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Original Article

Clinical characteristics and risk factors analysis of amalgamative infection of liver cirrhosis with hepatic decompensation

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Abstract: Objectives: This study is to characterize the clinic symptoms and analyze the risk factors of amalgamative infection for LCHD. Methods: 224 LCHD cases were divided into infection group and non-infection group according to their infection history. SPSS l6 statistical software was utilized to analyze the possible risk factors by unconditioned Logistic regression analysis, and calculate the odds ratio (OR). Results: Among these 224 LCHD patients, 105 cases had infection (46.88%) mainly from community infection. Infection occurred mainly in the respiratory tract and abdominal cavity, followed by urinary tract, digestive tract, biliary tract, skin and soft tissue infections. The major nosocomial infection is intraperitoneal infection and the main community infection is respiratory tract infection. 19 cases of 41 patients with hospital infection had fever (46.34%). Routine blood white blood cells analysis revealed that fever was not significantly associated with leukocyte count. Conclusion: Liver cirrhosis with hepatic decompensation was mainly from community infection. Infection occurred mainly in the respiratory tract and abdominal cavity. Age, gastrointestinal bleeding, liver function grade C and hospital time all contributed to the infection of LCHD. Therefore, early detection and timely treatment of LCHD can reduce the incidence of infection and mortality.

Keywords: Liver cirrhosis, decompensated, clinical characteristics, risk factors

Introduction

Liver cirrhosis with hepatic decompensation (LCHD) is a common disease. LCHD accounts for 4.3-14.2% of total inpatients of internal medicine in China and ranks the 4-6th of the total death worldwide [1]. The main reason for the high death rate of LCHD is the associated multiple complications, including infection, upper digestive tract bleeding, hepatic encephalopathy and hepatorenal syndrome [2]. Amalgamative infection is the most serious complication and an important factor for the induction of multiple complications [3]. Recently, the rate of amalgamative infection of LCHD is on the rise [4]. Zhu *et al*. [5] reported that the nosocomial and community infection rates were 34.27% and 39.44% in a cohort of 119 Chinese liver cirrhosis patients. A report from USA found that the nosocomial and community infection rates of liver cirrhosis patients were 34% and 32%, respectively [6]. It is widely believed that the high infection rate of LCHD patients is mainly due to reduced liver function and the associated immune dysfunction [7]; however the underlying mechanism remains elusive.

To explain the increased amalgamative infection of LCHD, Marshall et al. proposed a "gut-liver axis" concept in 1998. Numerous studies have shown that patients with liver diseases especially LCHD have abnormal intestinal mucosal barrier function, which is regulated by the immunity between liver and intestine. It was reported that the rate of infection in patients with complications increases significantly after resection of liver tissue [8]. Moreover, intestinal peristalsis affects bacterial translocation and increased intestinal peristalsis has been proven to reduce bacterial overgrowth and translocation, thereby reducing infection rate. In addition, decreased absorption of bile acids also

promotes the proliferation of intestinal bacteria. Alverdy *et al*. [9] found that downregulation of protein significantly reduced the number of lymphocytes of the intestinal mucosa in rats. It is thus possible that the hypoproteinemia of LCHD patients may lead to decreased intestinal mucosal immune function [10].

It has been reported that the most common infection site is urinary tract in American hospital and the respiratory tract in China hospital. Zhu *et al*. [5] reported that the most common site of infection in LCHD patients is the abdominal cavity, followed by intestine, upper respiratory tract, bacteremia, pulmonary infection, pleurisy, biliary tract and urinary tract. Nayasa *et al*. [11] showed that infection occurs mainly in LCHD patients with the liver function Child-Pughc grade and hypoproteinemia low protein blood, and there is no significant relationship with age, gender and liver disease. Ma *et al*. [12] found that the first cause of nosocomial infection is gastrointestinal bleeding after analysis of 320 LCHD cases with infection. A prospective study at Yale University [6] showed that bleeding and infection are common complications in LCHD. Since gastrointestinal bleeding decreases the effective circulating blood volume, resulting in the body stress response, intestinal vasoconstriction, intestinal mucosal ischemia, hypoxia, impairment of intestinal barrier function, it is possible that gastrointestinal bleeding promotes intestinal flora translocation.

Moreover, bleeding results in decline of platelet, which may in turn induce spontaneous bacterial peritonitis (SBP) [13]. SBP is a common and serious complication in patients with liver cirrhosis. SBP nosocomial infection rate is up to 10-30%. Without early antibiotic treatment, the mortality rate of SBP patients can reach 30-50%. With the effective use of antibiotics, bacteria can be eliminated within 48 hours. SBP can induce hepatic encephalopathy, hepatorenal syndrome and other complications, and often aggravates the progression of existing liver disease and even death. Therefore, it is very important for the early diagnosis and early treatment of SBP.

