JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Bacteremia in patients with liver cirrhosis in the era of increasing antimicrobial resistance: single-center epidemiology

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Abstract

Introduction: Liver cirrhosis is commonly associated with bacterial infections, which contribute to unfavorable outcome. This study aimed to investigate the epidemiology of bacteremia and patterns of antibiotic resistance in patients with cirrhosis, factors associated with multidrug-resistant infection, and predictors of mortality.

Methodology: This retrospective single-center study included patients with cirrhosis treated between January 2016 and December 2018. Data were collected from the patients' medical records. The severity of liver disease was determined using the Child–Pugh, Model for End-Stage Liver Disease-Na, Chronic Liver Failure-Consortium Acute-on-Chronic Liver Failure, and Chronic Liver Failure-Consortium Acute Decompensation scores.

Results: A total of 85 patients with cirrhosis and bacteremia were included (male: 82.4%, mean age 60.3 ± 9.4 years). The etiology of cirrhosis was mainly alcoholism (87.1%). After 30 days, lethal outcome occurred in 44.7% of the patients. The most commonly isolated pathogens were *Enterococcus* spp. (31.8%), methicillin-sensitive *Staphylococcus aureus* (15.3%), and *Escherichia coli* (14.1%), while 37.3% of all isolated microorganisms were multi-drug resistant. Multi-drug resistant infection [odds ratio (OR): 6.198, 95% confidence interval (CI): 2.326–17.540, $p = 0.006$] and neutrophil-to-lymphocyte ratio (OR = 1.181, 95% CI = 1.043–1.337, $p = 0.009$) are independent predictors of mortality. The aforementioned scores, which represent the extent of hepatic insufficiency, are significantly higher in patients with multi-drug resistant isolates, while multi-drug resistant bacteremia was more common in patients with more advanced liver disease.

Conclusions: Multi-drug resistant bacteremia is more common in patients in whom liver disease is more severe and is a major independent predictor of mortality.

Key words: Epidemiology; bacteremia; liver cirrhosis; mortality; multi-drug resistance.

J Infect Dev Ctries 2021; 15(12):1883-1890. doi:10.3855/jidc.14508

(Received 14 February 2020 – Accepted 17 January 2021)

Introduction

Liver cirrhosis (LC) remains one of the most common chronic liver diseases, with an immense impact on overall mortality rates, as LC is considered the 11th most common cause of death worldwide, and a constant increase in the proportion of total global deaths [1,2]. Numerous studies have revealed bacterial infection as the main risk factor for liver failure, and one of the most significant factors altering outcomes in patients with LC [3,4]. The prevalence of infections in hospitalized patients with cirrhosis is estimated to be approximately 25–35%, while bacteria remain the most commonly identified pathogens [5]. Abnormal translocation of intestinal pathogens is thought to lead to bacteremia; hence, the most commonly isolated pathogens are expectedly gram-negative bacteria [5,6]. Factors contributing to a high prevalence of bacteremia in patients with LC are numerous and include increased intestinal permeability and consequent bacterial translocation, prolonged intestinal transit time, and bacterial overgrowth [6–8]. Moreover, LC as a state of impaired immunity is associated with both the reticuloendothelial system and neutrophil malfunction [9]. Additionally, extensive porto-systemic collaterals, together with cirrhosis-associated immune dysfunction, contribute to decreased bacterial clearance from the circulation. The aforementioned co-existant mechanisms, have a synergistic effect, and contribute to

the high incidence and prevalence of bacteremia in this group of patients [5]. Infections which are most commonly reported in patients with LC are spontaneous bacterial peritonitis, urinary tract infections, and pneumonia (PNA) [3]. The presence of bacteremia is associated with an increased length of stay (LOS), excessive cost, increased mortality, and progression of liver dysfunction [10–12]. Three main goals were outlined in this study:

1. To determine the epidemiology of bacteremia and factors associated with multidrug-resistant (MDR) infection development in patients with LC in our center;
2. To identify patterns of antibiotic resistance in this specific group of patients;
3. To investigate possible influencing factors on lethal outcome occurrence.

