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Characteristics and Related Factors of Bacterial Infection Among Patients With Cirrhosis

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ABSTRACT

Background: Infection causes cirrhosis to decompensate, affecting liver function and resulting in several complications, including esophageal variceal hemorrhage, hepatic encephalopathy, and hepatorenal syndrome. Objective: This study aimed to identify the prevalence, essential features, and related factors of bacterial infection among patients with cirrhosis in Vietnam. **Methods:** This retrospective study included 317 patients diagnosed with cirrhosis, who were divided into two groups: group 1 including 125 patients with bacterial infection and group 2 including 192 patients without bacterial infection. Infection was diagnosed on the basis of its localization. **Results:** Spontaneous bacterial peritonitis (SBP; 31.2%) and pneumonia (28.8%) were the most common infections identified. The procalcitonin (PCT) level had a strong diagnostic value with an area under the curve value of 0.868. The most common type of gram-negative bacteria was Escherichia coli, while the gram-positive bacteria seen were Staphylococcus, Enterococcus, and Streptococcus among the patients with infection. In the logistic regression analysis, Child–Pugh class B and C ($p<0.001$, OR=4.14, CI=1.90–9.03; OR=4.76, CI=2.03–11.16, respectively) and the presence of acute kidney injury ($p=0.009$, OR=2.57, CI=1.27–5.22) and gastrointestinal hemorrhage ($p=0.035$, OR=0.39, CI=0.16–0.94) significantly differed between the groups. **Conclusion:** The most prevalent type of bacterial infection in patients with cirrhosis is SBP, with gram-negative bacteria being the most common cause. The PCT level is useful in identifying infection in patients with cirrhosis. Decompensated cirrhosis is linked to a higher risk of infection.

Keywords: Bacterial infection, Cirrhosis, Procalcitonin.

1. BACKGROUND

Globally, cirrhosis is the main cause of death among liver diseases (1). In 2019, cirrhosis was the seventh most common cause of death in Vietnam (2). The most significant factor of acute decompensated cirrhosis is infection, which is detected in 25–47% of hospitalized patients with cirrhosis (3, 4). The most prevalent bacterial infections in patients with cirrhosis are spontaneous bacterial peritonitis (SBP) (27%), urinary tract infection (22%), pneumonia (19%), bacteremia (8%), and cellulitis (8%) (5). In a previous study, culture results were positive in 57% of cases, in which gram-negative bacteria were the most common isolates, and gram-positive bacteria accounted for 38% of positive cultures. Escherichia coli and Klebsiella pneumoniae were the major causes of bacterial infection in patients with cirrhosis (6).

Infection triggers cirrhosis to decompensate, impairing liver function and yielding several consequences, such as esophageal variceal hemorrhage, hepatic encephalopathy, and hepatorenal syndrome. These issues prolong hospital stays beyond necessary lengths and increase the disease burden and mortality rates (7-9). Despite recent progress in the understanding of the pathogenic mechanism of bacterial infection in cirrhosis, mortality from infection-related multiorgan failure and septic shock remains disproportionately high (3, 10, 11). The mortality rate for patients with cirrhosis with infection is around 15% upon admission, which is twice as high as that for patients with cirrhosis without infection, but can increase up to 70% in the event of septic shock (10).

2. OBJECTIVE

In the present study, we investigated the distribution of infection at a single academic center and considered the factors linked to infection in patients with cirrhosis. Specifically, this retrospective study aimed to determine the frequency of infection among patients with cirrhosis at an urban university liver clinic and investigate any possible connections between infection and related factors among patients with cirrhosis.

3. PATIENTS AND METHODS

Patient Data

The institutional review board of Hanoi Medical University Hospital approved this retrospective study. Before study participation, written informed consent was obtained from all patients. A total of 317 patients who were diagnosed with cirrhosis from May 2021 to June 2022 were divided into two groups: group 1 including 125 patients with bacterial infection and group 2 including 192 patients without bacterial infection.

