Research Article

The Diagnostic and Prognostic Values of C-Reactive Protein and Procalcitonin during Bacterial Infections in Decompensated Cirrhosis

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Received 12 September 2018; Accepted 25 November 2018; Published 30 December 2018

Academic Editor: Hauke S. Heinzow

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Background. Bacterial infection (BI) represents the main cause of decompensation and death in cirrhotic patients. Procalcitonin (PCT) and C-reactive protein (CRP) are two widely used biomarkers that may be helpful for early detection of BI especially in the presence of inflammation. Their accuracy for the diagnosis of BI in patients with chronic liver disease has been a subject of debate. In this study, we aimed to learn whether PCT and CRP would be helpful as early markers of BI in patients with cirrhosis and to evaluate their prognostic value in terms of mortality. Subjects and Methods. We retrospectively included 92 adult patients with decompensated cirrhosis. PCT and CRP plasma levels were obtained within the first 24 hours of admission. Their diagnostic and prognostic values were compared using the appropriate statistical analysis. Results. Ninety-two patients were included. BI was diagnosed in 60 patients (65%). Mean white blood cell (WBC) count ($p=0.005$) and PCT and CRP serum levels ($p<0.001$) were higher in the BI group than in the non-BI (NBI) group. The diagnostic accuracy of CRP and PCT for the diagnosis of BI was better than that of WBC. CRP was the most sensitive marker (70%) while PCT was the more specific (96.6%). No one of those biomarkers was predictive of 3-month mortality in patients with BI. Conclusion. Regarding BI in patients with decompensated cirrhosis, CRP maintains efficiency slightly higher than that of the PCT without being discriminative. However, no prognostic value has been established for these markers.

1. Introduction

Cirrhosis is the advanced stage of a liver condition due to a chronic inflammatory and fibrosing prolonged evolving process. Cirrhotic patients are more susceptible to bacterial infection (BI) because of humeral and cell-mediated immunodeficiency, splanchnic ganglia colonization, bacterial translocation phenomena, and ventilatory disorders related to encephalopathy and ascites [1, 2]. BI is diagnosed in 30 to 50% of admitted cirrhotic versus 5 to 7% in noncirrhotic patients [3]. The diagnosis of BI in patients with cirrhosis is made difficult by some clinical and biological abnormalities commonly observed in those patients such as liver dysfunction, inflammation, chronic hypersplenism, abdominal distension, and neurological disorders in addition to the frequent use of beta-blockers. Despite the great improvement of BI management in cirrhotics, the mortality is still high. An early diagnosis and treatment of this condition, using biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP), can contribute to reduce this mortality. This work is aimed at evaluating and comparing diagnosis and prognosis performance of CRP and PCT during BI in patients admitted for decompensated cirrhosis.
2. Methods

This 14-month observational retrospective study was conducted in the Hepato-gastroenterology Department of the Charles Nicolle University Hospital of Tunis from 01 September 2015 to 30 October 2016. We included patients admitted for decompensate cirrhosis. Cirrhosis was diagnosed according to histological and/or clinical, biological, and ultrasound findings suggesting portal hypertension and hepatocellular insufficiency. Decompensated cirrhosis was defined by the presence of ascites, jaundice, variceal hemorrhage, or hepatic encephalopathy. Patients not included in the study were those who were receiving intravenous antibiotics and those who were suffering from a systemic disease or a cancer including hepatocellular carcinoma. CRP and PCT are part of the routine biological sample performed at admission; we did not have to get patients’ consent. The following severity and prognostic scores were used in our study: APACHE II score [4], Child-Turcotte-Pugh (CP) criteria [5], Model for End-Stage Liver Disease score (MELD) [6], CLIF-sequential organ failure assessment score (CLIF-SOFA), and Acute-on-chronic liver failure (ACLF) [7]. Blood samples for biological marker analysis as well as microbiological samples were obtained on admission. Serum CRP levels were measured using direct immunoturbidimetry on the Architect C 8000 Chemistry System (Abbott Diagnostics, USA). Enzyme-linked fluorescent immunoassay (ELFA) on mini-VIDAS (bioMérieux, France) was used for PCT tests. The patients were divided into a BI group and a non-BI (NBI) group. Dichotomous variables were expressed as percentages and continuous variables as mean ± standard deviation. Statistical comparisons were performed using, respectively, Student’s t-test and χ². Analysis of receiver operating characteristic (ROC) curves was used to determine diagnostic accuracy, sensitivity, and specificity and the Youden index to determine suggested cutoff. All analyses were conducted by SPSS 20.0 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered significant. Three-month mortality risk factors were determined by the application of multivariate logistic regression analysis. The authors state the absence of conflict of interest.

