A DIAGNOSTIC STUDY ON THE BACTERIAL INFECTION IN LIVER CIRRHOSIS DETECTED BY RESISTIN AND C-REACTIVE PROTEIN

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ABSTRACT

Background: In cirrhotic patients, the bacterial infection is associated with a poor prognosis yet might present with several diagnostic challenges. In patients with liver cirrhosis, the significance of clinical measures such as neutrophil count, leukocyte count, systemic inflammatory response syndrome, and other markers is still unknown.

Aim: The purpose of this study was to assess the use of inflammatory indicators and identify the most effective markers for the identification of infection in patients with decompensated cirrhosis.

Methods: This study was conducted at Nishtar Hospital Multan and the duration of this study was from August 2022 to July 2023. The presence of infection was evaluated. Markers of infection consist of leukocyte count, neutrophil count, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP) and resistin were measured. Accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined.

Results: Spontaneous bacterial peritonitis (SBP) was the most prevalent kind of illness, affecting twenty individuals (or 25%). The group with bacterial infections had greater levels of NLR, CRP, and resistin ($p < 0.05$). CRP and resistin were found to be predictive factors for the incidence of bacterial infections, according to multiple logistic regression analyses ($p < 0.05$). Baseline CRP, with a cut-off value of 11.65 mg/L, and resistin, with a cut-off value of 13 ng/mL, produced area under the receiver operating characteristic (ROC) curves of 0.796 and 0.787, respectively, for the diagnosis of infection. For CRP, the corresponding values were 90%, 73%, 52.9%, and 95.7% for sensitivity, specificity, PPV, and NPV. The corresponding values for resistin's sensitivity, specificity, PPV, and NPV were 90%, 59%, 41.9%, and 94.6%.

Conclusions: According to this study, resistin and CRP have moderate to high accuracy in diagnosing bacterial infections in liver cirrhosis.

KEY WORDS: Liver Cirrhosis, Urinary Tract Infections, Tachypnea, Neutrophil, C-Reactive Protein, Lymphocyte Ratio

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INTRODUCTION

The main causes of liver failure progression in individuals with liver cirrhosis is bacterial infections, which are a frequent comorbidity. Infection rates and severity are higher in the cirrhosis population than in the non-cirrhosis group. Infections strike 25–35% of people with liver cirrhosis. On the other hand, no national data about the incidence of bacterial infection in liver cirrhosis exist in Pakistan [1]. Because bacterial infections have the ability to seriously impair liver function and even cause death, it is imperative that they be identified as soon as possible. Arvaniti even discovered that infections can cause a four-fold increase in death. There are two types of bacterial infections in liver cirrhosis: hospital acquired and community acquired. Commonly occurring bacterial infections include bacteremia, skin and soft tissue infections, respiratory tract infections, urinary tract infections, and SBP. Culture is required to diagnose bacterial infections in individuals with liver cirrhosis; however, only 50–70% of patients respond, and this procedure takes time [2].

When there is a focal infection together with changes in vital signs that point to inflammatory response syndrome, an infection in general is identified. But since chronic liver disease is an inflammatory illness in and of itself, as well as the medications used to treat it, irregularities and changes in vital signs may occur, making the diagnosis of bacterial infections more challenging [3]. Tachycardia was brought on by hyperdynamic circulation, tachycardia was generated by betablocker medication, tachypnea was brought on by hepatic coma, white blood cell production was decreased by hypersplenism, and numerous acute phase reactants were produced less often by hepatocellular failure. A critical first step in the treatment of cirrhosis patients is the early detection of bacterial infections. Consequently, additional testing is required to identify the diagnostic significance of infection indicators, as they may differ from those in the non-cirrhotic group [4].

Researchers have looked at a number of indicators of bacterial infections in cirrhosis. In individuals with clinically evident infections, levels of acute phase proteins, including lipopolysaccharide-binding protein (LBP), procalcitonin (PCT), and CRP, were considerably higher. Two indicators with good sensitivity and specificity are PCT and CRP. Lin et al. (2022) conducted a meta-analysis which verified that PCT and CRP were similar in terms of diagnosing systemic infection in liver cirrhosis. however, a number of novel assays and inflammatory markers that can identify bacterial infections in liver cirrhosis still need to be investigated. The objectives of this research were to: (i) identify the infection markers that can be used to detect bacterial infections in cirrhosis patients and to determine the diagnostic utility of these markers in making the diagnosis of bacterial infections; and (ii) to determine the optimal cut-off values for these markers in order to detect bacterial infections in cirrhosis patients [5]. Patients with liver cirrhosis may be screened for bacterial infections using these indicators.