Infection was diagnosed on the basis of its localization. SBP was diagnosed when there were more than 250 neutrocytes in ascitic fluid or positive bacterial cultures but no other secondary causes of peritonitis 31. Urinary tract infection was diagnosed when the following findings were noted: dysuria, fever, >15 leukocytes in the urinalysis, and/or a positive urine culture (>100,000 CFU/mL)38. Coughing, expectoration, pulmonary sounds, and fever as well as positive radiologic (patchy alveolar opacities) and/or bacteriologic findings (sputum or hemoculture) indicated the presence of respiratory tract infection 32. Cutaneous and soft tissue infection was diagnosed when there were fever, local symptoms (blush, tumefaction, pain), leukocytosis with neutrophilia, and positive cultures of wound secretion or hemocultures 30. A number of criteria were employed to determine whether a patient had bacteremia, including a positive hemoculture for recognized germs or germs from saprophytic flora; symptoms such as fever, chills, and hypotension; and the absence of a relationship between the germ found in the hemoculture and infection elsewhere 33. Conversely, the following clinical criteria were used to determine whether a patient had sepsis or septic shock: high temperature (>38°C) or hypothermia (36°C), tachycardia (pulse rate of >90/min), tachypnea (respiratory rate of >20/min), hypoxemia (oxygen level of 70 mmHg), metabolic acidosis, and oliguria (urine output of 30 mL/min) 34.

Statistical analysis

A receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic efficiency for bacterial infection and obtain the area under the curve (AUC), cut-off, sensitivity, and specificity values. Multivariate logistic regression models were created to evaluate any association of bacterial infection with cirrhosis. P values of <0.05 were considered statistically significant. All statistical analyses were performed using the SPSS software version 22 (SPSS, Chicago, IL, USA).

4. RESULTS

The proportion of men was higher than that of women, and the men accounted for 79.2% and 89.1% of the patients with and without infection, respectively. The mean age of the patients with and without infection was 59.94 years and 57.84 years, respectively. Alcohol consumption was the most common etiology of cirrhosis both in the patients with (46.4%) and without infection (44%), closely followed by hepatitis B (44.3% in those with infection and 39.2% in those without infection). The other baseline data are shown in Table I. The model for end-stage liver disease–sodium (MELD-Na) score was noted to be significantly higher in the patients with infection than in those without (20.04 vs. 16.03, p<0.001). The Child–Pugh score was also significantly higher in the patients with infection (9.35 vs. 7.51, p<0.001).

Variable		Without infection (n=192)	With infection (n=125)	p
Age (y), mean (SD)		57.84 (11.07)	59.94 (11.32)	0.166
Men, n (%)		171 (89.1%)	99 (79.2%)	0.157
Etiology, n (%)	Alcohol consumption	89 (46.4%)	55 (44%)	0.681
	HBV	85 (44.3%)	49 (39.2%)	0.372
	HCV	10 (5.2%)	8 (6.4%)	0.654
	Other	8 (4.2%)	13 (10.4%)	
Hepatic encephalopathy		5 (2.6%)	15 (12%)	0.001
Gastrointestinal hemorrhage		37 (19.3%)	8 (6.4%)	0.001
AKI		16 (8.3%)	31 (24.8%)	<0.001
MELD-Na score, mean (SD)		16.03 (5.06)	20.04 (5.73)	<0.001
MELD-Na, n (%)	<10	12 (6.2%)	2 (1.6%)	<0.001
	10–14	81 (42.2%)	23 (18.4%)	<0.001
	>14	99 (51.6%)	100 (80%)	<0.001
Child–Pugh score, mean (SD)		7.51 (2.07)	9.35 (2.06)	<0.001
Child–Pugh class, n (%)	A	69 (35.9%)	10 (8%)	<0.001
	B	81 (42.2%)	55 (44%)	<0.001
	C	42 (21.9%)	60 (48%)	<0.001
SIRS, n (%)		24 (12.5%)	73 (58.4%)	<0.001
WBC count (×10⁹/L), median (IQR)		10.93 (5.38)	9.11 (4.76)	<0.001
Normal leukocyte count (≤10 G/L)			89/125 (71.2%)	
NLR, median (IQR)		5.74 (3.70)	9.75 (9.31)	<0.001
CRP level (mg/dL), median (IQR)		1.99 (2.05)	5.98 (8.55)	<0.001
Normal CRP level (≤1 mg/dL)			28/125 (22.4%)	
PCT level (ng/mL), median (IQR)		0.22 (0.14)	4.01 (9.34)	<0.001
Normal PCT level (≤0.5 ng/mL)			33/125 (26.4%)	

