ORIGINAL ARTICLE

Infectious Complications in Patients with Liver Cirrhosis

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Abstract. Introduction: *Liver cirrhosis (LC) represents a major public health problem, with high morbidity and mortality rates.* ***Materials and methods:*** *We conducted an observational, descriptive, retrospective study in which we included 198 patients with LC hospitalized in the Clinical Emergency Hospital Bucharest over a period of 2 years. They were divided into two primary groups: group A (83 patients with CH who had an infectious complication) and group B (115 patients with LC who did not have an infectious complication).* ***Results****: The predominant etiology of LC was excessive alcohol consumption, followed by viral infections, specifically hepatitis C virus and hepatitis B virus. The primary factors that contributed to the development of infectious complications were the presence of ascitic fluid, hypoalbuminemia, and a personal medical history of chronic kidney disease. The main infectious complications identified were bronchopneumonia (39%), urinary tract infections (27%), bacteremia (24%), Clostridioides difficile colitis (7%), spontaneous bacterial peritonitis (2%), and pleural empyema (1%). The average hospitalization duration and mortality rate were both twice as long for patients in group A as they were for patients in group B.* ***Conclusions:*** *In summary, infectious complications are a significant cause of morbidity and mortality in patients with LC and necessitate multidisciplinary management.*

Keywords*: hepatic cirrhosis; infectious complications; diagnosis; prognosis; mortality rate*

1. INTRODUCTION

Hepatic cirrhosis (HC) represents a major public health problem, with high morbidity and mortality rates. In 2019, 2.4% of all deaths worldwide were attributable to HC [1,2]. The increasing prevalence of obesity and alcohol consumption, in parallel with advances in the management of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, have influenced the changing epidemiology of HC [1,2]. Although viral hepatitis remains the leading cause of HC worldwide, non-alcoholic steatohepatitis (NAFLD) and alcohol-related HC are on the rise in several regions of the world [1,2]. The latest epidemiological data estimate that the number of HC-associated deaths will increase over the next decade [1,2]. Therefore, it is imperative to intensify efforts to facilitate primary prevention, early detection, and treatment of liver disease and improve access to health care [2]. The global burden of HC is increasing. In 2017, there were 520,000 new cases of HC, and in 2019, the condition led to 1.48 million deaths, marking an 8.1% increase [2].

HC patients have a two- to three times higher risk of developing bacterial infections and sepsis than other hospitalized patients [3].

Approximately 32-40% of patients hospitalized with HC develop bacterial infections either prior to admission or during hospitalization [3]. 32-50% of infectious complications are community-acquired, 25-41% are associated with medical care, and 25-37% are nosocomial [3]. The most common infections in patients with HC are spontaneous bacterial peritonitis (SBP, 20-35%), urinary tract infections (14-41%), pneumonia (8-17%), spontaneous bacteremia (8-21%), and tegumentary and soft tissue infections (6-13%). Specific type of infections can be very heterogeneous depending on local epidemiology [3].

Fungal infections are rarer in the community (4-7% of community infections), but are more common in hospital settings and in patients with alcoholic hepatitis [5]. Invasive candidiasis is associated with risk factors such as previous antibiotic administration, endoscopic procedures, and use of central venous catheters [5]. The most common multidrug-resistant (MDR) bacteria in HC patients are extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus*, vancomycin- resistant enterococci, carbapenemase-producing *Enterobacteriaceae* and carbapenem-resistant *Acinetobacter baumannii* [5]. Clinical predictors of infections due to MDR microorganisms are important in the clinical practice, as they can guide the selection of empiric antibiotic treatment. Among them, the most important are hospitalization for at least two days in the last three months, antibiotic use in the last month, and contact with an area with a high prevalence of MDR bacteria [5].

Lower respiratory tract infections and pneumonia are associated with the highest risk of mortality in HC patients [6]. These patients are more susceptible to pneumonia, have more complications, and develop bacteremia more often than non-HC patients [6]. *Streptococcus pneumoniae* is the most common etiologic agent isolated in community-acquired pneumonia [6]. Thus, pneumococcal vaccination is recommended as a preventive measure, despite reduced immunologic responses and accelerated antibody decline in HC patients [6].

Skin and soft tissue infections can be caused by Gram-positive bacteria penetrating the edematous skin, as well as by translocated Gram-negative bacteria. They are often recurrent, progress with renal failure, and are associated with a mortality of approximately 20% [7].

Patients with HC have an increased risk of infective endocarditis compared to the general population [8]. Infective endocarditis in patients with HC is predominantly nosocomial in origin, most commonly caused by *Staphylococcus aureus*, *β-hemolytic streptococci,* and *Enterococcus* species, predominantly affecting the aortic valves. In evolution, endocarditis is associated with renal failure in 60% of cases and mortality rates of approximately 50% [8].

Bacterial meningitis is a rare complication in HC (<1%), often with an atypical presentation driven by a spectrum of Gram-negative pathogenic germs. In most cases, it is associated with bacteremia, and mortality rates exceed 40% [9].

Patients with HC and infectious complications have four times higher mortality rates compared to patients with infectious conditions but without HC. The most common infections leading to death are bacterial infections, mainly respiratory tract infections, SBP, and bacteremia [10]. Because of excessive inflammation associated with HC, organ failure frequently occurs in the absence of septic shock. Three main factors determine the mortality of bacterial infection in cirrhosis, regardless of etiology: severity of underlying liver disease, concomitant renal failure, and persistence of infection because of antimicrobial resistance [10].

Bacterial infections are a particularly important complication in patients with cirrhosis, as they are associated with an increased risk of mortality. Early detection and effective treatment can improve the prognosis of these patients. The increasing prevalence of MDR bacteria is perhaps the most serious threat facing clinicians in the

management of cirrhosis today. Therefore, it is imperative to develop new strategies to improve diagnosis and treatment: development of new techniques for rapid identification of strains responsible for infections and their susceptibility to antibiotics; development of biomarkers to detect infections in early stages in asymptomatic patients and to determine the duration of treatment; discovery of new broad-spectrum antibiotics; development of strategies to prevent organ failure [10].