Methodology

This retrospective cohort study included patients treated between January 2016 and December 2018 at the Clinic for Gastroenterology and Hepatology, University Clinical Center of Serbia. All patients with confirmed LC who developed bacteremia during hospitalization were included. Patients in whom the diagnosis of LC was uncertain, those with acute hepatitis, hepatocellular carcinoma, or human immunodeficiency virus infection, as well as liver transplant recipients, were excluded.

Patients were diagnosed with LC based on physical examination, radiological and laboratory findings, and/or liver biopsy. In order to assess the extent of disease severity, the Child–Pugh and Model of End-Stage Liver Disease-Na (MELD-Na) scores were used, whereas the Chronic Liver Failure-Consortium (CLIF-C) Acute Decompensation (AD) and CLIF-C Acute-on-Chronic Liver Failure (ACLF) were used to predict 28-day mortality. Information regarding the Child–Pugh and MELD-Na score calculations is presented in the Appendix.

Demographic data, relevant clinical information, blood cultures with antibiograms, complete blood cell counts, and comprehensive metabolic panel were obtained from patients' medical records. The severitie of liver disease and acute liver failure was determined on the day of specimen collection, using the aforementioned clinical scores.

Diagnosis of bacteremia was established if one or more blood cultures tested positive, in addition to clinical or laboratory findings suggestive of infection. Microbial identification and antibiotic susceptibility testing were performed using the VITEK 2 Compact automated system (Biomerieux, Marcy l'Ẽtoile, France). MDR bacteria were defined according to the European Centre for Disease Prevention and Control and Centers for Disease Control and Prevention guidelines [13]. The antimicrobial agents analyzed in our study included the following: penicillins (ampicillin and amoxicillin), penicillins with beta-lactamase inhibitors (amoxicillin–clavulanic acid), cephalosporins (ceftriaxone, cefotaxime, ceftazidime, and cefepime), carbapenems (meropenem and imipenem), aminoglycosides (amikacin and gentamicin), oxazolidinones (linezolid), quinolones (ciprofloxacin), glycopeptides (vancomycin and teicoplanin), sulphonamides (trimethoprim–sulfamethoxazole), tigecycline, and colistin. During microbial susceptibility testing, different combinations of antibiotics in each panel were used.

Data regarding previous antibiotic treatment (within the last 3 months) and the presence of acute liver decompensation (including upper gastrointestinal bleeding, development of ascites, and/or hepatic encephalopathy) were recorded. Thirty-day outcome was recorded in each patient, and defined as favorable if the patient survived, and unfavorable if the patient did not survive.

This study was approved by the Ethics Committee of the Clinical Center of Serbia (number 562/3), in accordance with the Declaration of Helsinki.

Statistical analysis

For continuous variables, mean and standard deviation, or median and range were calculated depending on the normality of data distribution. Categorical data are presented as frequencies. The normality of the distribution was examined using the Kolmogorov–Smirnov test. Categorical variables were analyzed using the chi-squared or Fisher's exact test, where appropriate. Student's t-test was used for normally distributed continuous variables, and the Mann–Whitney–Wilcoxon test was used for non-normally distributed continuous variables. All tests were two-tailed, and a p-value < 0.05 indicated statistical significance. To identify predictors of mortality in patients with LC and bacteremia, we selected variables that were significantly different between survivors and non-survivors, and assessed the correlations among the selected covariates. Selection among the highly correlated variables (correlation coefficient ≥ 0.6) was based on clinical interpretations and domain knowledge. A logistic regression model was used to determine the final predictors of mortality, and adjusted odds ratios (ORs) and corresponding 95%

Table 2. Distribution of MDR and non-MDR pathogens isolated from blood culture in our patient cohort.