3. Results

Ninety-two patients were included with a sex ratio of 0.96 and a mean age of 63 ± 13 years (19–91). Mean follow-up time was 4.5 ± 4 years (3 months–26 years). Fifty-seven patients (61%) were CP class B and 32% class C. Hepatitis C was the most common etiology of cirrhosis (42%). They were mainly admitted for edema-ascitic decompensation and the main source of infection was pulmonary tract infection (62%) and spontaneous bacterial peritonitis (23%). Baseline characteristics, cirrhosis etiologies, causes for admission, infection sources, and severity scores are summarized in Table 1. Distributions of sex, age, and comorbidities were similar between the two groups (Table 2). BI group had significantly higher encephalopathy rate (p = 0.005), higher body temperature (p = 0.008), higher heart rate (p = 0.025), higher total serum bilirubin level (p = 0.021), higher international normalized ratio (p = 0.005), lower prothrombin time (p = 0.005), and higher MELD score (p < 0.01). Mean serum levels of CRP (p < 0.001), PCT (p < 0.001), and white blood cells (WBC) (p = 0.002) were significantly higher in the BI group than in the NBI group (Table 2). The results of the logistic regression analysis showed that only MELD score > 15,
encephalopathy, and PCT ≥ 0.5 were significantly correlated to BI (Table 3). We evaluated the effectiveness of WBC, PCT, and CRP measurements in predicting infection in decompensated cirrhosis using the assessment of ROC curves. The area under the curve (AUC), sensitivity, specificity, positive and negative predictive values, and suggested cutoff values for each marker are summarized in Table 4. ROC analysis of CRP serum level showed the slightly higher AUC (0.745). PCT was more specific (96.6% vs. 75%) whereas CRP was more sensitive (70 vs. 45%).

3.1 Three-Month Mortality. Three-month mortality rate was 27%. Patients in the BI group had higher 3-month mortality rate (34% vs. 3%, \( p = 0.008 \)) than those in the NBI group. However, multivariate risk factor analysis indicated that BI encephalopathy, and PCT ≥ 0.5 were significantly correlated to BI (Table 3). We evaluated the effectiveness of WBC, PCT, and CRP measurements in predicting infection in decompensated cirrhosis using the assessment of ROC curves. The area under the curve (AUC), sensitivity, specificity, positive and negative predictive values, and suggested cutoff values for each marker are summarized in Table 4. ROC analysis of CRP serum level showed the slightly higher AUC (0.745). PCT was more specific (96.6% vs. 75%) whereas CRP was more sensitive (70 vs. 45%).