METHODS

This study was conducted at Nishtar Hospital Multan and the duration of this study was from August 2022 to July 2023. The study was done to recognize infection markers for detection of bacterial infection in liver cirrhosis and to know their diagnostic value. Samples were obtained by consecutive sampling from liver cirrhosis patients who were admitted to Nishtar hospital Multan from August 2022 to July 2023. Patients with liver cirrhosis between the ages of 15 and 60 who had written informed consent were eligible to participate in this research. The following conditions have to be met in order to be excluded: use of insulin, steroids, anti-hyperglycemic medications, hypertension, coronary heart disease, hyperthyroidism, cancer, and chronic renal disease. Based on clinical, biochemical, and ultrasonographic characteristics, cirrhosis was diagnosed. At enrollment, laboratory tests and clinical information were obtained. This included information about the severity of cirrhosis, which was graded using the Child Turcotte-Pugh (CTP) classification, the presence of ascites, encephalopathy, blood chemistry, and blood cell counts, which included CRP, resistin, and ascitic fluid cell counts. An immunoturbidimetric test was used to determine the serum CRP level. Quantikine Human Resistin Immunoassay was used to assess serum resistin by the use of enzyme-linked immunosorbent assay (ELISA). By dividing the neutrophil count by the lymphocyte count, the NLR was computed. When an infection was suspected while the patient was in the hospital, cultures of the blood, urine, ascites, and sputum were obtained. Data that were gathered were examined descriptively. Kolmogorov-Smirnov test was used to perform the normalcy test. Initially, we used the independent t-test or Mann Whitney to assess a number of indicators, including leukocyte count, neutrophil count, NLR, CRP, and resistin, in order to identify bacterial infection in liver cirrhosis patients. After significant markers were found using univariate analysis, multivariate analysis was used to evaluate the markers. Then, markers with p values less than 0.05 were included

for examination. Using the ROC curve, cut-off values for indicators that distinguish between bacterial infections were established. Accuracy, sensitivity, specificity, PPV, NPV, positive likelihood ratios, and negative likelihood ratios were all assessed to determine the diagnostic value of the markers. It was used to calculate the diagnosis accuracy for bacterial infection caused by these markers. When a p-value was less than 0.05, it was deemed statistically significant. The SPSS, version 17.0, was used to conduct all two-tailed tests (SPSS, Chicago, IL, USA).

RESULTS

Eighty liver cirrhosis patients met the inclusion criteria from the 92 samples that were collected throughout the data collection process. There were 26 (32.5%) and 54 (67.5%) female participants in this study. Twenty (or twenty percent) of the patients had a bacterial infection, with SBP being the most prevalent diagnosis (fifty percent). Urinary tract infections accounted for thirty percent of the cases, pneumonia for ten percent, cholecystitis for five percent, and cellulitis for five percent. There was a 53.02 ± 13.64-year-old mean. The distribution of resistin, leukocyte count, neutrophil count, NLR, and CRP was not normal. All of the data was displayed in Table 1. Gender, age, encephalopathy, variceal haemorrhage, AST, ALT, total bilirubin, white blood cell count, and neutrophil count did not significantly differ between the two groups. In contrast to individuals without infections, those with infections experienced higher grades of CTP and greater ascites. The infection group had significantly greater levels of NLR, CRP, and resistin in comparison to the non-infected group.

Five factors that were statistically significant in the univariate analysis were then subjected to multivariate analysis. Ascites, CTP class C, resistin, NLR, and CRP were among the variables used to distinguish between the two situations. Nevertheless, multivariate analysis only identified two indicators (Table 2) that are sufficient for diagnosing bacterial infections. Resistin and CRP were two indicators that correctly identified bacterial infections in liver cirrhosis. The ROC curve (Fig. 2) was used to assess how well serum CRP and resistin performed for the diagnosis of infection. For the purpose of diagnosing infection, the areas under the ROC curves for resistin and CRP were 0.787 and 0.796, respectively. Cutoffs were selected to predict the presence or absence of infection based on the ROC curve (Table 3). CRP showed its highest overall performance at a cutoff of 11.65 mg/L. This score showed 77.5% accuracy, 90% sensitivity, and 73% specificity, in that order. The corresponding cutoff resistin values were 59% and 13 90%. ng/mL with 66.25% precision, sensitivity, and specificity,

Table 1: Demographic, Clinical and Laboratory Characteristics of Patients with Or Without Bacterial Infections in Liver Cirrhosis

