]
- 11 Suárez-Santamaría M, Santolaria F, Pérez-Ramírez A, Alemán-Valls MR, Martínez-Riera A, González-Reimers E. Prognostic value of inflammatory markers (notably cytokines and procalcitonin), nutritional assessment, and organ function in patients with sepsis. *Eur Cytokine Netw* 2010;21(1):19-26 [PMID:20146986]
- 12 Bouchon A, Dietrich J, Colonna M. Cutting edge: inflammatory responses can be triggered by TREM-1, a novel receptor expressed on neutrophils and monocytes. *J Immunol* 2000; 164:4991–4995 [PMID:10799849]
- 13 Colonna M, Facchetti F. TREM-1 (triggering receptor expressed on myeloid cells): a new player in acute inflammatory responses. *J Infect Dis* 2003; 187(suppl 2):S397–S401 [PMID:12792857]
- 14 Zhang J, She D, Feng D, Jia Y, Xie L. Dynamic changes of serum soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) reflect sepsis severity and can predict prognosis: a prospective study. *BMC*

Infect Dis 2011;11: 53.[PMID:21356122]

15 Barati M, Bashar FR, Shahrami R,Zadeh MH, Taher MT, Nojomi M.Soluble triggering receptor expressed on myeloid cells 1 and the diagnosis of sepsis. J Crit Care 2010, 25(2):362e1–6 [PMID:19914031]

16 Aksaray S, Alagoz P, Inan A,Cevan S, Ozgultekin A.Diagnostic value of sTREM-1 and procalcitonin levels in the early diagnosis of sepsis.North Clin Istanbul 2017 ,3(3):175-182.[PMID:28275748]

17 Larsen FF, Petersen JA.Novel biomarkers for sepsis: A narrative review. Eur J Intern Med 2017 ;45:46-50[PMID:28965741]

18 Bone RC, Sibbald WJ, Sprung CL . The ACCP-SCCM consensus conference on sepsis and organ failure. Chest 1992; 101:1481–3[PMID:1600757]

19 Angeli P, Tonon M, Pilutti C,Morando F, Piano S. Sepsis induced acute kidney injury in patients with cirrhosis. Hepatol Int 2016; 10(1): 115–23. [PMID:26141259]

20 Shi Y,Yan H,Zhou Z,Fang H, Li J, Ye H, Sun W, Zhou W, Ye J, Yang Q, Yang Y, Hu Y, Chen Z, Sheng J. Clinical course of cirrhosis patients hospitalized for acute hepatic deterioration: a prospective bicentric study. J Med (Baltimore) 2015; 94: e2031[PMID:26632701]

21 Bota DP, Van Nuffelen M, Zakariah AN,Vincent JL. Serum levels of C-reactive protein and procalcitonin in critically ill patients with cirrhosis of the liver. J Lab Clin Med 2005; 146:347–51.[PMID:16310518]

22 Lazzarotto C, Ronsoni MF, Fayad L ,Nogueira CL, Bazzo ML, Narciso-Schiavon JL, de Lucca Schiavon L, Dantas-Corrêa EB.Acute phase proteins for the diagnosis of bacterial infections and prediction of mortality in acute complications of cirrhosis. Ann Hepatol 2013; 1(4): 599–607.[PMID:23813138]

23 Cai ZH, Fan CL, Zheng JF,Zhang X, Zhao WM, Li B, Li L, Dong PL, Ding HG.Measurement of serum procalcitonin levels for the early diagnosis of spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis. BMC Infect Dis. 2015 ;13;15:55. [PMID:25887691]

24 Papp M, Vitalis Z, Altorjay I,Tornai I, Udvardy M, Harsfalvi J, Vida A, Kappelmayer J, Lakatos PL, Antal-Szalmás P. Acute phase proteins in the diagnosis and prediction of cirrhosis associated bacterial infections. Liver Int 2012, 32: 603-611 [PMID:22145664]

25 Park WB, Lee KD, Lee CS,Jang HC, Kim HB, Lee HS, Oh MD, Choe KW. Production of C-reactive protein in Escherichia coliinfected patients with liver dysfunction due to liver cirrhosis. Diagn Microbiol Infect Dis 2005; 51: 227-30 [PMID:15808312]