Table I. Distribution of the clinical data and trends across different infection categories. HBV: hepatitis B virus; HCV: hepatitis C virus; AKI: acute kidney injury; MELD-Na: model for end-stage liver disease–sodium; SIRS: systemic inflammatory response; WBC: white blood cell; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; PCT: procalcitonin.

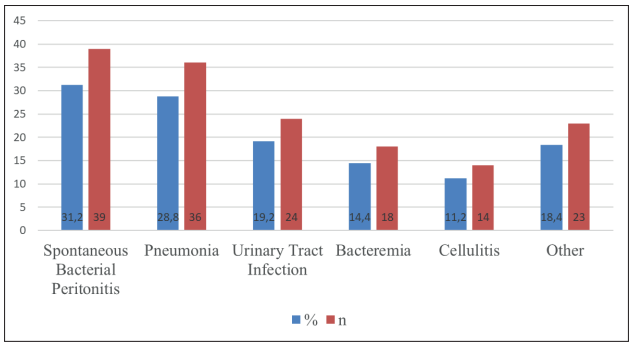

Figure 2. Top five most common infections noted in the patients with cirrhosis

Infection was present in 125/317 (39.4%) patients. SBP (31.2%) and pneumonia (28.8%) were the most common infections identified, followed by urinary tract infection (19.2%), bacteremia (14.4), and cellulitis (11.2%) (Figure 2).

Fever at presentation (≥37.5°C) was observed in 69/125 (55.2%) patients. Acute kidney injury (AKI; 24.8%), hepatic encephalopathy (12%), and gastrointestinal hemorrhage (6.4%) were the most common complications in the patients with infection. The mean white blood cell (WBC) count in the patients with infection was 9.11 G/L. Moreover, a significant number (89/125; 71.2%) of the patients with infection did not have an increased blood leukocyte count (>10 G/L). Approximately 58.4% of the patients with bacterial infection presented with systemic inflammatory response (SIRS) (Table I).

Figure 5. Prevalence of gram-positive bacteria in the patients with infection (n=6)

The patients with infection had a mean C-reactive protein (CRP) level of 5.98 mg/dL. Furthermore, despite having a known bacterial infection, 28/125 (22.4%) patients exhibited normal CRP levels (1 mg/dL) (Table I).

The mean serum procalcitonin (PCT) level was significantly higher in the patients with infection than in those without. The mean PCT level in the patients with infection was 4.01 ng/mL, while that in the patients without infection was 0.22 ng/mL (p<0.001) (Table I).

There was a significant difference in the mean WBC count, CRP level, PCT level, and neutrophil-to-lymphocyte ratio (NLR) and the presence of SIRS between the groups (Table I).

The next step in the analysis was to define which of the variables was the best predictor of infection among the patients with cirrhosis. ROC curves were calculated, and AUC values were compared. The highest AUC value (0.868) was found in the PCT level. Conversely, the presence of SIRS, CRP level, WBC count, and NLR had poor abilities to discriminate the patients with and without infection (AUC value=0.632, 0.65, 0.417, and 0.647, respectively). The ROC curves and AUC values with cut-off values are presented in Figure 3 and Table 2.