2. MATERIALS AND METHODS

We conducted an observational, descriptive, retrospective study, in which we included 198 patients with HC hospitalized in the Clinical Emergency Hospital of Bucharest (Romania) over a period of 2 years (01.01.2021 - 01.01.2023). The study was approved by the Ethics Committee of the Clinical Emergency Hospital of Bucharest (approval no. 798/29.01.2024).

The inclusion criteria were:

- Diagnosis of HC based on clinical and paraclinical criteria.
- Patients who have signed an informed consent form, agreeing to the processing of personal data and participation in medical education.

The exclusion criteria were:

- patients whose observation sheets did not provide information about the variables tracked in the study.
- patients who have not signed an informed consent.

The data needed for the study were collected from the observation sheets and the computer system of the hospital and were systematized in an Excel database. Following data collection, the patients were divided into two groups: group A (83 patients with HC who had an infectious complication) and group B (115 patients with HC without an infectious complication).

The variables followed in the study were age, gender, HC etiology, Child-Pugh class, smoking status, alcohol consumption, comorbidities such as obesity, hypertension, chronic heart failure (CHF), chronic coronary syndrome (CCS), diabetes mellitus, chronic kidney disease (CKD) or chronic obstructive pulmonary disease (COPD), complications such as infections and the implicated pathogen, ascites syndrome, esophageal varices, hepatic encephalopathy or hepatorenal syndrome, serum values of some laboratory tests (complete blood count, total bilirubin, transaminases, alkaline phosphatase, gamma-glutamyl transferase, erythrocyte sedimentation rate, C-reactive protein, urea, creatinine, albumin, International Normalized Ratio, sodium, potassium), outpatient treatment, antibiotic treatment during hospitalization, length of hospitalization and death rate of these patients.

Data were statistically analyzed in Microsoft Excel, and the results were presented in the form of tables and graphs.

3. RESULTS

In our study, we included 198 HC patients who were hospitalized for various conditions between 2021-2023. As previously mentioned, infectious complications were present in 83 of these patients, respectively 42% of the entire study cohort (Figure 1). Regarding the distribution of patients by sex groups, we identified a predominance of male sex (72% versus 28%). Thus, of the entire study cohort, 143 patients were male, and 55 patients were female. Furthermore, male predominance was preserved in both group A and group B (Figure 2). Thus, of the total 83 patients with HC and infectious complications, 61 were male and 22 were female (Figure 2).

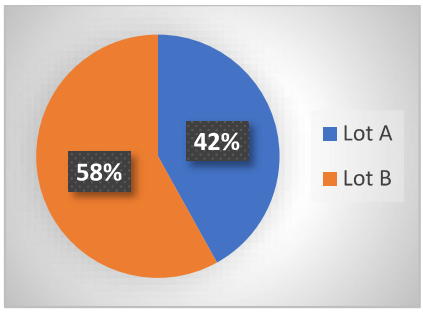

Figure 1. Distribution of patients included in the study according to the presence of infectious complications (Group A patients with HC and infectious complications; Group B patients with HC, without infectious complications).

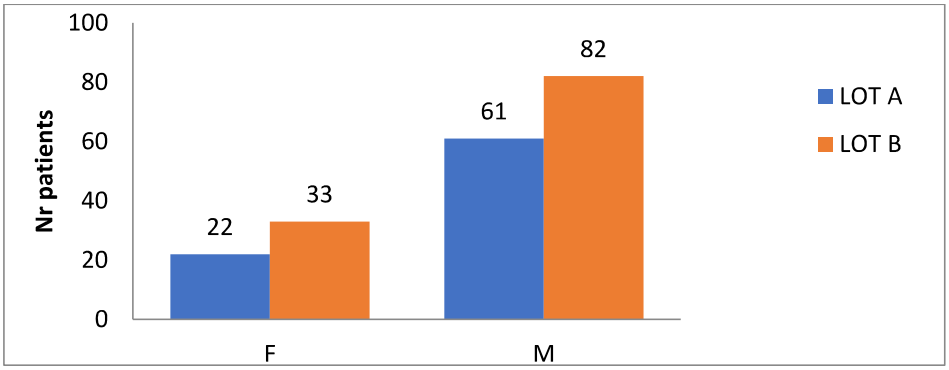

Figure 2. Distribution of patients by sex.

The patients included in the study ranged in age from 32 to 93 years, with an average age of approximately 64 years (Table 1). No significant differences in age were observed between group A and group B.

Table 1. Distribution of patients by age.

Variable	Group A/ infectious complication	Group B/without infectious complication
Minimum age (years)	34	32
Average age (years)	64	64
Maximum age (years)	92	93

The most common etiology of HC in our study was alcohol-related cirrhosis (AC, 59% of all patients). Moreover, this predominance of AC etiology was maintained in both group A (50 patients, 60.24%) and group B (67 patients, 58.26%) (Figure 3). Of the patients with AC who developed an infectious complication, 90% (45 patients) were male. HC secondary to HCV infection occurred in 14% of the total number of cases, respectively 16.86% of the cases in group A, affecting females and males equally. In contrast, HC secondary to HBV infection was less common, in 5% of cases respectively (3 patients in group A, 3.61%, and 7 in group B, 6.08%). Another important cause was the association between HBV or HCV infection and excessive alcohol consumption. This represents 8% of cases in group A and 6% of cases in group B. Also, other etiologies that were found in our study were primary biliary cholangitis, secondary biliary cirrhosis, nonalcoholic steatohepatitis, and idiopathic HC.

To assess the severity and prognosis of patients with HC, we calculated the Child-Pugh score. After statistical analysis, we identified that 47% of patients had Child-Pugh class B, 29% had Child-Pugh class C, and 24% had Child-Pugh class A (Figure 4 and Table 2). Most patients in both group A (36 patients, 43.37%) and group B (93

patients, 80.86%) were categorized as class B Child-Pugh. For Child-Pugh class C, the percentage of patients with at least one associated infectious complication predominated (Figure 4).

