# Presepsin and Other Inflammatory Markers among Cirrhotic Patients with Bacterial Infections

**Ahmed Abdelhakim Abdelmaksoud [1], Talaat Fathy [2], Heba Pasha [3], Maysaa A. Saeed [4]**

[1] M.B; B.Ch.; Faculty of Medicine, Zagazig University
[2] Professor of Tropical Medicine, Faculty of Medicine, Zagazig University
[3] Professor of Medical Biochemistry, Faculty of Medicine, Zagazig University
[4] Professor of Tropical Medicine, Faculty of Medicine, Zagazig University
Email: drahmedhakiem151993@gmail.com, ahmed.aa22@medicine.zu.edu.eg

**Article History:** Received 10th June, Accepted 5th July, published online 10th July 2023

## Abstract

**Background**: Recent biomarkers and inflammatory variables could contribute to early prompt identification & differentiation of septic patients from those with SIRS. Among different recent biomarkers that appear to be promising in diagnosis of early stages of septic process were procalcitonin, presepsin, IL-6 and CD64. Now there is multiple studies act on the important role of presepsis in patients with liver cirrhosis and bacterial infection. Bacterial infections complicate the course of liver cirrhosis and determine an increased rate of decompensation, acute-on-chronic liver failure, and mortality. The early diagnosis and prompt treatment of infections prevent liver cirrhosis from further decompensation and sepsis development and may decrease mortality rates. The serum presepsin level >980 pg/ml had the most appropriate specificity and sensitivity to identify bacterial infections in patients admitted with liver cirrhosis and overt hepatic encephalopathy. Moreover, the presepsin levels were directly correlated with liver cirrhosis severity assessed by the MELD score and the Child-Pugh class. This review article aiming to discuss Presepsin and Other Inflammatory Markers among Cirrhotic Patients with Bacterial Infections. Data were collected from review articles extracted from pub med and google scholar from 1990 till 2022.

**Keywords:** presepsin, Liver Cirrhosis, Bacterial infections

## Introduction

Patients with liver cirrhosis are at higher risk for developing bacterial infections as well as patients who present with advanced liver cirrhosis, ascites, variceal bleeding, and history of spontaneous bacterial peritonitis (SBP) **(1,2).**

Bacterial infections frequently cause decompensating events in the cirrhotic patient, such as variceal bleeding, hepatorenal syndrome (HRS) and hepatic encephalopathy (HE) and are also the most common factor identified for the development of acute-on-chronic liver failure (ACLF) . The increase in the prevalence of infections caused by multidrug-resistant (MDR) microorganisms (bacteria that are not susceptible to at least one agent in three or more antimicrobial categories) have been associated with reduced effectiveness of empiric antimicrobial treatment, one of the measures considered to greatly decrease the mortality rates in patients with sepsis **(2).**

### Pathophysiology and Predisposing factors for infections in cirrhosis

Numerous factors are associated with an increased risk of infections in cirrhotic patients as immunodeficiency and bacterial translocation **(3).**

1- *Immunodeficiency*

Liver Cirrhosis is a state of immune dysfunction and also a state of excessive activation of pro-inflammatory cytokines, this is called cirrhosis-associated immune dysfunction syndrome, which increases the risk of infections where monocyte spreading, chemo-taxis, bacterial phagocytosis, neutrophil mobilization, phagocytic activity and intracellular killing are impaired **(4).**

As a result of hypersplenism, cirrhotic patients may have neutropenia. They also have lower levels of immunoglobulins IgM, IgG and IgA, in serum and ascites fluid, in addition to the low levels of C3 and C4 that lead to diminished bactericidal activity **(5).**

*2- Bacterial translocation*

Bacterial translocation is the migration of bacteria or bacterial products from the intestinal lumen to the mesenteric lymph nodes. Changes in the intestinal mucosa like vascular congestion, edema, oxidative stress and local inflammation are factors associated with an increased intestinal permeability, additionally, autonomic dysfunction, increased nitric oxide synthesis and oxidative stress retard intestinal motility, which leads to intestinal bacterial over growth. The conjunction of increased intestinal permeability, bacterial overgrowth, dysbiosis and immune deficiency facilitate the spread of intestinal bacterial to extra intestinal sites and predispose patients with cirrhosis to infections **(6).**

Genetic polymorphisms of toll-like receptors and nucleotide-binding oligomerization domain 2 genes could be responsible for bacterial translocation **(5).**