The most common type of gram-negative bacteria was E. coli, which was found in 45% of the samples. The other common strains were Acinetobacter, Pseudomonas, Aeromonas, Klebsiella, Campylobacter, and Proteus. Staphylococcus accounted for 66.6% of the

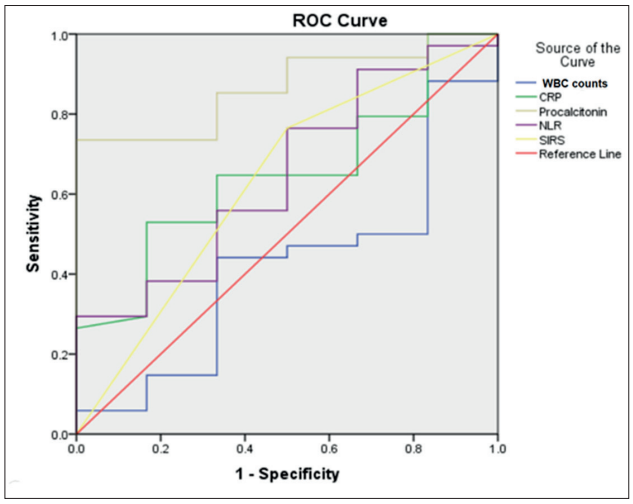

Figure 3. Performance of the WBC count, CRP level, PCT level, NLR, and presence of SIRS in the diagnosis of bacterial infection among the patients with cirrhosis

	Se (%)	Sp (%)	Cut-off value	AUC value	p
WBC count	44.1	66.7	9.63	0.417	0.520
CRP level	52.9	83.3	2.71	0.650	0.248
PCT level	73.5	100	0.46	0.868	0.004
NLR	29.4	100	11.8	0.647	0.256
Presence of SIRS				0.632	0.306

Table 2. Comparison of the AUC values of the biomarkers

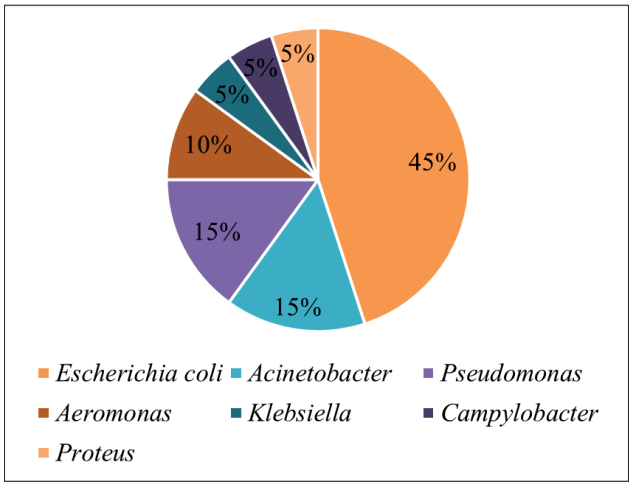

Figure 4. Prevalence of gram-negative bacteria in the patients with infection (n=20)

cultured gram-positive bacteria seen in the patients with infection, followed by Enterococcus and Streptococcus (16.7%) (Figures 4 and 5).

In the univariate analysis, Child–Pugh class B and C; the presence of gastrointestinal hemorrhage, AKI, and hepatic encephalopathy; and MELD score of >14 significantly differed between the groups. In the logistic regression analysis, Child–Pugh class B and C (p<0.001, OR=4.14, CI=1.90–9.03; OR=4.76, CI=2.03–11.16, respectively) and the presence of AKI (p=0.009, OR=2.57, CI=1.27–5.22) and gastrointestinal hemorrhage (p=0.035, OR=0.39, CI=0.16–0.94) significantly differed between the groups (Table 3).