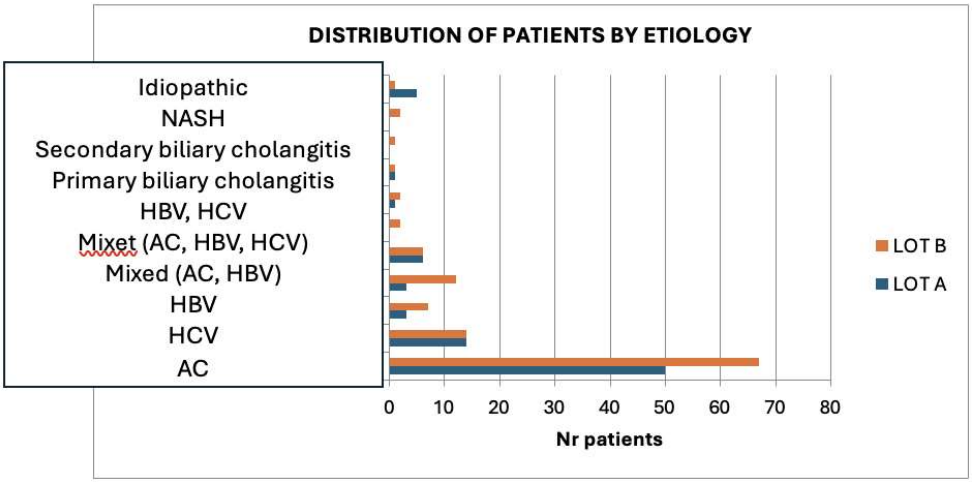

Figure 3. Distribution of patients by etiology of hepatic cirrhosis (NASH - nonalcoholic steatohepatitis, HBV – hepatitis B virus, HCV - hepatitis C virus, AC – alcohol-related cirrhosis).

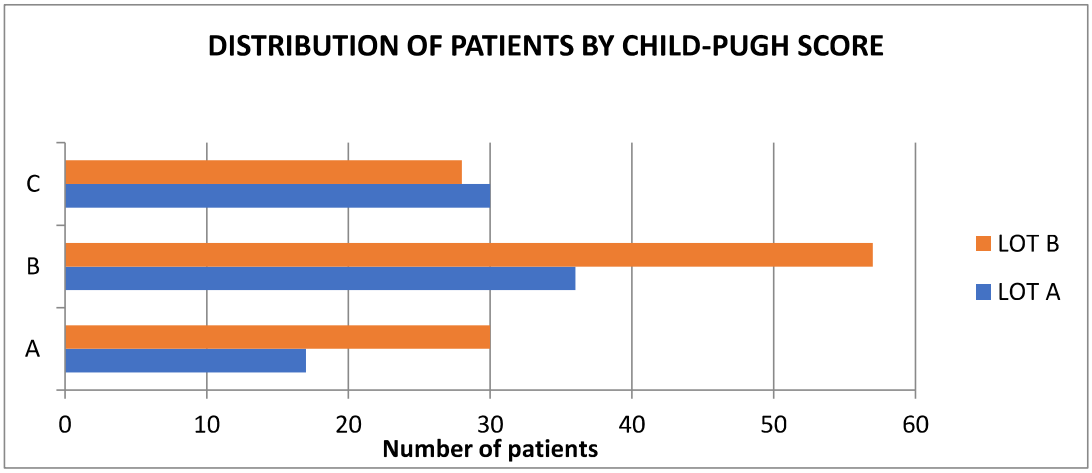

Figure 4. Distribution of patients by Child-Pugh class.

Table 2. Distribution of patients by Child-Pugh class.

Child class	Number of patients	Percentage
A	47	24%
B	93	47%
C	58	29%
Total	198	

We further tried to identify the parameters that influenced the risk of progression to different infectious complications. We thus identified that 47%, respectively 93 of HC patients were smokers. Of these, 39.78% (37 patients) developed an infectious complication, such as bronchopneumonia, sepsis, or a lower urinary tract infection. At the same time, the presence of infection was also observed in patients who were non-smokers or ex-smokers who had other associated risk factors.

In terms of alcohol consumption, 71% of the patients included in the study reported alcohol consumption, the majority of whom were male (N=122). 68.67% of the patients

in group A were alcohol consumers, and 73.04% in group B.

Of the total study group, 39% of the patients (77 patients) suffered from obesity. We identified no significant differences in the frequency of obesity between group A with infectious complications and group B without infectious complications (36.14% versus 40.86%).

Type 2 diabetes mellitus was present in 30% of all patients included in the study (60 patients). Of these, 35% developed infectious complications, especially in patients with toxic-nutritional HC and HC secondary to HCV infection (Figure 3.8). Among the 138 patients without diabetes mellitus, 62 (44.92%) developed infections. Thus, we did not observe a significant difference in the risk of developing an infectious complication between patients with HC and diabetes mellitus compared to those with HC but without diabetes mellitus.

Of the 198 patients included in our study, a very high proportion, respectively 151 patients (79%) had associated arterial hypertension. Moreover, all patients who made up our study cohort had associated different degrees of CHF, while only 57 patients (29%) had associated CKD, 46 patients (23.23%) had associated CCS, and 12 patients (6.06%) had associated COPD. Of these comorbidities, the only one that was found to increase the risk of infectious complications, with a higher proportion in group A compared to group B, was CKD (36.13% in group A versus 0.23% in group B). Regarding CHF, the distribution of patients according to NYHA class is shown in Figure 5, as follows: 84 patients had NYHA class I (42%), 65 patients had NYHA class II (33%), 36 patients NYHA class III (18%) and 13 patients, NYHA class IV (7%). Thus, no significant differences were observed between CHF severity and the risk of developing an infectious complication.

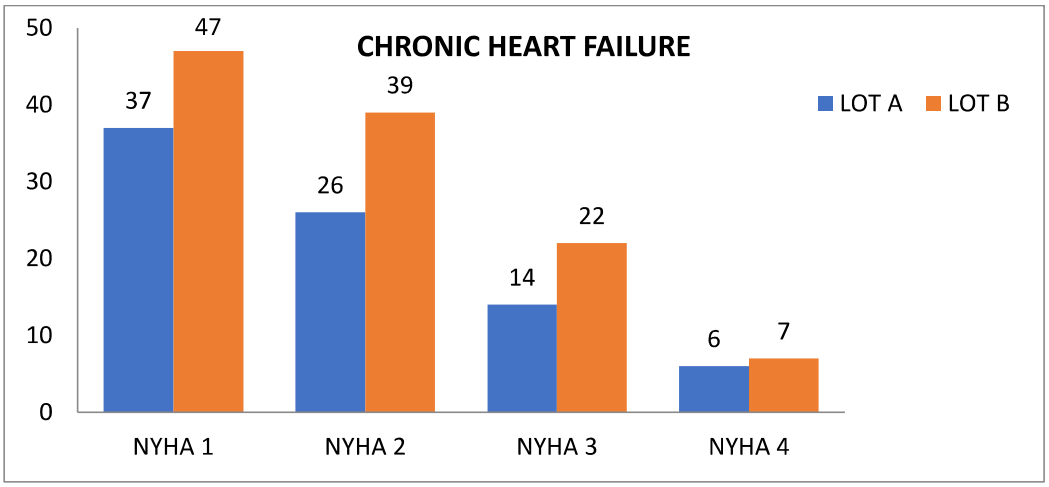

Figure 5. Relationship between CHF and the development of an infectious complication.