- **Implications of infections in cirrhosis**

Bacterial infections increase mortality four-fold in patients with cirrhosis. Thirty percent of cirrhotic patients with sepsis die within the first month after infection and another 30% within a year. Bacterial infection are the most common precipitating factor for hepatorenal syndrome and acute-on-chronic liver failure, the latter considered the main cause of death in patients with liver cirrhosis **(7).**

In the CANONIC study in 2013, the most comprehensive registry of ACLF, Bacterial infections were the major identifiable trigger (30%). The diagnosis and grade of ACLF is stablished according to the presence, type and number of organ failures calculated with the chronic liver failure score (CLIF-C ACLF score), this is based on the CANONIC study population and has a higher prognostic accuracy than the previous diagnose score system; chronic liver failure-sequential organ failure assessment (CLIF-SOFA) **(8).**

The severity is graded according to the number of organ failures in grade 1–3, mortality correlates with ACLF severity 22%, 32% and 73% respectively. The resolution rate depends on the initial ACLF grade, 55% in ACLF grade 1 and 15% in grade 3, but the clinical course is the most important determinant of short-term mortality, most of the patients reach their final grade of ACLF in the first week after diagnosis, therefore, the reassessment of ACLF should be done between the 3rd and $7^{th}$ day after diagnosis, this reassessment predicted 28-day and 90-day mortality more accurately than the calculated at diagnosis **(9).**

Patients with ACLF should be admitted to the ICU and ideally in a transplant center, the treatment is based on life support as well as management of the associated complications and precipitating factors. Liver transplant is the definitive treatment for patients with ACLF, in patients with ACLF grade 2or 3 survival without liver transplant is < 20% and increases to 80% when liver transplant is performed, as comparable with transplanted patients without ACLF **(10).**

Infections in cirrhotic patients have a wide range of clinical presentations: asymptomatic (cirrhotic patient usually immune-compromised due to associated pancytopenia with decrease response towards infection), classical presentation according to the infection site, sepsis, hepatic decompensation (hepatic encephalopathy or variceal bleeding) and ACLF. Thus, it is important to always rule out an infection in patients with a recently decompensating event (jaundice, hepatic encephalopathy, variceal bleeding and ascites) and have a low threshold of suspicion, in order to avoid a delay in the proper treatment **(11).**

It is well-known that bacterial infection can induce systemic inflammatory response syndrome (SIRS), which presents in 57–70% of infected cirrhotic patients. However, the diagnostic criteria for SIRS has a low sensitivity and specificity for diagnosing bacterial infection in cirrhotic patients (10–30% of the patients

with decompensated cirrhosis present with SIRS without bacterial infection). Therefore, other markers that suggest or confirm the presence of infection in patients with cirrhosis must be considered **(12).**

- *Biomarkers of bacterial infection:*

Some of the biomarkers currently available include C-reactive protein (CRP), procalcitonin (PCT), Interleukin-6 (IL-6), Plasma transforming growth factor-b1, Pro-vasopressin, pro-adrenomedullin (proADM), pro-atrial natriuretic peptide and myeloid cells expressing triggering receptor-1 (TREM-1), soluble urokinase-like plasminogen receptor (suPAR). Among the available biomarkers of sepsis, the CRP is still routinely used as a sepsis indicator **(13).**

Millions of deaths are reported due to sepsis throughout the world including both developed and developing nations. Sepsis has been attributed to occur in 1-2% of hospitalized patients including those who are undergoing treatment in intensive care units (ICU) **(14).**

Among the many biomarkers which have been evaluated for their prognostic significance, procalcitonin was found more useful. Although the available biomarkers of sepsis have proven to be useful, the drawbacks include their elevated activities during non septic conditions like trauma, surgery, myocardial infarction and other conditions like systemic inflammatory response syndrome (SIRS), and immune response during septic conditions. Considering the fact that sepsis due to infection is microbiologically confirmed only in 30% of the cases, it is inevitable that there is need for other indicators of sepsis **(15).**

Both C-reactive protein (CRP) and procalcitonin (PCT) are biomarkers that have been shown to be useful auxiliaries in the diagnosis of bacterial infection in cirrhosis and they have a higher sensitivity and a better negative predictive value when used together also there is a direct relation between serum CRP levels and the severity and speed of progression of sepsis **(16).**