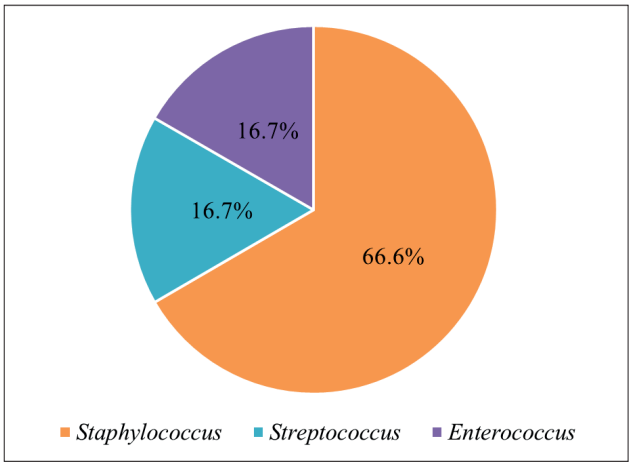

Figure 5. Prevalence of gram-positive bacteria in the patients with infection (n=6)

		Bacterial infection		Univariate		Multivariate	
		No (n=192)	Yes (n=125)	OR (95% CI)	p	OR (95% CI)	p
MELD-Na score	<10	12	2	1		1	
	10–14	81	23	1.70 (0.36–8.16)	0.505	0.88 (0.17–4.61)	0.879
	>14	99	100	6.06 (1.32–27.78)	0.020	1.88 (0.37–9.53)	0.448
Child–Pugh class	A	69	10	1		1	
	B	81	55	4.69 (2.22–9.88)	<0.001	4.14 (1.90–9.03)	<0.001
	C	42	60	9.86 (4.56–21.32)	<0.001	4.76 (2.03–11.16)	<0.001
Gastrointestinal hemorrhage	No	155	117	0.29 (0.13–0.64)	0.002	0.39 (0.16–0.94)	0.035
	Yes	37	8				
Hepatic encephalopathy	No	187	110	5.10 (1.80–14.42)	0.002	2.41 (0.77–7.53)	0.128
	Yes	5	15				
Acute kidney injury	No	176	94	3.63 (1.89–6.97)	<0.001	2.57 (1.27–5.22)	0.009
	Yes	16	31				

Table 3. Factors associated with bacterial infection in the patients with cirrhosis

5. DISCUSSION

Patients with cirrhosis are prone to a variety of adverse outcomes, with infection being one of the most clinically significant issues and being linked to a significantly shortened life expectancy. One important pathogenic mechanism in the development of infection, particularly SBP and bacteremia, is the pathological translocation of intestinal bacteria to extraintestinal locations. The dynamic spectrum of immunological disturbances known as cirrhosis-associated immune dysfunction that manifests in individuals with cirrhosis is another significant factor (12-14).

Among the patients with infection in the present study, alcohol consumption was the main cause of cirrhosis (46.4%), followed by hepatitis B (44.3%) and hepatitis C (5.2%). Generally, there are several remarkable differences in the demographic and clinical characteristics of patients among different geographic areas. The etiology of cirrhosis differs, with hepatitis B being more frequent in Asia than in Europe and America, where hepatitis C is more prevalent. Vietnam is located in an endemic area for hepatitis B virus, so hepatitis B virus was significantly more prevalent than hepatitis C virus in our study. Notably, regardless of the continent, alcohol consumption is still the leading cause of cirrhosis in patients with infection6 (15).

Approximately 39.4% of the hospitalized patients with cirrhosis in this study were found to have infection. Other research indicates that people with cirrhosis have an incidence of infection of 20–35%, four to five times higher than that in patients with other disorders (3, 17, 18). At 31.2%, SBP was the most common type of infection in the present study, followed by pneumonia (28.8%), urinary tract infection (19.2%), bacteremia (14.4%), and cellulitis (11.2%). With the exception of pneumonia and urinary tract infection, each site of infection in this research had rates that are almost identical to those in studies conducted elsewhere (6, 7, 19, 20).