We further analyzed the clinical signs of parenchymal or vascular decompensation of HC, respectively, the presence of ascites, esophageal varices, or hepatic encephalopathy. Thus, we observed that the majority of patients included in our study had ascites (150 patients, 75%) or esophageal varices (153 patients, 78%), regardless of whether or not infectious complications were associated. Regarding esophageal varices, in both group A and group B, we most frequently identified grade I or II varices. The prevalence of hepatic encephalopathy was also considerable, 30% (61 patients). This percentage may be underestimated, however, given the frequent cases of hepatic encephalopathy with subtle symptoms that are difficult to identify clinically. Of the patients with hepatic encephalopathy, approximately 34% died during

hospitalization and 44% within two years of initial presentation.

In the last part of our study, we comparatively evaluated the median serum values of some biological markers between the two groups (Table 3). The significant differences we identified were the presence of leukocytosis, with peak values of up to 60,920/mm^3 in patients in group A (normal mean leukocyte values in group B) and twice higher mean C-reactive protein values in group A compared to group B (56 mg/dL versus 22 mg/dL).

Table 3. Comparative analysis of median values of biological parameters between the two study groups (GGT - gamma-glutamyl transferase, AST - aspartate aminotransferase, ALT – alanine aminotransferase, ESR - erythrocyte sedimentation rate, CRP - C-reactive protein).

Biological marker	Group A, N=83 Median values	Group B, N=115 Median values
Hemoglobin	11 (3.6-15.5) g/dL	10.3 (3-16) g/dL
Thrombocytes	139.000 (4.000-123.800)/ mm^3	126.500 (10.000-652.000)/ mm^3
Leukocytes	10.000 (1.000-60.920)/ mm^3	7500 (1.680-16.700)/ mm^3
Total bilirubin	1.8 (0.12-40) mg/dL	1.8 (0.27-21) mg/dL
GGT	150 (14-1293) U/L	124 (10-1380) U/L
Alkaline phosphatase	121.5 (31-583) U/L	112 (27-1245) U/L
Creatinine	0.99 (0.28-10) mg/dL	0.87 (0.31-12) mg/dL
Urea	67 (5-425) mg/dL	43.5 (6-298) mg/dL
Sodium	135 (105-149) mmol/L	136 (116-147) mmol/L
Potassium	4.2 (2.2-6.9) mmol/L	4.2 (2.5-7.8) mmol/L
Albumin	2.72 (1-4.3) g/dL	2.77 (1-4.7) g/dL
INR	1.47 (0.85-6.9)	1.45 (0.97-3.62)
AST	60 (2.2-810) U/L	49 (11-579) U/L
ALT	33 (8-397) U/L	29 (8-450) U/L
ESR	37.5 (10-100) mm/h	26 (3-72) mm/h
CRP	56 (4-280) mg/dL	22 (0.2-237) mg/dL

Of the total patients included in the study, 75% (149 patients) had associated hypoalbuminemia (Figure 6) and 58% (115 patients) thrombocytopenia, with no significant differences in the proportion of these biological abnormalities between the two study groups.

In terms of serum ionogram, hyponatremia was slightly more prevalent in group A compared to group B (54% versus 42%).

The most common infectious complications identified were bronchopneumonia (39%), urinary tract infections (27%), bacteremia (24%), *Clostridioides difficile* colitis (7%), SBP (2%) and pleural empyema (1%) (Figure 6). The pathogens implicated in the occurrence of bronchopneumonia were both several Gram-positive bacteria, such as *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus*, and several Gram-negative bacteria, such as *Klebsiella*

pneumoniae and *Escherichia coli*. We also identified a fungal infection by *Candida albicans* (Figure 7). These germs were responsible for 20% of in-hospital deaths in group A patients.

Lower urinary tract infections accounted for 54% of infections in women and 22% of infections in men. The microorganisms implicated in their pathogenesis were *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecium, Enterobacter,* and *Staphylococcus epidermidis*. Also, 20% of patients with lower urinary tract infections died in the hospital (11.6% of all deaths).

Sepsis is a severe complication of HC, occurring in a significant number of patients included in our study, predominantly in male, alcohol-using patients. Laboratory investigations revealed the following pathogens responsible for sepsis: *methicillin-resistant Staphylococcus aureus, Streptococcus pneumoniae, Klebsiella pneumoniae, Escherichia coli, Enterococcus faecium, Acinetobacter baumannii, Pseudomonas aeruginosa, Proteus mirabilis,* and *Candida albicans* (Figure 7). Sepsis was associated with increased mortality, more than half of these patients died in the hospital. Also, deaths secondary to sepsis accounted for 28% of all deaths recorded in patients in our study.

The patients receiving outpatient treatment with antibiotics and proton pump inhibitors had a higher risk of *Clostridioides difficile* colitis. SBP and pleural empyema were observed in a small proportion in our study, the germs involved being *Enterococcus faecium* and *Klebsiella pneumoniae*.