### Table 2: Clinical and laboratory variables associated with infection on admission.

|                          | Bacterial infection group | Nonbacterial infection group |
|--------------------------|---------------------------|------------------------------|
|                          | \( n = 60 \)              | \( n = 32 \)                 | \( p \) value |
| Age (yr)                 | 60 ± 12                   | 64 ± 15                      | 0.509        |
| Male/female              | 30/30                     | 15/17                        | 0.775        |
| Medical history          |                           |                              |              |
| Diabetes mellitus        | 38%                       | 44%                          | 0.614        |
| Hypertension             | 28%                       | 41%                          | 0.231        |
| Tabagism                 | 28%                       | 19%                          | 0.350        |
| Alcoholism               | 15%                       | 13%                          | 0.786        |
| Child-Pugh (class)       |                           |                              |              |
| A                        | 1%                        | 6%                           | 0.123        |
| B                        | 28%                       | 44%                          | 0.256        |
| C                        | 70%                       | 50%                          | 0.456        |
| MELD score               | 20 ± 7                    | 15 ± 5                       | <.001        |
| APACHE II score          | 13 ± 8                    | 15 ± 6                       | 0.855        |
| CLIF-SOFA score          | 15 ± 6                    | 16 ± 6                       | 0.757        |
| ACLF                     |                           |                              |              |
| Grade 1                  | 32%                       | 38%                          | 0.573        |
| Grade 2                  | 33%                       | 28%                          | 0.609        |
| Grade 3                  | 34%                       | 34%                          | 0.952        |
| Duration of stay (d)     | 12 ± 8                    | 12 ± 6                       | 0.766        |
| 3-month mortality        | 34%                       | 3%                           | 0.008        |
| Vital signs              |                           |                              |              |
| Body temperature (°C)    | 38 ± 0.7                  | 37 ± 0.5                     | 0.008        |
| Heart rate (beats/min)   | 97 ± 15                   | 85 ± 18                      | 0.025        |
| Respiratory rate (breaths/min) | 21 ± 4               | 20 ± 5                       | 0.189        |
| Systolic blood pressure (mm Hg) | 108 ± 21              | 111 ± 20                     | 0.393        |
| Diastolic blood pressure (mm Hg) | 62 ± 13                | 66 ± 10                      | 0.193        |
| Encephalopathy           | 72%                       | 37%                          | 0.005        |
| Ascite                   | 85%                       | 84%                          | 0.647        |
| WBCs (cells/μL)          | 8750 ± 5005               | 5672 ± 2734                  | 0.002        |
| Neutrophil (cells/μL)    | 6430 ± 4456               | 3668 ± 2151                  | 0.001        |
| Platelet (cells/μL)      | 105056 ± 80901            | 91000 ± 42063                | 0.361        |
| Serum BUN (mmol/L)       | 8.8 ± 5.2                 | 7.4 ± 5.9                    | 0.282        |
| Serum creatinine (μmol/L) | 116 ± 101               | 90 ± 51                      | 0.167        |
| AST (IU/L)               | 78 ± 106                  | 56 ± 38                      | 0.350        |
| ALT (IU/L)               | 43 ± 55                   | 40 ± 55                      | 0.803        |
| Total bilirubin (mg/L)   | 102 ± 137                 | 43 ± 45                      | 0.021        |
| PT (%)                   | 48 ± 18                   | 58 ± 16                      | 0.007        |
| INR                      | 1.91 ± 0.64               | 1.55 ± 0.36                  | 0.005        |
| Albumin (g/L)            | 25 ± 5                    | 26 ± 5                       | 0.579        |

### Table 3: Univariate and multivariate analysis of factors associated with bacterial infection.

|                          | Bacterial infection group | Nonbacterial infection group |
|--------------------------|---------------------------|------------------------------|
|                          | \( n = 60 \)              | \( n = 32 \)                 | \( p \) value |
| Serum sodium             | 132 ± 5                   | 134 ± 4                      | 0.177        |
| CRP (mg/L)               | 46 ± 44.5                 | 19.61 ± 24.95                | <.001        |
| PCT (ng/mL)              | 1.84 ± 4.07               | 0.20 ± 0.48                  | <.001        |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; PCT: procalcitonin; INR: international normalized ratio; WBC: white blood cell; PT: prothrombin time; MELD: Model for End-Stage Liver Disease; APACHE II: Acute Physiology and Chronic Health Disease Classification System II; BUR: blood urea nitrogen; CLIF-SOFA: chronic liver failure-sequential organ failure assessment; ACLF: Acute-on-chronic liver failure.
was not an independent 3-month mortality risk factor (Table 5). PCT serum level was significantly associated with 3-month mortality ($p < 0.001$). ROC analysis of PCT serum level showed the AUC of 0.735 (CI 95%: 0.576-0.895). Suggested cutoff was 0.5 ng/mL; sensitivity, specificity, positive predictive value, and negative predictive value were, respectively, 66.7%, 77.6%, 59%, and 82% (Figure 1). In the BI group, deceased patients were more often Child-Pugh class C and had lower temperature on admission, higher Child-Pugh score, higher leukocyte, neutrophil, and platelet counts, lower prothrombin time, and higher serum CRP, PCT, and creatinine levels (Table 6). In multivariate logistic regression mode, CP class C, lower temperature on admission, higher CP score, and higher platelet count were retained as predictors' parameters for three-month mortality (Table 7).