Pathogen	n	MDR, n (%)	non-MDR, n (%)	*p*
Gram-positive	59 (69.4)	22 (37.3)	37 (62.7)	0.099
MSSA	13 (15.3)	2 (15.4)	11 (84.6)	0.026
MRSA	5 (5.9)	1 (20.0)	4 (80.0)	0.381
Coagulase-negative staphylococci	3 (3.5)	2 (66.7)	1 (33.3)	0.425
Corynebacterium spp.	3 (3.5)	1 (33.3)	2 (66.7)	0.425
Enterococcus spp.	27 (31.8)	17 (63.0)	10 (37.0)	0.014
Streptococcus gallolyticus	4 (4.7)	0 (0)	4 (100.0)	0.129
Actinomycesodontolyticus	4 (4.7)	0 (0)	4 (100.0)	0.129
Gram-negative	26 (30.6)	15 (57.7)	11 (42.3)	0.099
Klebsiella pneumoniae	4 (4.7)	2 (50.0)	2 (50.0)	0.789
Klebsiella -Enterobacter	4 (4.7)	3 (75.0)	1 (25.0)	0.317
E. coli	12 (14.1)	7 (58.3)	5 (41.7)	0.350
Morganellamorganii	2 (2.4)	1 (50.0)	1 (50.0)	1.000
Proteus mirabilis	2 (2.4)	0 (0)	2 (100.0)	0.504
Acinetobacter baumanii	2 (2.4)	2 (100.0)	0 (0)	0.187

MDR: multidrug-resistant; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

Table 3. Biochemical values and the scores in the two groups (MDR and non-MDR infection).

Parameter	MDR infection	non-MDR infection	*p*
CRP (mg/L), median (range)	26.4 (1.5-218.6)	14.8 (1.87-116.4)	0.58
WBC ($\times 10^9$/L), median (range)	6.9 (3.1-37.3)	6.23 (3.3-17.0)	0.35
Neu ($\times 10^9$/L), mean ± SD	8.6 ± 7.1	6.9 ± 4.2	0.293
Lym ($\times 10^9$/L), mean ± SD	1.1 ± 0.4	0.9 ± 0.5	0.158
NLR, median (range)	5.9 (1.7-34.6)	6.5 (2.3-28.5)	0.42
MELD-Na, mean ± SD	24.6 ± 4.8	19.2±5.3	< 0.001
CLIF-C ACLF, mean ± SD	49.6 ± 4.0	41.7 ± 3.4	< 0.001
CLIF-C AD, mean ± SD	74.1 ± 20.4	73.2 ± 17.2	0.841
Child-Pugh class, n (%)			
A	0 (0)	5 (100)	0.008
B	8 (28.6)	20 (71.4)	
C	29 (55.8)	23 (44.2)	

CRP: C-reactive protein; WBC: white blood cells; Neu: neutrophil; Lym: lymphocyte; NLR: neutrophil-to-lymphocyte ratio; MELD-Na: Model of End-Stage Liver Disease-Na; CLIF-C ACLF: Chronic Liver Failure-Consortium Acute-on-Chronic Liver Failure; CLIF-C AD:Chronic Liver Failure-Consortium Acute Decompensation.

Table 4. Values of evaluated parameters in the two groups (MDR and non-MDR infection).

Variables	MDR infection	non-MDR infection	*p*
Outcome, n (%)			
Favorable	24 (63.2)	14 (36.8)	0.002
Unfavorable	13 (27.7)	34 (72.3)	
LOS in days, median (range)	24 (1-92)	19.5 (2-126)	0.598
Active alcohol use, n (%)			
Yes	20 (39.2)	31 (60.8)	0.448
No	17(50.0)	17(50.0)	
Previous cephalosporin therapy, n (%)			
Yes	17 (39.5)	26 (60.5)	0.594
No	20 (47.6)	22 (52.4)	
Esophageal varices, n (%)			
Present	11 (42.3)	15 (57.7)	1
Absent	26 (44.1)	33 (55.9)	
Upper GIT bleeding, n (%)			
Yes	7 (35.0)	13 (65.0)	0.534
No	30 (46.2)	35 (53.8)	
Age, mean ± SD	59.4 ± 10.84	61 ± 8.14	0.449

MDR: multridrug-resistant; LOS: length of stay; GIT: gastrointestinal; SD: standard deviation.