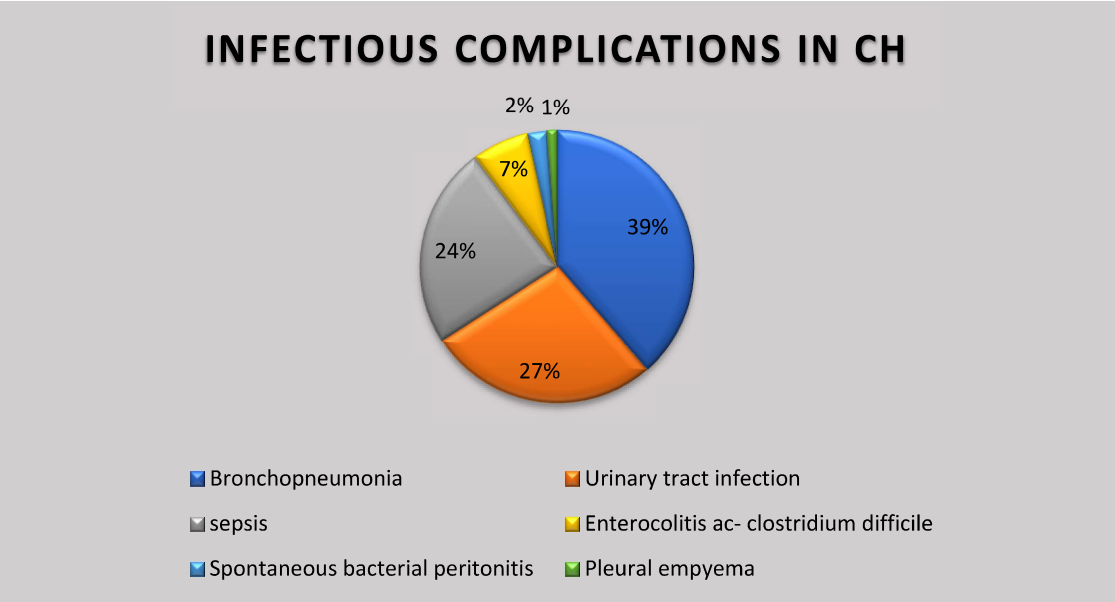

Figure 6. Infectious complications in patients with HC.

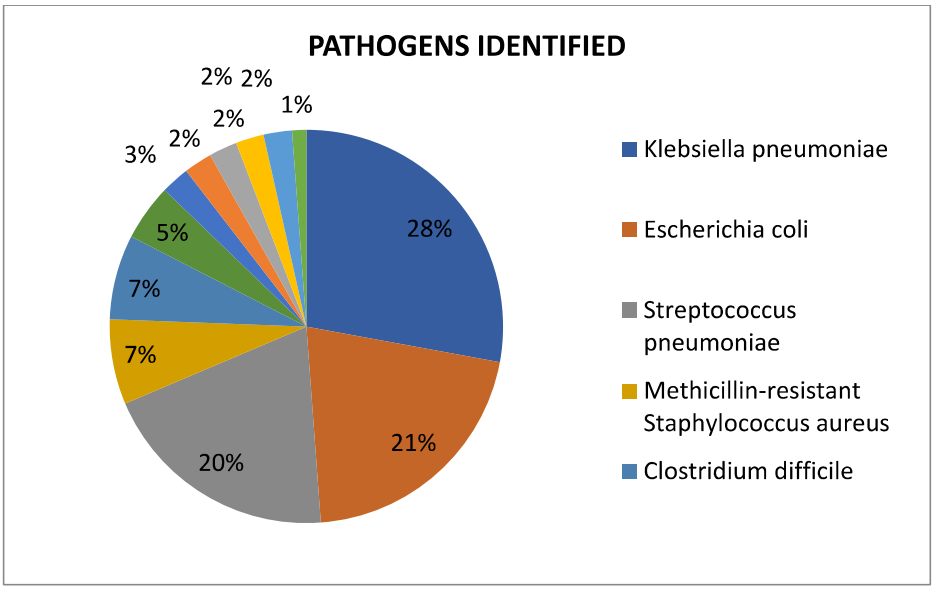

Figure 7. Pathogenic microorganisms identified in patients with HC and infectious complications.

The following antibiotics were used to treat infectious complications in HC patients:

- Ceftriaxone in 28% of cases.
- Piperacillin/tazobactam in 14% of cases.
- Fluoroquinolone in 13% of cases.
- Vancomycin in 10% of cases.
- Meropenem in 10% of cases.
- Linezolid in 5% of cases.
- Fosfomycin in 9% of cases.
- Other antibiotics: amoxicillin/clavulanic acid, ampicillin/ sulbactam, trimethoprim/sulfamethoxazole, cefoperazone, ceftazidime, tigecycline (Figure 8).

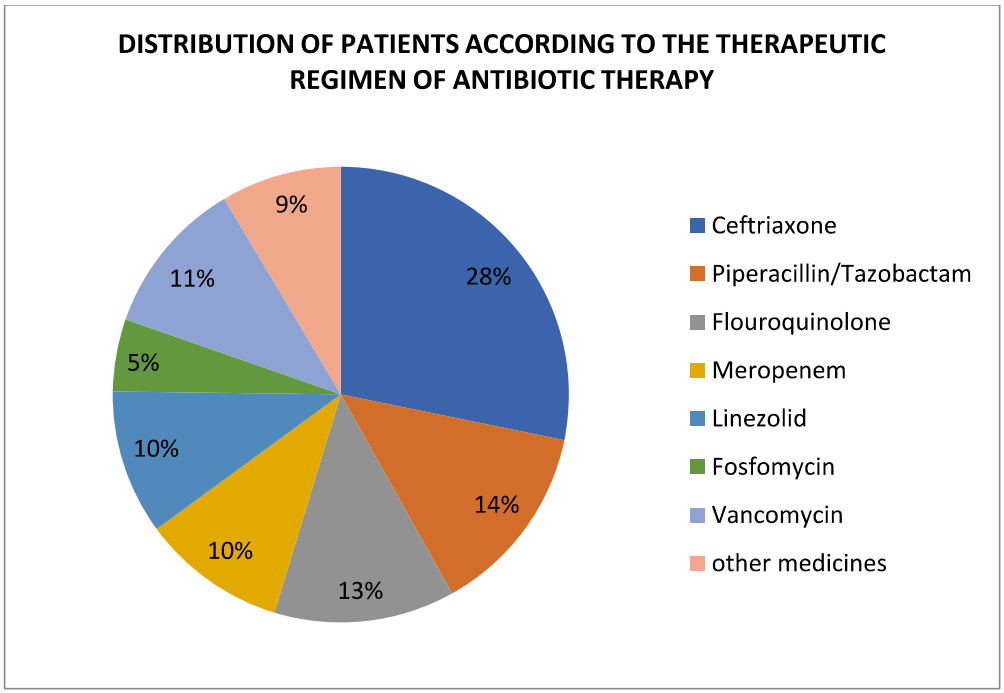

Figure 8. Classes of antibiotics used in patients with HC and infectious complications.