### 4. Discussion

In our study, the high rate of BI among patients with decompensated cirrhosis can be explained by the advanced liver failure observed in these patients. Our results showed that PCT and CRP serum levels were significantly higher in the BI group, and thus, these markers were useful in the diagnosis of BI in decompensated cirrhosis. Although they are mainly produced by the liver, hepatic insufficiency does not affect their diagnostic accuracy [8]. That is explained by a maintained hepatic production [9–11] and/or an extrahepatic production [12–15] of those two biomarkers during cirrhosis. On the other side, WBC count is deeply influenced by hypersplenism even if their production may be maintained. That can explain the less BI diagnosis accuracy of WBC observed in our study. Several studies have shown the reliability of PCT and CRP for the diagnosis of infection during cirrhosis with important AUC. In a recent meta-analysis including 1144 patients with liver cirrhosis, AUC for PCT and CRP was, respectively, 0.92 (95% CI: 0.89-0.94) and 0.87 (95% CI: 0.84-0.90) [16]. This is probably due to differences in demographic characteristics and cirrhosis severity observed in our population. The cutoffs used are also different from ours. In the present study, diagnostic accuracy of CRP and PCT was comparable but it is still relatively low. That is why we think that PCT and CRP cannot be used alone to either confirm or exclude BI diagnosis. We found that,

### Table 4: The results of ROC curve analysis for bacterial infection diagnosis.

|                | AUC (95% CI) | p    | Suggested cutoff | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|----------------|-------------|------|------------------|----------------|-----------------|--------|--------|
| WBC            | 0.694 (IC 95%: 0.585-0.803) | **<.002** | 6635             | 65             | 65.5            | 78     | 50     |
| CRP            | 0.745 (IC 95%: 0.635-0.855) | **<.001** | 20               | 70             | 75              | 84     | 57     |
| PCT            | 0.741 (IC 95%: 0.639-0.843) | **<.001** | 0.5             | 45             | 96.6           | 97.5   | 59     |

WBC: white blood cells. CRP: C-reactive protein; PCT: procalcitonin; PPV: positive predictive value; NPV: negative predictive value.

|                | Univariate analysis | Multivariate analysis |
|----------------|---------------------|-----------------------|
| Child-Pugh (class) | 0.006               | 0.007                 |
| Encephalopathy   | 0.013               | 0.005                 |
| Infection        | 0.001               | 0.485                 |
| Heart rate       | 0.005               | 0.092                 |
| Temperature      | 0.055               | 0.547                 |
| WBC              | 0.001               | 0.331                 |
| Neutrophil count | <0.001              | 0.155                 |
| Platelets        | <0.001              | 0.490                 |
| PT %             | 0.029               | 0.321                 |
| INR              | 0.036               | 0.962                 |
| CRP              | 0.001               | 0.053                 |
| PCT              | 0.018               | <0.001                |
| Serum creatinine | 0.014               | <0.001                |
| AST              | 0.095               | <0.001                |
| Child-Pugh (score) | 0.009              | 0.006                 |
| MELD             | <0.001              | 0.091                 |