Furthermore, the highest proportion of MDR isolates was registered in patients with Child–Pugh class C disease, which was statistically significant. On the other hand, in patients with Child–Pugh class A disease, no MDR isolates were observed (Table 3).

MDR-associated conditions

Patients' outcome, LOS, active alcohol consumption, preceding cephalosporin therapy, presence of esophageal varices, age older than 60 years, and occurrence of upper gastrointestinal bleeding, relative to whether the isolated pathogen was MDR or not are shown in Table 4. Lethal outcome occurred more frequently in those in whom bacteremia was caused by MDR microorganisms, compared to those patients with non-MDR infection (27.7% *vs*. 72.3%, $p = 0.002$). There was no statistically significant difference between the two groups regarding the other examined variables.

Resistance rates

Absolute and relative resistance rates of the isolated pathogens are shown in Table 5. The observed overall resistance rates to ampicillin, amoxicillin, and amoxicillin–clavulanic acid were 72.9%, 70.5%, and 51.3%, respectively. Furthermore, high cephalosporin resistance rate was noted (ranging from 43.9% to 48.7%),, including fourth-generation agents. Unexpectedly high resistance rates to amikacin and trimethoprim–sulfamethoxazole were also recorded (54.0% and 50.9%, respectively). The observed resistance rates to carbapenems were 20.0% for meropenem, and 14.8% for imipenem. Regarding glycopeptides, the observed resistance to vancomycin and teicoplanin was 15.4% and 45.0%, respectively. Resistance rates of MDR microorganisms were, as anticipated, greater than those of non-MDR microorganisms for the majority of antibiotics tested. Statistically significant differences were found in patients with MDR infection treated with ampicillin (100% *vs*. 47.2%), amoxicillin (97.3% *vs*. 46.3%), amoxicillin–clavulanic acid (77.1% *vs*. 29.3%), ceftriaxone (88.2% *vs*. 18.2%), cefotaxime (85.7% *vs*. 17.9%), ciprofloxacin (67.6% *vs*. 6.8%), ceftazidime (85.2% *vs*. 15.8%), cefepime (85.2% *vs*. 15.4%), meropenem (45.8% *vs*. 0%), and imipenem (40% *vs*. 0%).

Predictors of 30-day lethal outcome

In univariate analysis, the occurrence of encephalopathy, presence of a gram-negative isolate, MDR infection, Child–Pugh class, C-reactive protein (CRP) value, and the neutrophil-to-lymphocyte ratio (NLR) were all found to be associated with lethal outcome. Multivariate analysis was used to identify variables independently associated with lethal outcome. MDR infection (OR = 6.198, 95%, CI = 2.326–17.540, $p = 0.006$) and the NLR (OR = 1.181, 95% CI = 1.043–1.337, $p = 0.009$) were found to be independent

Table 5. Absolute and relative resistance rates of isolated pathogens to antibiotics.