	Infected (n = 20)	Non-infected (n = 60)	P value
Gender (male/ female, n)	14/6	40/20	NS
Age (mean ± SD, yr)	50.90 ± 16.55	53.73 ± 12.61	NS
Ascites present (n [%])	16 (80%)	27 (45%)	0.007
Encephalopathy (n [%])	5 (25%)	10 (17%)	NS
Variceal bleeding (n [%])	4 (20%)	24 (40%)	NS
CTP (A and B/ C, n)	5/15	39/21	0.004
AST (U/L, median [IQR])	80.70 (10.50 – 2411.22)	58.55 (10.50 – 2411.22)	NS
ALT (U/L, median [IQR])	49.50 (20.08 – 424.30)	41.90 (7.50 – 974.90)	NS
TBIL (mg/dL, median [IQR])	4.63 (1.02 – 28.37)	1.99 (0.28 – 21.13)	NS
WBC (x 10^9 cells/L, median [IQR])	8.96 (2.78 – 25.40)	6.48 (0.87 – 18.86)	NS
Neutrophil count (x 10^9 cells/L, median [IQR])	5.91 (2.15 – 21.37)	4.64 (0.63 – 15.99)	NS
NLR (median [IQR])	5.72 (2.68 – 13.29)	3.49 (1.23 – 17.36)	0.018
CRP (mg/L, median [IQR])	24.60 (1.10 – 89.20)	7.30 (0.02 – 66.80)	< 0.001
Resistin (ng/mL, median [IQR])	31.79 (6.53 – 69.63)	12.34 (3.59 – 66.77)	0.001

Abbreviations: TBIL, total bilirubin; WBC, white blood cell; NLR, neutrophil lymphocyte ratio; CRP, C-reactive protein; IQR, interquartile range; NS, not significant.

Table 2: Multivariate Analysis on Factors Which Determine Bacterial Infections in Liver Cirrhosis

	Infected (n = 20)	Non-infected (n = 60)	P value	Multivariate analysis P value
Ascites present (n [%])	16 (80%)	27 (45%)	0.007	0.08
CTP (A and B/ C, n)	5/15	39/21	0.004	0.442
NLR (median [IQR])	5.72 (2.68 – 13.29)	3.49 (1.23 – 17.36)	0.018	0.16
CRP (mg/L, median [IQR])	24.60 (1.10 – 89.20)	7.30 (0.02 – 66.80)	< 0.001	0.001
Resistin (ng/mL, median [IQR])	31.79 (6.53 – 69.63)	12.34 (3.59 – 66.77)	0.001	0.019

Abbreviations: NLR, neutrophil lymphocyte ratio; CRP, C-reactive protein; IQR, interquartile range

Table 3: Diagnostic Accuracy Of C-Reactive Protein and Resistin in Diagnosing Infection in Liver Cirrhosis

Markers	Cutoff	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
CRP	11.65 mg/L	77.5	90	73	52.9	95.7	3.33	0.14
Resistin	13 ng/mL	66.25	90	59	41.9	94.6	2.20	0.17

CRP: C-reactive protein (mg/L), PPV: positive predictive value, NPV: negative predictive value

DISCUSSION

Due to its immunocompromised state, liver cirrhosis is particularly vulnerable to the spread of infections that impair liver function and cause serious consequences from the illness [6]. Changes in the intestinal flora and intestinal barrier, impaired reticuloendothelial function, deficits in C3 and C4, decreased ascetic fluid opsonic activity, and malfunction of neutrophil leukocytes are all associated with cirrhosis. As a result, early infection detection and treatment are essential. Finding a novel clinical laboratory test to anticipate infections and support the doctor in treating patients is obviously critical [7]. While prior research has linked the levels of inflammatory markers to the identification of bacterial infection in cirrhosis patients, there is still a dearth of knowledge regarding the use of these tests in patients hospitalised for liver disease complications. We evaluated the therapeutic usefulness of inflammatory markers in the current investigation to detect bacterial infections in liver cirrhosis [8,9].

According to our statistics, bacterial infections resulting in liver cirrhosis hospitalised 20 out of 80 patients, or 25% of the total. The statistics showed a strong resemblance to the global prevalence of roughly 2535%. Thus, in order to minimize an increase in mortality, it is imperative that patients with liver cirrhosis who are hospitalised have a fast diagnosis of bacterial infections [10]. In the group with bacterial infections, ascites and a higher degree of CTP class were more common. These circumstances made sense because the majority of bacterial infections in individuals with liver cirrhosis were spontaneous bacterial peritonitis, with ascites serving as a major risk factor. CTP class C was found to be a major risk factor for bacterial infections in our investigation. Seventy-five percent of the patients with bacterial illnesses had Child C status. This disorder may be brought on by decreased liver function, which increases vulnerability to infection because of immune system flaws such as immunoglobulin's impaired bactericidal action, decreased polymorphonuclear leukocyte activity [11], complement deficiency, and decreased Kupffer cell count. Compared to Child A and B patients, there is a notable rise in gut bacterial translocation in Child C.