We also followed the influence of outpatient treatment on the decompensation of HC and the development of infectious complications by comparative analysis between the two groups of patients. Non-selective beta-blockers were used by 155 patients (78.28%) of the entire study cohort, 57 patients (68%) in group A and 98 patients (85%) in group B. We thus identified the protective role of non-selective beta-blockers in preventing infectious complications (relative risk<1). In contrast, outpatient treatment with proton pump inhibitors (PPI) (RR>1) increased the risk of infections among patients included in the study. 50 patients (60%) in group A and 62 patients (53%) in group B reported PPI use.

The administration of antibiotics also increased patients' susceptibility to developing infections (RR>1). Of the 45 patients who reported outpatient antibiotic use, 30 patients presented with an infectious complication. As for antibiotics, they did not influence the risk of infectious complications.

Only 13.25% of patients in group A received outpatient treatment with lactulose and rifaximin. In group B, the prevalence of the use of these drugs was much higher, i.e., 46.95% of the patients used lactulose and 59.13% used rifaximin. We can thus conclude that these classes of drugs have a potential protective role against infectious complications in HC patients.

Figure 9 compares the deaths in the two groups of patients, with a significantly higher mortality rate in group A compared to group B (30% versus 15.6%). Of the 25 patients who died in group A, 14 fell into the Child-Pugh class B, 9 into the Child-Pugh class C, and 2 into the Child-Pugh class A. Half of these patients also developed sepsis. We allocated the patients in group B as follows: 11 patients to class C Child-Pugh and 7 patients to class B Child-Pugh.

In terms of average length of hospitalization, patients in group A had twice the length of hospitalization compared to patients in group B (11 days versus 5 days).

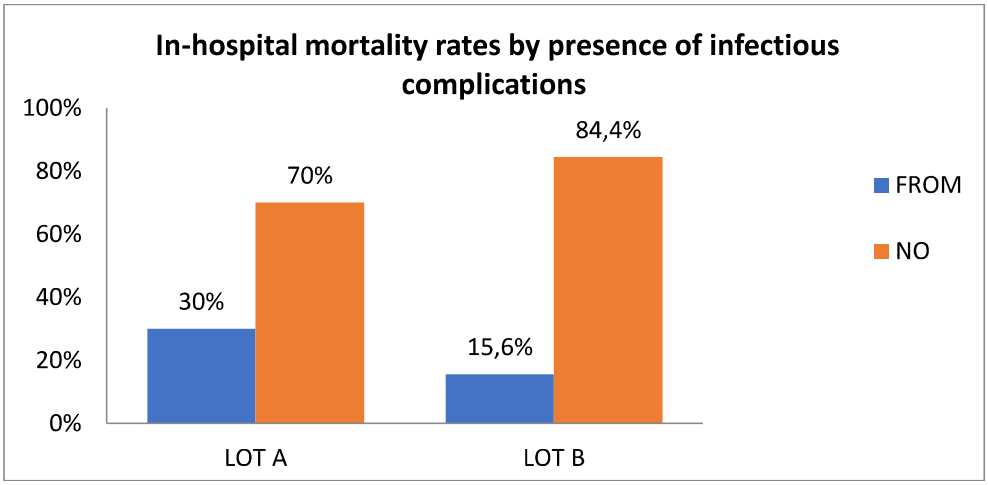

Figure 9. In-hospital mortality rate.

In our study, we identified 129 deaths within two years of the first hospitalization, 43 of which were in-hospital within a few days of presentation.

4. DISCUSSION AND CONCLUSIONS

HC is a globally prevalent condition with multiple etiologies, such as excessive alcohol consumption, HBV, HCV, and HDV infections, autoimmune diseases, cholestatic diseases, non-alcoholic steatohepatitis, Wilson's disease, or hemochromatosis. The course of the disease progresses from asymptomatic (compensated HC) to symptomatic (decompensated HC), with complications frequently requiring hospitalization. Patients with cirrhosis are two to three times more likely to develop bacterial

infections and sepsis than other hospitalized patients. Approximately 32–40% of patients hospitalized with HC develop bacterial infections either prior to admission or during hospitalization [3]. Among these infections, 32-50% are community-acquired, 25-41% are associated with medical care, and 25-37% are nosocomial infections [3]. The most common infections in HC patients are SBP (20-35%), urinary tract infections (14-41%), pneumonia (8-17%), spontaneous bacteremia (8-21%), and skin and soft tissue infections (6-13%). Of note is the high variability of infectious complications, depending on local epidemiology [3].

Our study aimed to detect the main infectious complications in patients with HC, to assess the etiology of HC and the severity of liver dysfunction in these patients, to identify associated comorbidities, and to assess outpatient management and their prognostic implications. We also followed the antibiotic treatment regimens used in these patients. Understanding the types of infections may contribute to the development of more effective protocols for managing complications, optimizing treatment, reducing mortality, and ultimately improving patients' quality of life. To this end, we performed a comparative analysis between two groups of patients: group A—patients with HC and infectious complications; group B—patients with HC without associated infections.

After analyzing the epidemiological data, we observed a higher frequency of HC in males (72% of cases) compared to females (28% of cases). Of all patients included in the study, 42% developed an infectious complication, with a male:female ratio of 3:1.

In general, the average age of HC patients may vary depending on several factors, including the underlying cause of the disease, lifestyle, genetic factors, and other comorbidities. However, from a general perspective, the average age of patients at the time of diagnosis with HC may vary between 40 and 60 years, depending on the population studied and the specific factors involved in the development of this disease. In the study by Sajja et al., the mean age of patients with alcoholic liver disease was 51±10 years, those with HCV hepatitis 50±9 years, and those with non-alcoholic steatohepatitis or cryptogenic HC 60±12 years [11]. In our study, the age of patients with HC ranged from 32 to 93 years, with an average age of approximately 64 years in both groups, which is in agreement with the literature.