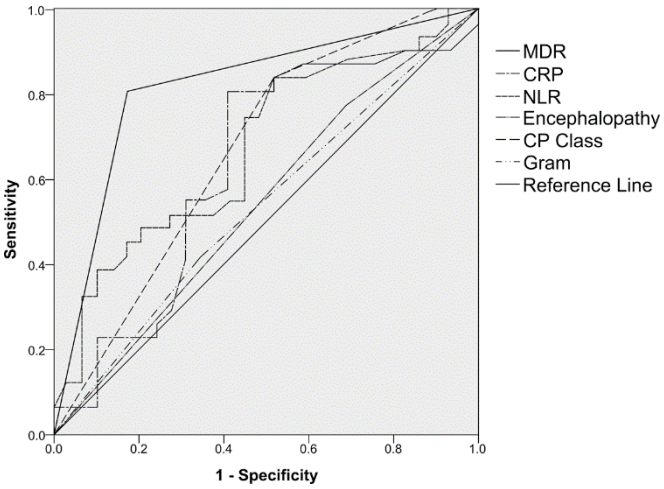
Antibiotic	Gram-positive isolate (n = 59)		Gram-negative isolate (n = 26)		Total (n = 85)		*p*	Overall (n = 85)
	MDR (n = 22)	non-MDR (n = 37)	MDR (n = 15)	non-MDR (n = 11)	MDR (n = 37)	non-MDR (n = 48)		
AMP	20/20 (100)	15/30 (50.0)	14/14 (100)	2/6 (33.3)	34/34 (100)	17/36 (47.2)	< 0.001	51/70 (72.9)
AMX	21/22 (95.5)	15/33 (45.5)	15/15 (100)	4/8 (50.0)	36/37 (97.3)	19/41 (46.3)	< 0.001	55/78 (70.5)
AM-CL	16/20 (80.0)	9/33 (27.3)	11/15 (73.3)	3/8 (37.5)	27/35 (77.1)	12/41 (29.3)	< 0.001	39/76 (51.3)
MER	6/9 (66.6)	0/23 (0)	5/15 (33.3)	0/8 (0)	11/24 (45.8)	0/31 (0)	< 0.001	11/55 (20.0)
IMI	3/6 (50.0)	0/25 (0)	5/14 (35.7)	0/9 (0)	8/20 (40.0)	0/34 (0)	< 0.001	8/54 (14.8)
CFTX	19/22 (86.4)	7/33 (18.9)	11/15 (73.3)	1/11 (9.1)	30/34 (88.2)	8/44 (18.2)	< 0.001	38/78 (48.7)
CEFO	13/22 (59.1)	6/30 (16.2)	11/15 (73.3)	1/9 (11.1)	24/28 (85.7)	7/39 (17.9)	< 0.001	31/67 (46.3)
CFTA	12/22 (54.5)	5/29 (13.5)	11/15 (73.3)	1/9 (11.1)	23/27 (85.2)	6/38 (15.8)	< 0.001	29/65 (44.6)
CEFP	12/22 (54.5)	5/30 (16.7)	11/15 (73.3)	1/9 (11.1)	23/27 (85.2)	6/39 (15.4)	< 0.001	29/66 (43.9)
AMI	13/22 (59.1)	5/17 (29.4)	9/13 (69.2)	0/7 (0)	22/26 (84.6)	5/24 (20.8)	< 0.001	27/60 (54.0)
GEN	7/10 (70.0)	0/21 (0)	2/10 (20.0)	0/7 (0)	9/20 (45.0)	0/24 (0)	< 0.001	9/44 (20.5)
CIP	16/19 (84.2)	1/34 (2.9)	7/15 (46.7)	2/10 (20.0)	23/34 (67.6)	3/44 (6.8)	< 0.001	26/78 (33.3)
TEI	7/19 (36.8)	5/14 (35.7)	5/6 (83.3)	1/1 (100.0)	12/25 (48.0)	6/15 (40.0)	0.747	18/40 (45.0)
VAN	3/15 (20.0)	0/9 (0)	1/2 (50.0)	-	4/17 (23.5)	0/9 (0)	0.263	4/26 (15.4)
T-SX	8/10 (80.0)	6/25 (24.0)	10/11 (90.9)	3/7 (42.9)	18/21 (85.7)	9/32 (28.1)	< 0.001	27/53 (50.9)
LIN	3/22 (13.6)	0/5 (0)	0/1 (0)	-	3/4 (75.0)	0/4 (0)	0.048	3/9 (33.3)
TIG	1/2 (50.0)	0/3 (0)	0/1 (0)	0/1 (0)	1/3 (33.3)	0/4 (0)	0.429	1/7 (14.3)
COL	1/1 (100)	-	0/2 (0)	0/0	1/3 (33.3)	0/0 (0)	1.000	1/3 (33.3)

AMP: ampicillin; AMX: amoxicillin; AM-CL: amoxicillin-alavulanic acid; MER-meropenem; IMI-imipenem; CFTX: ceftriaxone; CEFO: cefotaxime; CFTA-ceftazidime; CEFP- cefepime; AMI-amikacin; GEN: gentamicin; CIP: ciprofloxacine; TEI-teikoplanin; VAN: vankomycin; T-SX: trimethoprim-sulfametoxazole; LIN-linezolid; TIG: tigecycline; COL: colistin.

predictors of 30-day lethal outcome in our study (Table 6).