Only 55.2% of our participants with bacterial infection experienced fever. Patients with cirrhosis might have infection without having an elevated temperature, which lessens the likelihood that infection can be diagnosed clinically based only on fever. The degree of fever or the lack thereof does not correspond with the severity of infection in patients with severe cirrhosis since they frequently experience moderate hypothermia (4, 15). Since infections in individuals with cirrhosis frequently present clinically with few or no symptoms (21), the diagnosis cannot be made exclusively based on clinical indicators and must additionally consider laboratory results. SIRS, which is frequently assessed in situations of infection, has both clinical and laboratory manifestations. In this research, 58.4% of the patients with bacterial infection had SIRS. In other studies, SIRS has been documented in 57–70% of individuals with cirrhosis and infection (22-24). However, SIRS may be misrepresented in individuals with cirrhosis owing to the low pulse rate caused by beta-blockers and normal WBC count. While 12.5% of the patients with cirrhosis in this study did not have infection, they had SIRS, which may be associated with ascites, endocrine abnormalities that cause hyperdynamic circulation, or hepatic encephalopathy, raising the core temperature, pulse rate, respiratory rate, and WBC count. Herein, 71.2% of the patients with infection had a normal WBC count. The WBC count is often raised in the presence of infection; however, in individuals with cirrhosis, this is typically not the case owing to hypersplenism, and the count may be impacted by a variety of non-infection-related variables, such as hematological disorders.

In this study, the mean CRP level in the patients with infection was 5.98 mg/dL. In addition, 28/125 (22.4%) patients with cirrhosis had normal CRP levels (1 mg/dL) despite having a confirmed bacterial infection. Regarding the relationship between the CRP level and infection

in patients with cirrhosis, Pieri et al. concluded that although the CRP level rises during bacterial infection, it does not increase as much in individuals with cirrhosis owing to the severity of the underlying liver failure. Accordingly, the CRP level has a poor diagnostic ability for infection in patients with decompensated/advanced cirrhosis (35).

The patients with bacterial infection had an average PCT level of 4.01 ng/mL in the present study. PCT is produced in all soft tissues, not just the liver, when exposed to bacterial toxins and chemical mediators. Since it is important to distinguish between bacterial and non-bacterial infections, the PCT level is commonly employed in clinical practice as a reliable biomarker of infection. Herein, 26.4% of the patients with infection had a PCT level of ≤0.5 ng/mL. Because the PCT level starts to rise 3–6 h after infection, it is likely that people who have their PCT level checked shortly after the illness starts would not show high levels. We discovered that the PCT level had a strong diagnostic value with an AUC value of 0.868 when it was included in the ROC curve analysis model. The other markers including the presence of SIRS, WBC count, NLR, and CRP level had a minimal value in diagnosing infection among the patients with cirrhosis. Several studies have also reported that the PCT level has a good diagnostic value with an AUC value of >0.826 (27). The European Association for the Study of the Liver currently recommends using the CRP and PCT levels to identify infection in people with cirrhosis despite limits in their utility for infection detection when the following cut-off values are used: ≥1 mg/dL for the CRP level and/or ≥0.5 ng/mL for the PCT level (19). With a cut-off value of 0.46 ng/mL for the PCT level in our study, the sensitivity and specificity in identifying infection among the patients with cirrhosis were 73.5% and 100%, respectively.

Approximately 20.8% of attempts at bacterial culture are successful; some research has shown a higher success rate (6). The disparity is explicable by the fact that up to 39% of research participants had previously received antibiotics, including antibiotic prophylaxis. The majority (76.9%) of isolates were gram-negative bacteria. Most previous research on gram-negative infection in individuals with cirrhosis has shown similar results. This finding can be explained by the transfer of bacteria from the gut into the blood in individuals with cirrhosis, whose intestinal microbiota is primarily made up of bacteria, via the mesenteric lymph node system and the portal vein. Furthermore, several studies have found that gram-negative bacteria are marginally more likely to translocate than gram-positive bacteria (28). Recent hospitalization, prior antibiotic usage, and invasive intervention are risk factors of gram-positive infection (25). In the current study, E. coli was the most prevalent strain of gram-negative bacteria (45%), followed by Acinetobacter (15%), Pseudomonas (15%), Aeromonas (10%), Klebsiella (5%), Campylobacter (5%), and Proteus (5%). In a previous study, E. coli, Klebsiella, and Pseudomonas were the most prevalent gram-negative causes of bacterial infection in people with cirrhosis (26). The gram-positive bacteria cultured in our study were Staphylococcus (66.6%) as well as Enterococcus and Streptococcus (16.7%). This finding is in line with the literature, which states that the most prevalent pathogenic gram-positive bacteria are Streptococcus, Staphylococcus, and Enterococcus (29).