CRP is produced by the liver and is raised in response to cytokines triggered by inflammation. It is an acute phase reactant raised in the early phases of the infection. In response to bacterial infection, it rises after 12 hours, peaks after 36-50 hours, and has a moderate specificity for bacterial infections. It is commonly used as a biomarker in the early stages of infection to screen infants for sepsis because of high sensitivity in the first 24 hours of life. Although it has low specificity in adult sepsis, considering its early rise in levels in response to the trigger **(17).**

Procalcitonin (PCT), a protein consisting of 116 amino acids used to identify and monitor sepsis. PCT is a precursor protein for calcitonin produced by the thyroid; calcitonin is a distinct protein like PCT. PCT rapidly processes to mature hormone calcitonin; therefore, the levels are very low at less than 0.1 µg/L. However, in the case of bacterial infection, PCT is induced outside the thyroid in other organs and parenchymal tissues and is released into circulation in large amounts.

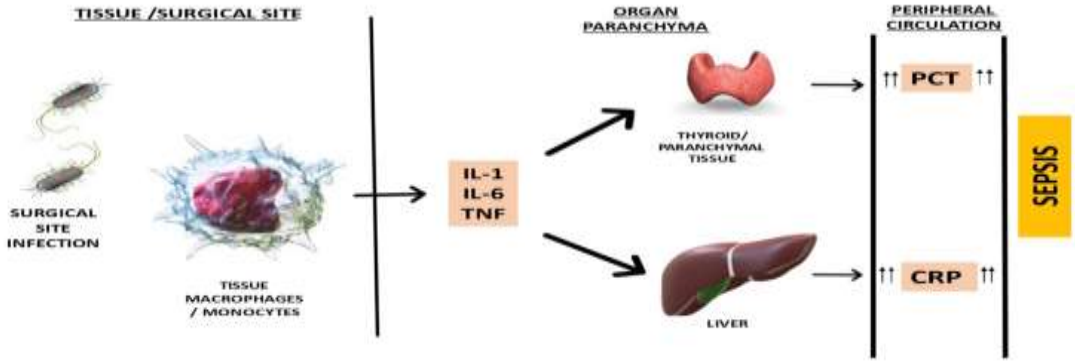


**Figure 1:** Mechanism of CRP and PCT production **(18)**

Ferritin is an evolutionarily conserved protein and it has been suggested to be involved in response to infection **(19).**

High levels of serum ferritin at the time of sepsis's diagnosis were associated with an unfavorable outcome. This has been reported particularly in pediatric patients from 28 days to 18 years old. Although hyper-ferritinemia has been increasingly acknowledged as a marker of critical illness, neither the reasons for increased ferritinemia nor the consequences of this for disease outcome are known **(20).**

Lactate dehydrogenase enzyme (LDH) nearly found in all living cells as a result of anaerobic glycolysis, this enzyme produce lactate from pyruvate. High levels of LDH indicate tissue damage and that occurs in many conditions as acute liver cell failure, hemolytic anemia, malignancy, infarction, such as bowel infarction, myocardial infarction and lung infarction. Also it significantly increase in infections such as infectious mononucleosis, meningitis, encephalitis, HIV **(21)**

The erythrocyte sedimentation rate (ESR or sed rate) is the rate at which red blood cells in anticoagulated whole blood descend in a standardized tube over a period of one hour. It is a common hematology test, and is a non-specific measure of inflammation. In inflammatory conditions, fibrinogen, other clotting proteins, and alpha globulin are positively charged, thus increasing the ESR. ESR begins to rise at 24 to 48 hours after the onset of acute self-limited inflammation, decreases slowly as inflammation resolves, and can take weeks to months to return to normal levels **(22).**

Culture samples in all patients are recommended in accordance with clinical suspicion of the infection site. When organ failure is present, blood cultures should be taken, ideally before antibiotic administration. Ascites fluid cultures must be collected in blood culture bottles. The recent surviving sepsis guidelines recommend obtaining blood cultures within 1 hour of presentation to the hospital. Blood cultures are essential for pathogen identification and selection of appropriate antibiotics. Standard microbiological blood cultures (STD) can have variable yields, long turnaround times, and low sensitivity, which contribute to inappropriate antibiotic therapy **(23).**

A blood culture is thus still considered as the "gold standard" test in the detection of bloodstream pathogens despite its low clinical positivity. Ascitic fluid culture usually play an important role in the diagnosis of spontaneous bacterial peritonitis (SBP) in patients with decompensated liver cirrhosis. positive ascitic fluid culture confirm the diagnosis of SBP while negative ascitic fluid culture can not exclude SBP**.**