The main etiologies of HC were excessive alcohol consumption (59%), HCV infection (14%), or HBV (5%); mixed etiology, between HBV or HCV infection and excessive alcohol consumption, accounted for 8% and 6% of cases, respectively. We also identified other etiologies such as primary biliary cholangitis, secondary biliary cirrhosis, nonalcoholic steatohepatitis, and idiopathic HC. In both groups of patients, toxic-nutritional and HBV-associated were predominantly found in men, whereas HCV infection affected both men and women equally.

A study by Becker et al. emphasized that women are more sensitive to the toxic effects of alcohol, and the risk of developing alcohol-associated liver disease is higher in women, even with moderate alcohol consumption [12]. However, our study shows a lower diagnosis rate of alcoholic HC in women. We can explain this by the higher frequency of alcohol consumption in men in Romania. Liaw et al. argue that male sex is a risk factor for reactivation of HBV infection and for the development of cirrhosis and hepatocellular carcinoma [13]. Regarding HCV infection, some studies have concluded a more frequent progression to severe liver disease in men [14].

We examined the influence of vicious behaviors, such as smoking and alcohol consumption, on liver cirrhosis decompensation and the occurrence of infectious complications and we found that 47% of patients diagnosed with HC were smokers. However, smoking did not appear to influence the risk of infectious complications, with a similar proportion between the two study groups. Literature data support the involvement of smoking in the pathogenesis of HC, independent of alcohol consumption [15]. Alcohol consumption is an important risk factor for HC decompensation and may

influence the development of infections by increasing intestinal permeability, facilitating bacterial translocation (BT), suppressing the immune system, and worsening liver injury [16]. A study that examined the impact of excessive alcohol consumption on the prognosis of HC patients hospitalized in a hospital in southern Brazil noted a higher prevalence of liver and infectious complications in those who consumed alcohol, as well as a higher mortality rate among them [17]. In our study, in both groups of patients, we identified a similar prevalence of alcohol consumption, approximately 70%.

Obesity is a key risk factor for the development of nonalcoholic steatohepatitis and subsequently HC [18]. It is also associated with an altered immune response, chronic inflammation, and the risk of drug underdosing, factors that may further increase the risk of infections in HC patients [19]. In our study, around 40% of patients in each group had associated obesity, without identifying a significant difference between groups.

We also looked for the influence of a personal pathologic history of hypertension, CHF, CKD, CCS, and COPD on the risk of developing infectious complications. In statistical analysis, the only significant correlation was for a personal pathological history of CKD, which was a factor favoring the development of infections. A group of researchers investigated the link between CKD and increased mortality in sepsis using studies in mice [20]. The results showed that mice with CKD and sepsis had higher mortality compared to those without the condition [20]. Sepsis was also found to aggravate kidney damage [20].

HC and diabetes are chronic conditions that compromise the immune system and increase susceptibility to infection. However, it is uncertain whether the presence of both conditions increases the risk of infections to a greater extent than hepatic HC itself. The results of these authors show that the risk of infections was similar between patients with cirrhosis and ascites who also had diabetes and those without diabetes [21]. Therefore, the combined effects of liver cirrhosis and diabetes do not outweigh the impact of cirrhosis itself on the risk of infections [21]. These results are also confirmed by our statistical analysis. Another study by Rosenblatt et al. demonstrated an increased risk of infections in patients with advanced HC associated with uncontrolled diabetes mellitus [22].

A favorable environment for the proliferation of bacteria is provided by frequent complications of HC, such as the presence of ascites fluid and hemorrhage through the effraction of esophageal varices. The results of our study are in agreement with the literature. Thus, we identified the presence of ascites with a higher frequency in group A compared to group B (82% versus 70%) and suggest that ascites represents an essential risk factor in the pathology of infections. Regarding esophageal varices, we did not show a significant difference between their grade, presence and type of infection. According to some authors, bacterial infections in patients with variceal hemorrhage may lead to recurrence of bleeding and are associated with difficulty in controlling variceal bleeding [23]. In a retrospective study, antibiotic therapy and proven bacterial infection were found to be the only factors independently predictive of failure in hemorrhage control [23]. Conversely, in patients with controlled bleeding, the incidence of sepsis was significantly lower than in those with uncontrolled bleeding, a finding confirmed in subsequent studies [23].

Some studies suggest that prophylactic antibiotics for variceal bleeding may not be necessary in all cases. In the context of growing concerns about the overuse of antibiotics and the emergence of MDR bacteria, together with advances in the treatment of esophageal variceal hemorrhage and HC, a global reassessment of the need for routine antibiotic prophylaxis is needed [24].

Excessive proliferation of intestinal bacteria produces hyperammonemia, contributing to the development of hepatic encephalopathy [25]. Hung et al. demonstrated that concomitant infections increase mortality in HC patients hospitalized with hepatic encephalopathy [26]. Our study validates existing data in the literature, such that hepatic encephalopathy

was present in 35% of patients in group A compared with 26% of patients in group B.

Next, we performed a comparative analysis between the two groups of patients on several biological parameters in peripheral blood. Hypoalbuminemia has been recognized as an adverse prognostic factor in various medical conditions, including severe infections such as community-acquired pneumonia and severe sepsis [27].The association between SBP and hypoalbuminemia indicates an unfavorable prognosis with an increased risk of mortality. Albumin administration may have significant benefits in these patients, reducing mortality rates and the incidence of acute renal failure. Hung et al. have shown that hypoalbuminemia is an important prognostic indicator, independent of renal function, for both short-term and long-term outcomes in patients with SBP [28]. The results of our study support these data, with hypoalbuminemia being present in approximately 80% of patients who developed an infection, such as sepsis, bronchopneumonia or SBP. Also, 72% of patients in group B without infectious complications presented with hypoalbuminemia.

According to literature data, anemia can be observed in most HC patients, with iron deficiency being the most common cause [29]. In addition to anemia, thrombocytopenia and leukopenia are other hematologic abnormalities commonly seen in HC patients [29]. Most of the patients included in our respective study, 76%, presented with anemia. Moreover, 25% of them presented with severe anemia.