The present univariate analysis showed that Child–Pugh class B and C, the presence of AKI and hepatic encephalopathy, and MELD score of >14 were predictors of de novo infection. Child–Pugh class B and C and the presence of AKI remained as the independent predictors of de novo infection in the multivariate analysis, emphasizing the strong association between liver function, the presence of AKI, and an increased risk of infection. Infection is one of the factors promoting AKI, and AKI is a predictor of mortality in patients with cirrhosis with infection (36, 37). As soon as decompensation takes place, cirrhosis develops into a multiorgan/multisystem dysfunctional illness (5). Owing to complicated cirrhosis-associated immunological failure including both innate and acquired immunities, patients at this stage develop a high susceptibility to bacterial infection. Conversely, bacterial infection is accompanied with significant mortality and severe morbidity, including ACLF (6, 7). In the retrospective research by Preda et al., the amount of bacterial infection discovered was significantly influenced by the severity of the liver illness (4). Only 14% of patients with Child–Pugh class A cirrhosis had concurrent bacterial infection. Child–Pugh class C liver disease was present in 60% of patients with infection; the OR for having Child–Pugh class C liver disease was 1.99 (95% CI=1.04–3.8, p=0.02 [chi-squared test]). Decompensated cirrhosis was found in 98% of patients with concurrent bacterial infection according to the liver cirrhosis stage compared with 46.22% of patients with cirrhosis with no bacterial infection. In the multicenter prospective analysis by Baijal et al., individuals with infection had much more severe liver failure. A high Child–Pugh class (class B vs. A: OR=3.04, 95% CI=1.63–5.68; class C vs. A: OR=4.17, 95% CI=2.12–8.19; p=0.006) was an independent predictor of infection (16).

According to the literature, gastrointestinal hemorrhage is one of the risk factors of bacterial infection (10, 30, 38, 39). However, in our study, the presence of gastrointestinal hemorrhage reduced the risk of bacterial infection in the patients with cirrhosis in both univariate (OR=0.29, 95% CI=0.13–0.64) and multivariate analyses (OR=0.39, 95% CI=0.16–0.94). Antibiotics were administered in all patients with gastrointestinal hemorrhage in the local hospital to prevent SBP. Accordingly, the bacterial infection rate in the patients with cirrhosis was reduced in our study.

6. CONCLUSION

The most prevalent type of bacterial infection in patients with cirrhosis is SBP, with gram-negative bacteria being the most common cause. The PCT level is useful in identifying infection in individuals with cirrhosis. Decompensated cirrhosis is linked to a higher risk of infection.

- **Ethic statement:** This study was approved by the Institution Review Board of Hanoi Medical University Hospital.
- **Patient consent form:** Informed consent was obtained from all participants.
- **Data availability statement:** Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- **Author's contribution:** Study concept and design: Nguyen-Thi Ngoc Lan and Tran Ngoc Anh; acquisition of data: Dau Quang Lieu and Tran Ngoc Anh; analysis and interpretation of data: Dau Quang Lieu and Tran Ngoc Anh; drafting of the manuscript: Nguyen-Thi Ngoc Lan and Mai Hong Bang; critical revision of the manuscript: Nguyen-Thi Ngoc Lan and Mai Hong Bang; study supervision: Nguyen-Thi Ngoc Lan and Dau Quang Lieu confirm the authenticity of all the raw data. All authors read and approved final version of this manuscript.
- **Conflicts of interest:** There are no conflicts of interest.
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