WBC: white blood cells; INR: international normalized ratio; CRP: C-reactive protein; PT: prothrombin time; PCT: procalcitonin; AST: aspartate aminotransferase; MELD: Model for End-Stage Liver Disease.
for the diagnosis of BI, CRP was more sensitive (70% vs. 45%) while PCT was more specific (96.9% vs. 75%). Similar results were reported by Lin et al.: CRP sensitivity was higher (87% vs. 79%) while PCT was more specific (89% vs. 85%) [16]. In addition, the CRP had a more discriminative value in the Papp study [17]. In order to enhance the diagnostic performance of CRP and PCT, the use of an algorithm that integrates clinical data with PCT or CRP can be helpful. In addition, it may be interesting to study the usefulness of an algorithm combing CRP and PCT.

4.1. Mortality. We have recomfirmed the gravity of BI in cirrhotics as already attested [18]. Three-month mortality was twelve times higher in infected patients compared to noninfected patients (34% vs. 3%, \( p = 0.08 \)). However, multivariate risk factor analysis indicated that BI was not an independent 3-month mortality risk factor. Lazzarotto et al. did not find any association between infection at admission and death before the seventh day of hospitalization [19]. In Khot et al. study, sepsis was not objectively an independent predictor of mortality [20]. In our study, only serum PCT level was significantly related to 3-month mortality. The relationship between PCT and CRP levels and mortality reported in previous studies was contradictory [19, 21–23]. However, in the BI group, PCT and CRP did not show any prognostic value. That can be explained by the high severity of cirrhosis in the NBI group. In fact, the CP score influenced death.

Our study has limitations. It is a monocentric study with a relatively small number of patients. In addition, PCT measurement was performed on admission regardless of the presence or the absence of infection.

5. Conclusion

Regarding BI in patients with decompensated cirrhosis, CRP maintains efficiency slightly higher than that of the PCT without being discriminative. However, no prognostic value has been established for these markers. In order to improve

### Table 6: Clinical and laboratory variables associated with 3-month mortality in the BI group.

| Variable                        | Surviving          | Deceased          | \( p \) value |
|---------------------------------|--------------------|-------------------|---------------|
| Sex                             | 16/21              | 9/14              | 0.184         |
| Child-Pugh (class)              |                    |                   |               |
| A                               | 0%                 | 3%                | 0.427         |
| B                               | 4%                 | 43%               | 0.001         |
| C                               | 96%                | 54%               | 0.001         |
| Child-Pugh score                | 10 ± 2             | 11 ± 1            | 0.004         |
| Respiratory rate                | 21 ± 3             | 21 ± 4            | 0.720         |
| Temperature                     | 38 ± 0.8           | 37 ± 0.6          | 0.004         |
| WBC (cells/IL)                  | 7632 ± 3651        | 10549 ± 6314      | 0.027         |
| Neutrophil count (cells/IL)     | 5369 ± 3049        | 8137 ± 5771       | 0.018         |
| Platelets (cells/IL)            | 83659 ± 66387      | 139478 ± 91280    | 0.008         |
| PT (%)                          | 51 ± 19            | 41 ± 13           | 0.031         |
| CRP (mg/L)                      | 37 ± 29            | 61 ± 60           | 0.041         |
| PCT (ng/mL)                     | 1.21 ± 2 ± 88      | 2.84 ± 5.39       | 0.131         |
| Creatinine (μmol/L)             | 96 ± 63            | 150 ± 139         | 0.045         |
| AST (IU/L)                      | 63 ± 44            | 91 ± 162          | 0.396         |
| MELD                            | 18 ± 7             | 23 ± 6            | 0.005         |

PT: prothrombin time; WBC: white blood cells; CRP: C-reactive protein; PCT: procalcitonin; AST: aspartate aminotransferase; MELD: Model for End-Stage Liver Disease.