26 Gibot S, Cravoisy A.Soluble form of the triggering receptor expressed on myeloid cells-1 as a marker of microbial infection.Clin Med Res 2004 ;2(3):181-7. [PMID:15931355]

- 27 Jedynek M, Siemiatkowski A, Mroczko B, Groblewska M, Milewski R, Szmitkowski M. Soluble TREM-1 Serum Level can Early Predict Mortality of Patients with Sepsis, Severe Sepsis and Septic Shock. *Arch Immunol Ther Exp (Warsz)* 2017 ; 27:1-8 [PMID: 29282483]
- 28 Plachouras D, Routsis C, Giamarellos-Bourboulis EJ, Spyridaki E, Andrianakis I, Metzelopoulos S, Tsaganos T, Floros I, Douzinas EE, Armaganidis A, Roussos C, Giamarellou H. Monocytes as a site of production of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in the septic host. *Scand J Infect Dis* 2006;38(10):909-915. [PMID: 17008237]
- 29 Liu CL, Hsieh WY, Wu CL, Kuo HT, Lu YT. Triggering receptor expressed on myeloid cells-1 in pleural effusions: a marker of inflammatory disease. *Respir Med.* 2007;101(5):903-9. Epub 2006 Nov 13. [PMID:17097866]
- 30 Larsen FF, Petersen JA. Novel biomarkers for sepsis: A narrative review. *Eur J Intern Med.* 2017;45:46-50. [PMID:28965741]
- 31 Su L, Han B, Liu C, Liang L, Jiang Z, Deng J, Yan P, Jia Y, Feng D, Xie L. Value of soluble TREM-1, procalcitonin, and C-creative protein serum levels as biomarkers for detecting bacteremia among sepsis patients with new fever in intensive care units: a prospective cohort study. *BMC Infect Dis* 2012; 12:157. [PMID:22809118]
- 32 Jedynek M, Siemiatkowski A, Mroczko B, Groblewska M, Milewski R, Szmitkowski M. Soluble TREM-1 Serum Level can Early Predict Mortality of Patients with Sepsis, Severe Sepsis and Septic Shock. *Arch Immunol Ther Exp (Warsz)*. 2018; 66(4): 299–306. [PMID: 29282483]
- 33 Nguyen-Lefebvre AT, Ajith A, Portik-Dobos V, Horuzsko DD, Arbab AS, Dzutsev A, Sadek R, Trinchieri G, Horuzsko A. The innate immune receptor TREM-1 promotes liver injury and fibrosis. *J Clin Invest.* 2018 Nov 1;128(11):4870-4883. [PMID:30137027]
- 34 Andus T, Bauer J, Gerok W. Effects of cytokines on the liver. *Hepatology* 1991;13:364-375 [PMID:1995444]
- 35 Simpson KJ, Lukacs NW, Colletti L, Strieter RM, Kunkel SL. Cytokines and the liver. *J Hepatol* 1997;27:1120-1132. [PMID:9453442]
- 36 Llorent L, Richaud-Patin Y, Alcocer-Castillejos N, Ruiz-Soto R, Mercado MA, Orozco H, Gamboa-Domínguez A, Alcocer-Varela J. Cytokine gene expression in cirrhotic and noncirrhotic human liver. *J Hepatol* 1996;24:555-563. [PMID:8773910]
- 37 Fisić E, Poropat G, Bilic-Zulle L, Licul V, Milic S, Stimac D. The role of IL-6, 8, and 10, sTNF α , CRP, and pancreatic elastase in the prediction of systemic complications in patients with acute pancreatitis. *Gastroenterol Res Pract* 2013; 2013: 282645. [PMID:23476635]