Gender, age, encephalopathy, and variceal haemorrhage were comparable between the two groups in our study. individuals with liver cirrhosis who also had infections had considerably greater quantities of NLR, CRP, and resistin than individuals without infections [5]. These days, NLR is recognized as a straightforward indicator of systemic inflammation in the general population. Additionally, NLR has been shown to be a reliable indication of infection in people who are not cirrhotic. The increase in proinflammatory conditions caused by neutrophils would block their apoptosis and boost neutrophils' ability to destroy bacteria may help to explain why there is a rise in NLR in bacterial infections. The spleen and thymus also experienced lymphocyte apoptosis at the same period [12]. A study conducted in Asia revealed the value of NLR and CRP in predicting the prognosis of liver cirrhosis patients. According to these investigations, NLR was unable to identify infection; however, in patients with liver cirrhosis, this marker was able to predict survival for one month. The number of studies that have been done that discuss NLR is few. This research provided insight into the use of NLR in liver cirrhosis patient survival, outcome, and mortality prediction [13]. NLR was discovered to be one of the methods in this investigation for bacterial infection detection. The study's cut-off point was 4.14. But when combined with additional factors, NLR was no longer a reliable, all-in-one instrument for infection diagnosis. When combined with other factors, NLR's incapacity to predict liver cirrhosis may be explained by splenomegaly and hypersplenism, conditions that resulted in an accelerated breakdown of blood cells, including white blood cells. The role of NLR as a prognostic factor rather than a marker of bacterial infections was also noted in a number of studies [14].

Our study indicates that CRP and resistin may be useful in the identification of bacterial infections, in contrast to NLR. Numerous research has

assessed the diagnostic and prognostic use of resistin and CRP in liver disorders. Because CRP and PCT have commonalities with noncirrhotic individuals, they may be utilised to diagnose infection in cirrhosis patients, according to a 2013 EASL position paper. CRP, which is mostly generated by hepatocytes, has been shown to have a comparable predictive value for infection detection in individuals with and without cirrhosis, despite a reduction in its production. According to a 2022 literature analysis by Pieri et al., CRP is still a good indicator of bacterial infection in cirrhosis [15]. Regarding the best way to use CRP in this patient population, there are still a lot of unanswered concerns. This serves as the justification for evaluating CRP's prediction ability in the current investigation. The optimal CRP cut-off value in the current investigation was 11.65 mg/L for the identification of infections. Similarly, the cut-off number used to distinguish between bacterial infection and non-infection in the general population is 10 mg/L. The sensitivity and specificity were 90% and 73%, respectively, at a threshold level of 11.65 mg/L. In contrast, Papp et al [16]. prospectively assessed 368 patients with liver cirrhosis who were admitted to a hospital unit and discovered that, with a sensitivity of 84% and specificity of 91%, 10 mg/L was the ideal cut-off value for CRP in the diagnosis of infection [7]. Our results indicate that serum CRP cut-off levels greater than 10 mg/L will result in lower specificity. CRP more than 11.65 mg/L with 90% sensitivity may reduce the likelihood of missing some cirrhotic individuals who have infections and need to get early empirically based antibiotic therapy.

This study also revealed a substantial difference in serum resistin levels between patients with bacterial infections and liver cirrhosis. With a cut-off of 13 ng/mL, serum resistin levels served as a biomarker for the detection of bacterial infections. 90% and 59%, respectively, were the sensitivity and specificity. Research on resistin as a novel class of inflammatory indicators in the liver cirrhosis population is still in its infancy [17]. Thus far, it has been observed that resistin increases with increasing CTP class and is associated with both insulin resistance and inflammation. There are few studies that focus solely on non-cirrhotic populations and discuss the impact of resistin in bacterial infections. A study by Johansson et al. revealed that individuals experiencing septic shock or severe sepsis had higher resistin levels. The literature contains no information about the resistin levels of individuals with bacterial infections and liver cirrhosis. The primary producers of resistin are adipocytes or macrophages [18]. Increased resistin demonstrated that, even in cases of immunosuppression such liver cirrhosis, the macrophage response remains sufficient. The area under the ROC curve for resistin in the current investigation was 0.787 when it came to infection diagnosis. As of right present, no research has assessed resistin's ability to anticipate infection. Resistin may therefore be a diagnostic tool to help in the detection of bacterial infections.

Higher CRP and resistin levels were linked to the presence of infection in the current investigation. A diagnostic test's sensitivity must be high in order to be used as a screening tool. CRP of 11.65 mg/L and resistin of 13 ng/mL appear to be sufficient indicators to rule out infections [19].

We acknowledge that our analysis has certain limitations. the data' limited interpretation due to the very small patient population. Nonetheless, our sample size was comparable to that of the majority of research examining inflammatory markers for the identification of infection in cirrhosis patients [20]. Nevertheless, the findings reported here need to be independently verified by prospective, randomised multicenter investigations, particularly in relation to the selected acute-phase marker cut-offs.

CONCLUSION

In the conclusion of our study, resistin and CRP demonstrated high diagnostic accuracy when used as screening tests to identify bacterial infections in individuals with cirrhosis. These methods could help doctors in the future identify patients who are more susceptible to infections.

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