### Table 7: Univariate and multivariate analysis of factors associated with 3-month mortality in the BI group.

| Variable                        | Univariate analysis | Multivariate analysis |
|---------------------------------|---------------------|-----------------------|
| Sex                             | 0.184               | 0.900                 |
| Child-Pugh (class)              |                     |                       |
| B                               | <0.001              | 0.887                 |
| C                               | <0.001              | <0.001                |
| Child-Pugh (score)              | 0.004               | 0.627                 |
| Respiratory rate                | 0.720               | 0.111                 |
| Temperature                     | 0.004               | 0.01                  |
| WBC                             | 0.027               | 0.131                 |
| Neutrophil count                | 0.018               | 0.075                 |
| Platelets                       | 0.008               | 0.018                 |
| Prothrombin time                | 0.031               | 0.874                 |
| CRP                             | 0.041               | 0.225                 |
| PCT                             | 0.131               | 0.318                 |
| Serum creatinine                | 0.045               | 0.197                 |
| AST                             | 0.396               | 0.300                 |
| MELD score                      | 0.005               | 0.411                 |

WBC: white blood cells; CRP: C-reactive protein; PCT: procalcitonin; AST: aspartate aminotransferase; MELD: Model for End-Stage Liver Disease.
the diagnosis and reliability of prognosis, it may be interesting to combine them with each other or with other biological and/or clinical parameters.

**Abbreviations**

ACLF: Acute-on-chronic liver failure  
ALL: Alanine aminotransferase  
APACHE II: Acute Physiology and Chronic Health Disease Classification System II  
AST: Aspartate aminotransferase  
BI: Bacterial infection (group)  
CP: Child-Turcotte-Pugh  
CLIF-SOFA: Chronic liver failure-sequential organ failure assessment  
CRP: C-reactive protein  
INR: International normalized ratio  
MELD: Model for End-Stage Liver Disease  
NBI: Nonbacterial infection (group)  
NPV: Negative predictive value  
PCT: Procalcitonin  
PPV: Positive predictive value  
PT: Prothrombin time  
WBC: White blood cells.

**Data Availability**

The data used to support the findings of this study are available from the corresponding author upon request.

**Disclosure**

Our study is within the scientific research framework of the Faculty of Medicine of Tunis.

**Conflicts of Interest**

We have no conflict of interest.

**References**

[1] T. Gustot, F. Durand, D. Lebrec, J. L. Vincent, and R. Moreau, “Severe sepsis in cirrhosis,” Hepatology, vol. 50, no. 6, pp. 2022–2033, 2009.

[2] S. Ben-Eliyahu, G. G. Page, R. Yirmiya, and A. N. Taylor, “Acute alcohol intoxication suppresses natural killer cell activity and promotes tumor metastasis,” Nature Medicine, vol. 2, no. 4, pp. 457–460, 1996.

[3] M. Navasa, J. Fernandez, and J. Rodes, "Bacterial infections in liver cirrhosis," Italian Journal of Gastroenterology and Hepatology, vol. 31, no. 7, pp. 616–625, 1999.

[4] W. A. Knaus, E. A. Draper, D. P. Wagner, and J. E. Zimmerman, “APACHE II: a severity of disease classification system,” Critical Care Medicine, vol. 13, no. 10, pp. 818–829, 1985.

[5] R. N. H. Pugh, I. M. Murray-Lyon, J. L. Dawson, M. C. Pietroni, and R. Williams, “Transection of the oesophagus for bleeding oesophageal varices,” The British Journal of Surgery, vol. 60, no. 8, pp. 646–649, 1973.

[6] P. S. Kamath, R. H. Wiesner, M. Malinchoc et al., “A model to predict survival in patients with end-stage liver disease,” Hepatology, vol. 33, no. 2, pp. 464–470, 2001.

[7] R. Moreau, R. Jalan, P. Gines et al., “Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis,” Gastroenterology, vol. 144, no. 7, pp. 1426–1437.e9, 2013.

[8] D. P. Bota, M. Van Nuffelen, A. N. Zakariah, and J. L. Vincent, “Serum levels of C-reactive protein and procalcitonin in critically ill patients with cirrhosis of the liver,” The Journal of Laboratory and Clinical Medicine, vol. 146, no. 6, pp. 347–351, 2005.