- 38 Kothari N, Bogra J, Abbas H, Kohli M, Malik A, Kothari D, Srivastava S, Singh PK. Tumor necrosis factor gene polymorphism results in high TNF level in sepsis and septic shock. *Cytokine* 2013;61(2):676-681 [PMID:23317877]
- 39 Tanno D, Akahori Y, Toyama M, Sato K, Kudo D, Abe Y, Miyasaka T, Yamamoto H, Ishii K, Kanno E, Maruyama R, Kushimoto S, Iwakura Y, Kawakami K. Involvement of Gr-1 dull+ cells in the production of TNF- α and IL-17 and exacerbated systemic inflammatory response caused by lipopolysaccharide. *Inflammation*. 2014 37(1):186-95. [PMID:24022599]
- 40 Marton A1, Kolozsi C, Kusz E, Olah Z, Letoha T, Vizler C, Pecze L. Propylene-glycol aggravates LPS-induced sepsis through production of TNF- α and IL-6. *Iran J Immunol*. 2014 Jun;11(2):113-22. [PMID:24975968]
- 41 Rau S, Kohn B, Richter C, Fenske N, Küchenhoff H, Hartmann K, Härtle S, Kaspers B, Hirschberger J. Plasma interleukin-6 response is predictive for severity and mortality in canine systemic inflammatory response syndrome and sepsis. *Vet Clin Pathol* 2010;36(3):253–260. [PMID:17806073]
- 42 Ventetuolo CE, Levy MM. Biomarkers: diagnosis and risk assessment in sepsis. *Clin Chest Med*. 2008; 29(4): 591–603. [PMID:18954695]
- 43 Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC. Assessment of Clinical criteria of sepsis: For the third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama*, 2016;315(8):762-774. [PMID:26903335]

Tables

Table 1. Comparative clinical features of LC patients with and without SIRS during hospitalization (n = 123)

Characteristics	Total (n=123)	With SIRS (n=64)	Without SIRS (n=59)	Pvalue
Age (yrs)	62.37±13.64	65.04±13.67	59.23±11.53	0.224
Gender (male%)	63.41 [72/123]	64.06 [41/64]	62.71 [37/59]	0.907
Etiologies of cirrhosis				
Viral hepatitis	39.84(49/123)	34.38(22/64)	45.76(27/59)	0.135
HBV	38.21(47/123)	32.81 [21/64]	44.07 [26/59]	0.266
HCV	1.63(2/123)	1.56(1/64)	1.69(1/59)	0.731
Alcohol	15.45(19/123)	12.5(8/64)	18.64(11/59)	0.244
Mixed etiology	15.45(19/123)	21.87(16/64)	5.08(3/59)	0.011
HBV+HEV	0.81(1/123)	1.56(1/64)	0	0.520
HBV + alcohol	13.01(16/123)	20.31(13/64)	5.08(3/59)	0.015
Alcohol+ Schistosomal	1.63(2/123)	3.13(2/64)	0	0.269
Schistosomal cirrhosis	3.25(4/123)	3.13(2/64)	3.39(2/59)	0.647
Autoimmune hepatitis	8.94(11/123)	9.38(6/64)	8.47(5/59)	0.557
Cryptogenic cirrhosis	17.07(21/123)	15.63(10/64)	18.64(11/59)	0.418
ALT (U/L, ±s)	35.11(21,38)	38.66 [20.25 40.25]	31.27 [22.00 38.00]	0.899
ALB (g/L, ±s)	29.83±4.14	27.98±4.38	31.82±2.71	<0.001
TB (mmol/L, ±s)	49.37 [25.8 51.00]	65.89(32.00,76.13)	31.45±12.74	<0.001
PT (s, ±s)	14.61 [12.60 16.10]	15.88±2.90	13.29±1.36	<0.001
Cr (µmol/L, ±s)	133.13 [98.00 175.00]	168.03±46.41	96.27±17.13	<0.001
WBC	5.48±3.08	6.95±3.37	3.89±1.61	<0.001
N%	65.52±16.79	79.61±6.79	50.24±9.18	0.019
PLT (mmol/L, ±s)	83 [02 42.00 109.00]	73.34±44.42	93.53±60.62	<0.001
Child-Pugh Class A(%)	26.02(32/123)	6.25 [4/64]	47.46 [28/59]	<0.001
B(%)	44.72(55/123)	48.44 [31/64]	40.68 [24/59]	0.247

C(%)	29.27(36/123)	45.31(29/64)	11.86(7/59)	<0.001
Child-Pugh score	8.90±2.24	9.61±2.00	7.29±1.84	<0.001
Infection	51.22(63/123)	95.31(61/64)	3.39(2/59)	<0.001
90-day mortality, n (%)	20.32(22/123)	37.50(24/64)	1.69(1/59)	<0.001

Mean ± standard deviation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TB, total bilirubin; PT, prothrombin time; Cr, creatinine; ChE, cholinesterase;