Additionally, the generated ROC curve implied that the presence of MDR isolates, compared to other evaluated variables, was advantageous in discriminating between survivors and non-survivors in our group of patients (Figure 1).

Figure 1. The ROC curve comparing the ability of the occurrence of encephalopathy, gram-negative pathogens, MDR isolates, Child–Pugh class, CRP values, and NLR to discriminate between survivors and non-survivors among patients with liver cirrhosis and bacteremia;the areas under the curve were 0.648, 0.583, 0.817, 0.658, 0.696, and 0.738, respectively.



Discussion

Bacteremia is more common in patients with cirrhosis than in the general population. The mean age in our patient cohort was 60 years, which is in concordance with studies conducted by Bartoletti *et al.,* as well as Smith *et al*. [11,14]. The mean age did not differ between those who developed MDR infection and those who did not, which is similar to the findings of Alexopoulou *et al.* and Smith *et al.* [14,15]. The majority of our patients were male, and LC was most commonly the result of alcohol abuse. Previous studies have revealed that alcoholic LC is more common in men than in women, which is in concordance with our results [11]. Studies conducted thus far have not demonstrated an association between active alcohol use prior to hospitalization and the presence of MDR isolates in patients who develop bacteremia. A study by De Roux *et al.* showed that there was no difference in patterns of bacterial resistance between patients with bacterial community-acquired PNA who were abusing alcohol at the time of admission, and those who were not, which is in concordance with our results. As expected, hepatic comorbidities were more common in the group of "drinkers" compared to that in the group of "non-drinkers". On the other hand, patients who abuse alcohol presented with more severe forms of PNA [16]. A potential explanation for this observation lies in compromised immune function, as a result of alcohol abuse [17]. Antibiotic resistance is a growing problem in our country as well as worldwide. Patients with cirrhosis are particularly susceptible to complications caused by MDR infection, which results in increased mortality rates. While few studies have demonstrated that the LOS is increased in patients with MDR bacterial infections, our study failed to confirm these findings in patients with LC and MDR bacteremia [18].

Mortality rates in patients with LC and infections range from 9% to 29%, depending on the study [19]. In our cohort, lethal outcome occurred in 47.4% of the patients. Overall, gram-positive bacteria were more commonly isolated (69.4%), which is in contrast to the results of many other previously performed relevant studies [14,20,21]. In addition, Shizuma *et al.* demonstrated that MRSA is the most commonly isolated gram-positive pathogen in patients with cirrhosis, while in our study *Enterococcus* spp. was predominant. Furthermore, in the study by Shizuma *et al.*, *Enterococcus* spp. was the 4th most common isolate [20]. In our study, the second and third most commonly isolated pathogens were MSSA and *E. coli*, respectively. Cheol-In Kang *et al*. also found *S. aureus* to be the most commonly isolated gram-positive pathogen [21]. Among gram-negative pathogens, the most commonly isolated bacteria were *E. coli*, which is in line with the results of previously conducted studies

Table 6. Risk factors for 30-day lethal outcome occurrence in LC patients with bacteremia.

Risk factor	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Encephalopathy	1.725 (1.130-2.632)	0.012	1.582 (0.682-3.673)	0.286
Gram negative isolate	2.691 (1.041-6.959)	0.041	1.302 (0.221-7.655)	0.771
MDR infection	4.484 (1.790-11.229)	0.001	6.198 (2.326-17.540)	0.006
CP - class	6.462 (2.372-11.604)	< 0.001	4.169 (0.825-21.060)	0.084
CRP	1.023 (1.002-1.044)	0.029	1.022 (0.988-1.057)	0.208
NLR	1.126 (1.037-1.223)	0.005	1.181 (1.043-1.337)	0.009

* Hosmer-Lemeshow goodness-of-fit test $p = 0.590$; OR: odds ratio; 95% CI: 95% confidence interval; MDR-multidrug-resistant; CP-class: Child-Pugh class; CRP-C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio.