[9] B. Campillo, E. Sherman, J. Richardet, and P. Bories, “Serum leptin levels in alcoholic liver cirrhosis: relationship with gender, nutritional status, liver function and energy metabolism,” European Journal of Clinical Nutrition, vol. 55, no. 11, pp. 980–988, 2001.

[10] H. Tilg, A. Wilmer, W. Vogel et al., “Serum levels of cytokines in chronic liver diseases,” Gastroenterology, vol. 103, no. 1, pp. 264–274, 1992.

[11] R. Meliconi, O. Parracino, A. Facchini et al., “Acute phase proteins in chronic and malignant liver diseases,” Liver, vol. 8, no. 2, pp. 65–74, 1988.

[12] P. Calabrò, J. T. Willerson, and E. T. H. Yeh, “Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells,” Circulation, vol. 108, no. 16, pp. 1930–1932, 2003.

[13] W. J. Jabs, B. A. Lögering, P. Gerke et al., “The kidney as a second site of human C-reactive protein formation in vivo,” European Journal of Immunology, vol. 33, no. 1, pp. 152–161, 2003.

[14] K. Yasojima, C. Schwab, E. G. McGeer, and P. L. McGeer, “Human neurons generate C-reactive protein and amyloid P: upregulation in Alzheimer’s disease,” Brain Research, vol. 887, no. 1, pp. 80–89, 2000.

[15] Q. Dong and J. R. Wright, “Expression of C-reactive protein by alveolar macrophages,” Journal of Immunology, vol. 156, no. 12, pp. 4815–4820, 1996.

[16] K.-H. Lin, F.-L. Wang, M.-S. Wu et al., “Serum procalcitonin and C-reactive protein levels as markers of bacterial infection in patients with liver cirrhosis: a systematic review and meta-analysis,” Diagnostic Microbiology and Infectious Disease, vol. 80, no. 1, pp. 72–78, 2014.

[17] M. Papp, Z. Vitalis, I. Altorjay et al., “Acute phase proteins in the diagnosis and prediction of cirrhosis associated bacterial infections,” Liver International, vol. 32, no. 4, pp. 603–611, 2012.

[18] M. Borzio, F. Salerno, L. Piantoni et al., “Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study,” Digestive and Liver Disease, vol. 33, no. 1, pp. 41–48, 2001.

[19] C. Lazzarotto, M. F. Ronsoni, L. Fayad et al., “Serum procalcitonin and C-reactive protein levels in the diagnosis of bacterial infection and prediction of mortality in acute complications of cirrhosis,” Annals of Hepatology, vol. 12, no. 4, pp. 599–607, 2013.

[20] A. A. Khot, P. Somani, P. Rathi, and A. Amarapurkar, “Prognostic factors in acute-on-chronic liver failure: a prospective study from western India,” Indian Journal of Gastroenterology, vol. 33, no. 2, pp. 119–124, 2014.

[21] J. P. Cervoni, A. Amorós, R. Bañares et al., “Prognostic value of C-reactive protein in patients with cirrhosis:
external validation from the Canonic cohort,” *European Journal of Gastroenterology & Hepatology*, vol. 28, no. 9, pp. 1028–1034, 2016.

[22] S. Chirapongsathorn, W. Bunraksa, A. Chaiprasert, D. Punpanich, O. Supasyndh, and P. S. Kamath, “Adding C-reactive protein and procalcitonin to the model of end-stage liver disease score improves mortality prediction in patients with complications of cirrhosis,” *Journal of Gastroenterology and Hepatology*, vol. 33, no. 3, pp. 726–732, 2018.

[23] J. U. Jensen, L. Heslet, T. H. Jensen, K. Espersen, P. Steffensen, and M. Tvede, “Procalcitonin increase in early identification of critically ill patients at high risk of mortality,” *Critical Care Medicine*, vol. 34, no. 10, pp. 2596–2602, 2006.