Table 2 Comparison of tested biomarkers between LC patients with SIRS and LC patients without SIRS (n = 123)

biomarker	With SIRS (n=64)	Without SIRS (n=59)	<i>P</i> value
CRP	19.68(4.63,30.75)	5.85±3.69	<0.001
PCT	0.77(0.50,1.77)	0.12(0.03,0.09)	<0.001
sTREM-1	596.08±483.68	84.99±55.67	<0.001
IL-11β(pg/ml)	2.79(0.59,2.24)	2.11(0.64,2.40)	0.625
IL-2(pg/ml)	0.37(0.12,0.42)	0.28(0.09,0.26)	0.140
IL-4(pg/ml)	0.17(0,0)	0.21(0,0.01)	0.678
IL-6(pg/ml)	526.02(14.17,62.23)	43.46(1.34,15.06)	<0.001
IL-8(pg/ml)	163.09(46.88,183.44)	118.11±98.42	0.515
IL-10(pg/ml)	22.25(0.43,19.95)	3.38(0.05,2.51)	0.002
IL-12(70) (pg/ml)	9.87(1.12,8.32)	5.69(1.27,8.14)	0.625
IL-17A(pg/ml)	8.15(2.62,7.63)	5.53(2.51,5.73)	0.907
TNF-α(pg/ml)	50.22(22.73,48.89)	19.22±14.01	<0.001

sTREM-1, soluble triggering receptor expressed on myeloid cells-1; CRP, C-reactive protein; PCT, procalcitonin;

Table 3 Capability of tested biomarkers for differentiating SIRS from LC

Biomarkers	AUC	Cut- off	Std. Error	P value	Asymptotic 95% Confidence Interval		sen	spe	Yi
					Lower limit	Upper limit			
WBC(109/L)	0.792	6.375	0.040	<0.001	0.713	0.871	0.688	0.712	0.400
NE(%)	0.863	74.30	0.033	<0.001	0.800	0.927	0.781	0.847	0.628
CRP(mg/L)	0.729	15.025	0.050	<0.001	0.632	0.827	0.672	0.864	0.536
PCT(ng/L)	0.714	0.425	0.047	<0.001	0.622	0.805	0.516	0.881	0.397
sTREM-1(pg/ml)	0.940	179.230	0.041	<0.001	0.899	0.982	0.844	0.932	0.776
IL-6(pg/ml)	0.779	5.855	0.044	<0.001	0.692	0.866	0.922	0.644	0.566
IL-10(pg/ml)	0.688	5.185	0.048	<0.001	0.595	0.781	0.453	0.881	0.334
TNF- α (pg/ml)	0.788	10.345	0.041	<0.001	0.708	0.868	0.875	0.576	0.451

sTREM-1 had the highest AUC and accuracy, followed by neutrophil percentage and interleukin-6. AUC, area under the receiver operating characteristic curve; Sen, sensitivity; Spe, specificity; Yi, Youden Index; WBC, white blood cell; N%, neutrophil percentage; CRP, C-reactive protein; PCT, procalcitonin; IL, interleukin; TNF- α , tumor necrosis factor-alpha.

Table 4 Comparison of biomarkers in cirrhotic patients with SIRS, grouped according to survival (n = 64)

Biomarker	Survival group	No-survival group	P value
	(n=43)	(n=21)	
WBC (109/L)	6.46 \pm 2.95	8.12 \pm 4.05	0.144
N(%)	71.57 \pm 9.35	82.41 \pm 8.06	0.008
CRP(mg/L)	18.06(3.0,20.60)	26.90 \pm 14.32	0.044
PCT(ug/L)	0.60(0.05,1.05)	1.10 \pm 1.54	0.002
sTREM-1 (pg/ml)	506.33 \pm 387.62	808.64 \pm 619.45	0.040
IL-6(pg/ml)	27.28 \pm 10.01 \pm 32.91	1545.98 \pm 35.54 \pm 1990.07	<0.001
IL-10(pg/ml)	11.21 \pm 0.48 \pm 15.60	49.77 \pm 0.35 \pm 77.67	0.093
TNF- α (pg/ml)	32.34 \pm 20.91 \pm 42.06	92.57 \pm 25.33 \pm 71.64	<0.001

WBC, white blood cell, N%, Neutrophil ratio; CRP, C-reactive protein; PCT, procalcitonin; IL, interleukin; TNF- α , tumor necrosis factor-alpha.