Urinary tract infection (UTI) is a common bacterial infection and is the second most frequent infection after SBP and it accounts for 12–29% of infectious complications in decompensated cirrhosis. Most of the isolated organisms (70–80%) using urine culture are gram-negative bacteria such as *E. coli* and *K. pneumonia*. UTI can be asymptomatic and asymptomatic bacteriuria can also be encountered at high frequency. This could possibly be related to the frequently found residual urinary volume and vesical dysfunction in those with cirrhosis**(24).**

In the hospitalized patients with cirrhosis, pneumonia carries the highest risk of mortality than other infections Development of pneumonia is associated with a more severe form of community-acquired pneumonia (CAP), and may be associated with bacteremia, multi-lobar involvement, impaired consciousness, renal failure, and septic shock The risk of hospital-acquired pneumonia (HAP) is increased in the setting of hepatic encephalopathy and tracheal intubations(**25**).

The most common pathogen for CAP pneumonia in those with cirrhosis is still *Streptococcus pneumoniae*, and similar to patients without cirrhosis. The predominant pathogens for HAP pneumonia are gram-negative bacilli and staphylococci, and which is also associated with high mortality.Diagnosis confirmed by sputum culture. Several immunologic biomarkers have been assessed in order to develop the best indicator of infections. Soluble CD14 subtype (sCD14-ST), known as presepsin, is a biomarker which has been demonstrated as a new, emerging, early indicator for the detection of different infections. Presepsin elevated in response to bacterial infections and decreased after healing or efficient treatment **(25).**

**Chemistry of presepsin.**

Presepsin: Soluble Subtype of CD14 (SCD14-ST) : Research in this direction has paved the way for identification of CD14, it is a glycopeptides expressed on macrophages and monocytes, which serves as a receptor for lipopolysaccharide-lipopolysaccharide binding protein (LPS-LPB) of microorganisms as a potential biomarker. CD14 is a 55-kDa glycosyl phosphatidyl inositol-anchored protein lacking a cytoplasmic domain. CD14 is expressed on most innate immune response cells and exists either in an anchored membrane form (mCD14) or in a circulating soluble form (sCD14). The latter is a 43-53 kD glycoprotein that derives from either protease-mediated membrane CD14 shedding or liver synthesis as a type II acute-phase reactant. During inflammation, plasma protease activity generates CD14 fragments **(26).**

**Mechanism of presepsin secretion and response in bacterial infection.**

The SCD14-ST, a soluble CD14 subtype, a 13 kDa truncated N terminal fragment of 64 amino acid residues is called as presepsin. This has been found to activate proinflamatory cascade on encountering microorganisms. It has been noted that plasma protein activity results in the production of SCD14 fragments. Among the fragments the SCD14 –ST fragment is recognised as a sepsis marker **(27).**