[11,22,23]. These data support the proposed pathophysiological mechanism of bacteremia in patients with LC. While bacterial translocation through the gastrointestinal wall is present to a certain extent in healthy individuals as well, it is augmented in patients with cirrhosis, due to severely altered pathophysiology of portal and systemic blood flow and gastrointestinal transit time. In addition, altered microbiota composition and function, together with the immune system malfunction, contribute to increased incidence of bacterial infections in patients with LC. One should bear in mind the possibility of yeast infections, as well as those caused by commensal pathogens, particularly in this specific group of patients [24,25]. In our study cohort, coagulase-negative staphylococci, *Corynebacterium* spp., *Actinomyces odontolyticus,* and *Acinetobacter baumannii* were isolated in 3 (3.5%), 3 (3.5%), 4 (4.7%), and 2 (2.4%) patients, respectively. Fungi were not isolated, mostly due to the institutional deficiency of yeast-specific media.

Increasing antibiotic resistance is a major public health issue worldwide. Current guidelines recommend third-generation cephalosporins as the first-line empiric therapy for the majority of infections occurring in patients with cirrhosis [26]. The resistance ratesto cefotaxime and ceftazidime in our study were slightly lower than those previously reported, but still unacceptably high to consider these agents as first-line empirical treatment option (46.3% and 44.6%, respectively). Furthermore, even more concerning is the fact that 43.9% of all pathogens were resistant to fourth-generation cephalosporins.

Finally, in our study, it has been shown that MDR infection and NLR, are the most significant predictors of a lethal outcome in patients with cirrhosis and bacteremia. Therefore, sharing experiences about the pattern of MDR is of great importance for tailoring further treatment strategies. Several studies have investigated the importance of the NLR in predicting outcomes in patients with decompensated LC and concluded that the NLR is a reliable, readily available, and objective marker of long-term mortality risk in patients with cirrhosis, and may serve as surrogate marker of immune dysregulation in cirrhosis [27].

Limitations of the study

We are aware of the limitations of this study. This was a single-center study with all Caucasian subjects, with a relatively small sample size. Nevertheless, this is the first step in collecting national data, which would enable tailoring of the local guidelines and improvement in patient care.

Conclusions

The presence of infection, especially one caused by MDR pathogens, in patients with LC is associated with poor prognosis and increased mortality. Timely administration of appropriate antibiotics may contribute to better outcome. Therefore, it would be of great value to identify a model which would accurately identify patients who are in greater risk of developing MDR infection. This would allow us to initiate appropriate antibiotic therapy earlier. Hence, this would lead to a decrease in the overall mortality associated with these difficult-to-treat infections. Future studies should focus on establishing the scores and models that may accurately predict the presence of MDR organisms in this group of patients. In turn, this would lead to earlier appropriate treatment and potentially improved survival.

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Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Supplementary Table 1. Child-Pugh score.

Factor	Child-Pugh score		
	1 point	**2 points**	**3 points**
Total bilirubin (µmol/L)	< 34	34-50	> 50
Serum albumin (g/L)	> 35	28-35	< 28
INR	< 1.7	1.7-2.3	> 2.3
Ascites	None	Mild	Moderate to severe
Encephalopathy	None	Grade I-II	Grade III-IV
	Class A	**Class B**	**Class C**
Points	5-6	7-9	10-15
1-year survival	100%	80%	45%

INR: international normalised ratio.

Supplementary Table 2. MELD-Na score and 90-day mortality prediction.

MELD-Na score	90-day mortality
< 17	< 2%
17-20	3-4%
21-22	7-10%
23-26	14-15%
27-31	27-32%
≥ 32	65-66%

Supplementary Figure 1. Model of End-Stage Liver Disease-Na (MELD-Na) score.