Figures

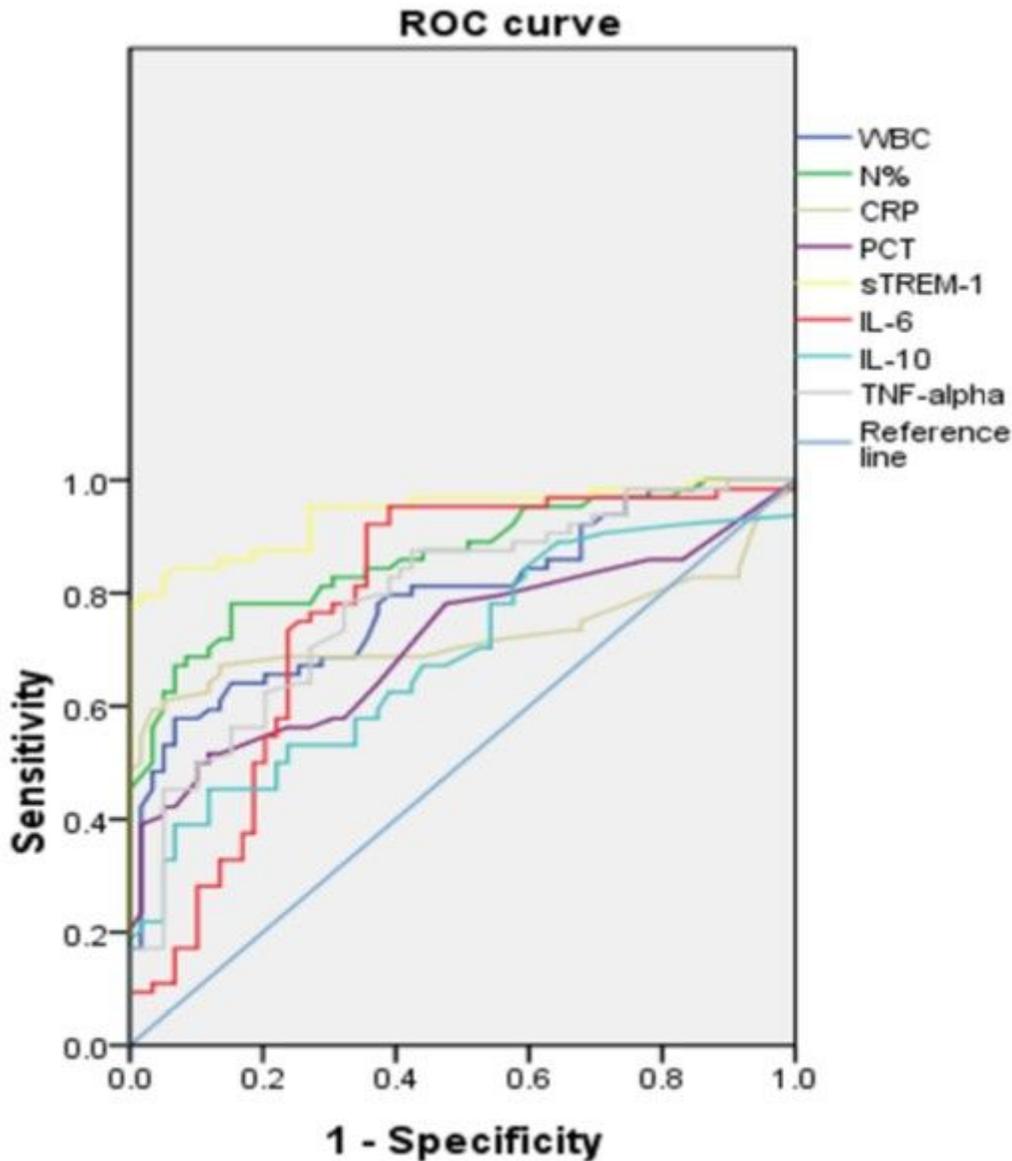


Figure 1

ROC curves for the test biomarkers upon hospital admission for early identification of patients with LC with SIRS. sTREM-1 had the highest AUC and accuracy. AUC, area under receiver operating characteristic curve; WBC, white blood cell; N%, neutrophilpercentage; PCT, procalcitonin; CRP, C-reactive protein; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; IL-6, interleukin 6; TNF- α , tumor necrosis factor-alpha