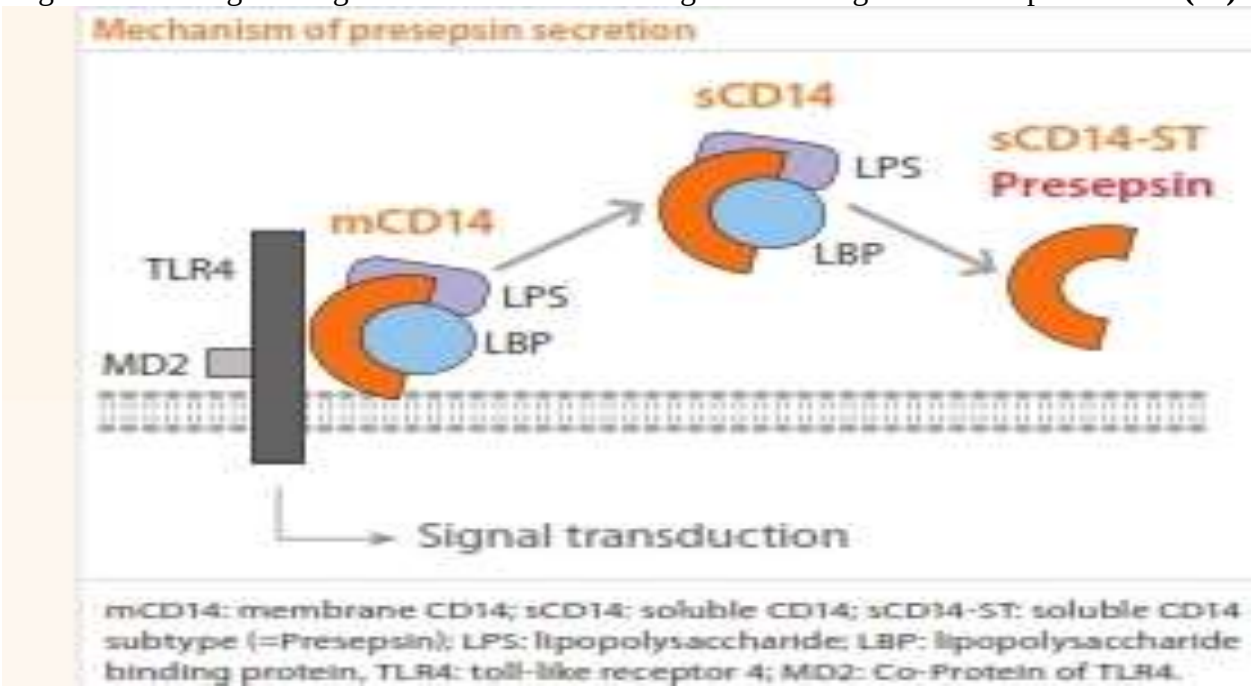


**Figure 2 :** mechanism of presepsin secretion **(28)**

Severe Immunological response to microbial infection (commonly by bacteria and occasionally by fungi, viruses and parasites) presenting as a systemic illness which may lead to multiple organ dysfunctions is termed as sepsis. Emergency laboratory and clinical management of patients suffering from bacterial infection is required to reduce the resultant morbidity and mortality. Neonates, pregnant women, patients undergoing transplantations, burns patients and geriatric age group are more susceptible to severe bacterial infection. Many laboratory biomarkers either singly or in combination have been routinely used for the laboratory diagnosis of bacterial infection. Presepsin has a potential role not only as a diagnostic marker but is also efficient in knowing the prognosis and survival chances of patients with bacterial infection **(29)**.

**Nature and role of presepsin in patients with liver cirrhosis**

Presepsin is one of the biological markers efficient in the early diagnosis of infections in liver cirrhosis. Presepsin is a biological marker produced by the cleavage of soluble CD14. CD14 is a co-receptor for bacterial ligands, including the lipopolysaccharide (LPS) complex of gram-negative bacteria (GNB), making presepsin a biomarker of innate immune activation. Presepsin can recognize gram-negative and gram-positive bacteria and represent the activation of monocytes in contact with bacterial pathogens; however , it is not synthesized by the liver. **(30).**

In the general population, presepsin was an acceptable marker for diagnosing sepsis and systemic infections . A few studies have evaluated the diagnostic value of presepsin in infection diagnosis in patients with liver cirrhosis. Some concluded that presepsin is an acceptable biological marker for the diagnosis of infections in liver cirrhosis and that increased presepsin level could be associated with a poor prognosis regarding the Model of End-Stage Liver Disease (MELD) score **(30**).

Now there is multiple studies act on the important role of presepsis in patients with liver cirrhosis and bacterial infection. Bacterial infections complicate the course of liver cirrhosis and determine an increased rate of decompensation, acute-on-chronic liver failure, and mortality. The early diagnosis and prompt treatment of infections prevent liver cirrhosis from further decompensation and sepsis development and may decrease mortality rates **(25).**

An increased intestinal permeability characterizes liver cirrhosis due to portal hypertension. This determines a high level of lipopolysaccharides (LPS) in cirrhotic patients' blood without evidence of bacterial infections. Presepsin is the soluble part of CD14, a co-receptor for lipopolysaccharides ligands having higher levels in the cirrhotic population without infections than in the general population. For this reason, different presepsin values should be identified in patients with liver cirrhosis **(31)**

The serum presepsin level >980 pg/ml had the most appropriate specificity and sensitivity to identify bacterial infections in patients admitted with liver cirrhosis and overt hepatic encephalopathy. Moreover, the presepsin levels were directly correlated with liver cirrhosis severity assessed by the MELD score and the Child-Pugh class**.** Prospective studies, including patients with compensated and decompensated liver cirrhosis, demonstrated that high level of serum presepsin was associated with an increased liver-related mortality. They also documented that cirrhotic patients have higher levels of presepsin even at the compensated stage and without infection complications than presepsin levels previously reported in the general population. This fact could reflect spontaneous bacterial translocation associated with liver cirrhosis **(32).**

presepsin had better diagnostic accuracy in patients with liver cirrhosis and infections-associated organ failure. The association between CRP and presepsin increases the diagnostic accuracy of these biomarkers in terms of infection diagnosis in patients with liver cirrhosis. A high presepsin level in the first 24 h after admission was a predictor of mortality **(33)**