BT associated with endotoxemia is common in HC and may accelerate platelet consumption and development of thrombocytopenia. This hematologic abnormality frequently occurs in patients with infections, particularly in sepsis. In a retrospective analysis evaluating patients hospitalized in an intensive care unit with severe sepsis or septic shock, thrombocytopenia was present in half of them [30]. In our study, serum analysis detected thrombocytopenia in 58% of patients, normal platelet values in 34% and thrombocytosis in 8% of them. In both groups, about 10% of patients had associated severe thrombocytopenia.

In terms of leukocyte counts, 71% of patients in group A had leukocytosis, 18% had values within normal limits and 11% had leukopenia. In group B, 48% of patients had within normal limits, 39% had leukocytosis and 13% had leukopenia.

Renal function was assessed by serum creatinine and BUN. We identified elevated creatinine values in 45% of patients in group A and 28% of patients in group B respectively, elevated serum BUN values in 73% of patients in group A and 55% of patients in group B.

Concerning serum ionogram, in group A most patients had hyponatremia (54%) and in group B most patients had sodium values within normal limits (57%). Also, the analyses showed normal potassium values in group A in about 70% of cases and in group B in about 77% of cases.

The median value of the biological parameters described in the study reported a significant difference for C-reactive protein (CRP). Thus, we identified in group A twice higher median values of CRP compared to group B. For the other biological parameters, no significant difference in median values was observed between the two groups.

Our study also investigated the frequency and impact of infectious complications in HC patients. The most common complications identified were bronchopneumonia (39%) and urinary tract infections (27%), followed by sepsis (24%), *Clostridioides difficile* enterocolitis (7%), SBP (2%) and pleural empyema (1%).

With regard to the etiology of HC-associated infectious complications, our results slightly differ from those in the literature. Although SBP is characterized as the most common infection in cirrhosis, in our study it was found in a lower proportion [31]. This may be explained by the presence of sepsis with an unspecified starting point in a significant number of patients. Of these, we consider that an important proportion had SBP as the starting point of sepsis.

To date, pneumonia and sepsis have been shown to be independent predictors of 28-day mortality in HC patients [32]. In addition, Díaz-Hernández et al. found that pneumonia was an

independent predictor for increased mortality at 30, 60 and 365 days of follow-up [33]. Bacterial infections increase mortality fourfold in patients with decompensated cirrhosis [33]. In a retrospective study, an increased risk of 90-day mortality was observed in patients with advanced cirrhosis in the presence of urinary tract infection, defined by significant pyuria or bacteriuria. Renal dysfunction and comorbidities are predictors of death in these patients [34].

The in-hospital mortality of patients with cirrhosis and infectious complications is twice that of patients without infection. In addition, infection is directly responsible for the majority of deaths in patients with HC [35]. The incidence of sepsis in HC patients is significant and their nosocomial infection rate is higher compared to patients hospitalized for various conditions but without HC [35].

The in-hospital mortality data were also assessed in our study. Thus, we observed a significantly higher mortality rate in patients with infection. Most deaths among patients with infections were recorded in those with sepsis (48%), followed by bronchopneumonia (20%) and urinary tract infections (20%). We also observed a significant difference in the mean length of hospitalization, which was about twice as long in group A compared to group B. The mortality rate was about 65% within 2 years of presentation, and most deaths were associated with AC, followed by viral etiology.

The therapeutic recommendations are similar to those for the general population, following international guidelines. Antibiotics such as piperacillin-tazobactam or third generation cephalosporins in combination with macrolides, levofloxacin, or moxifloxacin are recommended [36]. For nosocomial infections, given the risk of antibiotic-resistant bacteria, carbapenems or ceftazidime are used as needed [36]. For patients with organ failure or at risk of MRSA infections, broad-spectrum antibiotics with activity against resistant bacteria are recommended. It is important to consider local epidemiology and the likelihood of antibiotic-resistant bacteria in the choice of therapy [36].

Patients with *Clostridioides difficile*, SBP, and pneumonia have higher rates of mixed infections. The use of antibiotics such as cefotaxime or ceftriaxone, penicillin, meropenem, imipenem, levofloxacin, piperacillin/tazobactam, and vancomycin is therefore recommended [37]. The duration of antibiotic treatment for uncomplicated nosocomial pneumonia is 7 days. For patients with HC and severe sepsis, the duration of empiric antibiotic treatment should be 7-10 days, and in many cases a longer duration is recommended. The complications associated with nosocomial pneumonia, including empyema or bacteremia, require longer periods of antibiotic treatment [36]. Regarding antibiotic treatment, our study supports the data from the literature. However, information regarding the duration of antibiotic therapy was insufficient.

In our study, we also evaluated the influence of outpatient treatment on the decompensation of HC and occurrence of infections by a comparative analysis between the two groups of patients. Non-selective beta-blockers were found in the outpatient treatment of 68% of patients in group A and 85% in group B. We mention a potential protective role of non-selective beta-blockers in preventing infectious complications in HC patients (relative risk < 1). A 2014 study investigating the effects of non-selective beta-blockers in patients with HC and ascites (with or without SBP) observed a longer duration of hospitalization, a higher risk of developing hepatorenal syndrome, and a higher number of hemodynamically unstable patients among those who associated SBP [38]. Another observational study of 1198 patients with HC and ascites found a lower risk of developing sepsis in patients on non-selective beta-blockers, but precise estimates were limited by the number of sepsis episodes [39].

Outpatient treatment with PPIs and antibiotics (RR>1) increased the risk of infections among patients included in our study. In diuretic treatment, no influence on infection risk was found. In contrast, rifaximin and lactulose had a protective role. PPI use is associated with a three-fold increased risk of developing SBP in hospitalized patients, according to a recent

meta-analysis suggesting that the indication for PPI treatment in HC should be carefully evaluated in relation to possible risks [40].

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Conceptualization, V.A.I., I.B., G.G., and C.L.T.; methodology, G.G.; software, V.A.I.; validation, C.C.D..; formal analysis, G.G.; investigation, I.B., V.A.I.; resources, C.C.D.; data curation, V.A.I. and G.G.; writing—original draft preparation, V.A.I., I.B., G.G.; writing—review and editing, G.G.; visualization, C.C.D.; supervision, G.G.; project administration, C.C.D. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:
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"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"
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