**correlation between presepsin and other inflammatory markers in bacterial infection and sepsis.**

CRP is one of the acute phase inflammation proteins synthesized by the liver, its main advantage is its great sensitivity, but unfortunately it is weakly specific for bacterial infections. Moreover, the evolution of sepsis is poorly correlated with changes in serum CRP level. Recent biomarkers and inflammatory variables could contribute to early prompt identification & differentiation of septic patients from those with SIRS. Among different recent biomarkers that appear to be promising in diagnosis of early stages of septic process were procalcitonin, presepsin, IL-6 and CD64 (**34).**

Procalcitonin level increases 4 hours after infection, reaches a plateau slowly at 8-24 hours, and reaches the peak one day after infection. While, presepsin being increased earlier and faster in patients with sepsis (2 hours after infection, peaked at 3 hours of infection)**.**presepsin assay is available and could be used on a point-of-care testing basis, thus allowing the emergency physician to get presepsin values in a short time from whole blood samples. Presepsin as a biomarker is not only suitable for the early diagnosis of sepsis, but also for the assessment of its severity and prognosis.The presepsin level was significantly higher in septic shock than in sepsis patients (**35)**

**References**

1. **Piano S, Brocca A, Mareso S, et al., (2017).** Infections complicating cirrhosisLiver Int 2018;38:126–33.
2. **Fernández J, Acevedo J, Castro M, et al.( 2012):**Prevalence and risk factors of infections by multiresistant bacteria in cirrho-sis: a prospective study. Hepatology;55(5):1551–61.
3. **Ferrer R, Martin-Loeches I, Phillips G, et al. (2014):** Empiric antibiotic treatment reduces mortality in severe sepsis and septicshock from the first hour: results from a guideline-based performance improve-ment program. Crit Care Med;42(8):1749–55.
4. **Bonnel AR, Bunchorntavakul C and Reddy KR (2011).** Immune dysfunction and infectionsin patients with cirrhosis. Clin Gastroenterol Hepatol;9(9):727–38.
5. **Bajaj JS, Heuman DM, Hylemon PB, et al. (2014):**Altered profile of human gut microbiome is associated with cirrhosis and itscomplications. J Hepatol;60(5):940–7.

6. **Nahon P, Lescat M, Layese R, et al (2017):**Bacterialinfection in compensated viral cirrhosis impairs 5-year survival (ANRS CO12CirVir prospective cohort). Gut;66(2):330–41.
7. **Moreau R, Jalan R, Gines P, et al.( 2013):** Acute-on-chronicliver failure is a distinct syndrome that develops in patients with acute decom-pensation of cirrhosis. Gastroenterology;144(7):1426–37.
8. **Gustot T, Fernandez J, Garcia E, et al. (2015):** Clin-ical Course of acute-on-chronic liver failure syndrome and effects on prognosis.Hepatology;62(1):243–52.
9. **Solé C and Solà E. (2018):** Update on acute-on-chronic liver failure. Gastroenterol Hepatol;41(1):43–53.
10. **Bunchorntavakul C, Chamroonkul N and Chavalitdhamrong D (2016):** Bacterial infec-tions in cirrhosis: a critical review and practical guidance. World J Hepatol;8(6):307–21.
11. **Singer M, Deutschman CS, Seymour C, et al.( 2016):** The third international consensus definitions for sepsis and septic shock(sepsis-3). JAMA;315(8):801–10.
12. **Nadim MK, Durand F, Kellum JA, et al. (2016):**Management of the critically ill patient with cirrhosis: a multidisciplinary per-spective. J Hepatol;64(3):717–35.
13. **Dupuy F, Philippart Y, Pean, et al., (2013):** "Role of biomarkers in the management of antibiotic therapy: an expert panel review. I: currently available biomarkers for clinical use in acute infections," Annals of Intensive Care, vol. 3, no. 22, article 1.
14. **Dellinger RP, Levy MM, Carlet JM, et al.( 2008):** Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med; 34: 17-60.global death.
15. **Cesar Henriquez-Camacho and Juan Losa,( 2014):** "Biomarkers for Sepsis," BioMed Research International, vol. 2014, Article ID 547818, 6 pages.
16. **Campos A (2017):.** Predictores de mortalidad en pacientes con cirrosis hepática queingresan al servicio de urgencias, vol. 18.
17. **Page MJ, McKenzie JE, Bossuyt PM, et al.( 2021):** The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* ;372:0.
18. **Mahmoud EI, Algendy MA, Al-Ansary AM, et al.,( 2022):** Evaluation of procalcitonin (PCT) as a marker of infection in early post living donated liver transplant period. *Transpl Immunol.* ;71:101549.
19. **Wang D., Yu S., Zhang Y., et al(2019):** Caspse-11-GSDMD pathway is required for serum ferritin secretion in sepsis. *Clin. Immunol.* ;205:148–152.
20. **Carcillo J.A., Halstead E.S., Hall M.W., et al.( 2017):** Three Hypothetical Inflammation Pathobiology Phenotypes and Pediatric Sepsis-Induced Multiple Organ Failure Outcome. *Pediatr. Crit. Care Med.* ;18:513–523.
21. **Khanam A and Kottilil S (2021).** Acute-on-Chronic Liver Failure: Pathophysiological Mechanisms and Management. Front Med (Lausanne) ;8:752875.
22. **Saha, Amit K; Schmidt, Brendan R; Wilhelmy, Julie; et al., (2019).** "Erythrocyte Deformability As a Potential Biomarker for Chronic Fatigue Syndrome". Blood. 132 (Suppl 1): 4874.
23. **Florio W, Morici P, Ghelardi E, et al.( 2018):** Recent advances in the microbiological diagnosis of bloodstream infections. *Crit Rev Microbiol.* ;44(3):351–370.
24. **Cruz Rde C, Tanajura D, Almeida D, et al.( 2006):** Urinary tract infection in non-hospitalized patients with cirrhosis and no symptoms of urinary tract infection: a case series study. Braz J Infect Dis.;10(6):380–3.
25. **Hung TH, Tseng CW, Hsieh YH, et al., (2013).** High mortality of pneumonia in cirrhotic patients with ascites. BMC Gastroenterol.;13:25.
26. **Qi Zou, Wei Wen and Xin-chao Zhang.( 2014):** Presepsin as a novel sepsis biomarker. World J Emerg Med; 5 (1): 16-19
27. **Puxeddu E, Mussap M, Burrai P, et al., (2012):** Soluble CD14 subtype (sCD14-ST) presepsin in critically ill preterm newborns: preliminary reference ranges. J Matern Fetal Neonatal Med, 25(Suppl 5):51-53.

28. **Mussap M, Noto A, Fravega M, et al., (2011):** Soluble CD14 subtype presepsin (sCD14-ST) and lipopolysaccharide binding protein (LBP) in neonatal sepsis: new clinical and analytical perspectives for two old biomarkers. J Matern Fetal Neonatal Med, 24(Suppl 2): 12-14.
29. **A. Piccioni, M. C. Santoro, and T. de Cunzo (2021.):** "Presepsin as early marker of sepsis in emergency department: a narrative review," Medicina (Kaunas), vol. 57, no. 8.
30. **Fischer, P.; Grigoras, C.; Bugariu, A.; et al (2019):** Are presepsin and resistin better markers for bacterial infection in patients with decompensated liver cirrhosis? Dig.Liver Dis., 51, 1685–1691.
31. **G. Morino, G. Takahashi, S. Kan, et al., (2021 ):"**Antibody-mediated soluble CD14 stabilization prevents agitation-induced increases in presepsin levels in blood component specimens," Biotechniques, vol. 70, no. 3, pp. 160–166.
32. **Memar MY and Baghi HB. Presepsin (2019):** a promising biomarker for the detection of bacterial infections. Biomed Pharmacother.;111:649–656.
33. **Pierrakos C, Velissaris D, Bisdorff M, et al., (2020).** Biomarkers of sepsis: Time for a reappraisal. Critical Care.;24(1):287.
34. **Opal SM and Wittebole X (2020):.** Biomarkers of infection and sepsis. Critical Care Clinics.;36(1):11-22.
35. **Azim A.( 2021):** Presepsin: A promising biomarker for sepsis. Indian Journal of Critical Care Medicine.;25(2):117-118.