In addition, the infection of patients with decompensated liver function is different from general infection. Importantly, there is no typical and mostly no symptoms of amalgamative infection of LCHD. For example, Boraio *et al*. [3] reported that 64 cases have no symptom in 150 LCHD cases and fever is common in the patients with symptoms. Moreover, there might exit relatively independent risk factors for the infection of LCHD [14, 15]. Further, there is still controversial about the risk factors, the relationship between gastrointestinal bleeding and infection, a common site of infection, and the use of prophylactic antibiotics. In this study, we performed in-depth characterization of clinical features and analyzed the relationship of infection with serum albumin, age, gastrointestinal bleeding, liver cancer and diabetes in 224 LCHD patients.

Subjects and methods

Study subjects

We collected 224 LCHD cases with complete medical data in the Department of Gastroenterology of our hospital between January 2010 and January 2012. The diagnosis was based on the medical history, clinical signs, biochemical tests and imaging studies in line with decompensated liver function diagnostic criteria, and the exclusion of the heart, brain, kidney and other organic diseases. There were 144 males (64.29%) and 80 females (35.71%), with mean age of 56.67 ± 11.87 years (range: 28-87 years). After explanation of the purpose of the study, written informed consent was obtained from each patient. This study was approved by the Institutional Ethical Review Boards of the Third Hospital of Jilin University.

Statistical analysis

All data were analyzed using SPSS 16.0. Noncondition Logistic regression analysis was used to analyze the possible risk factors for non-continuous variables: gastrointestinal bleeding, liver function grade, length of stay, the abnormal white blood cells, age, ALB, diabetes, liver cancer and others. The significant variables were further analyzed by multivariate Logistic regression analysis to calculate the odds ratio (OR) and *P* values. Two samples of measurement data as age and number of days of hospitalization were compared using t test. Chi-square test was used to compare the rates of count data. Measurement data are expressed as mean ± SD. A *P* value <0.05 was considered statistically significant.

Table 1. Sources and sites of infection

Infection sites	n	Nosocomial infection (n=41)		Community infection (n=64)	
		n	%	n	%
Respiratory tract	37	7	17.1%	30	42.9%
Gastrointestinal	16	8	19.5%	8	11.4%
Urinary tract	17	4	9.8%	3	18.5%
Intraperitoneal	31	17	41.5%	14	20.0%
Non-specified	3	2	4.9%	1	1.4%
Biliary tract	3	1	2.4%	2	2.9%
Septicemia	3	1	2.4%	2	2.9%
Skin	1	1	2.4%	0	0%
Total	111	41	100.0%	70	100.0%

Table 2. The infection rate distribution in different Child classification grades

Ch1ld-pugh grade	Non-infection (n=119)	nosocomial infection (n=41)	Community infection (n=64)	Total
A	80	5	27	112
B	34	26	23	83
C	5	10	14	29
Total	119	41	64	224

Table 3. The hospitalized time between the infected and non-infected groups

Infection status	n	$\bar{x}$ ± sd (days)	*t*	P
Non-infection	119	12.61 ± 7.89		
Infection	105	15.19 ± 10.29		
Total	224	13.82 ± 9.16	2.117	0.035

Results

General information of patients

The 224 patients of liver cirrhosis with hepatic decompensation (LCHD) included 144 males (64.29%), 80 females (35.71%), aged 28-87 years (mean 56.67 ± 11.87 years). According to etiology analysis, 150 cases (66.96%) had hepatitis B liver cirrhosis, 40 cases (17.86%) had hepatitis C cirrhosis, 17 cases (7.59%) were alcoholic cirrhosis, 7 cases (3.13%) were autoimmune liver cirrhosis disease, 10 patients (4.46%) were hepatic cirrhosis with no confirmed etiology. 43 cases were diabetes, 49 cases had primary carcinoma. According to Child classification, 112 cases were grade A, 83 cases were grade B and 29 cases were grade C.

Source of infection and its relationship with age

In these 224 cases of LCHD patients, 105 cases had infection (46.88%) (**Table 1**). 64 cases were community infection (60.95%) and the rest 41 were nosocomial infection (39.05%). Among the 224 LCHD cases, 111 were ≥65 years. 72 of these patients had amalgamative infection with infection rate of 64.86%. Among the rest 113 cases whose ages were <65 years, 33 had amalgamative infection with infection rate of 29.20%. The infection rates between these two groups were significantly different (P< 0.05). These data demonstrated community infection was significantly higher than nosocomial infection and older age patients had more possible of infection for LCHD patients.

One-year mortality rates between infection group and non-infected group

Six cases died within one year after diagnosis in non-infection group of 119 LCHD with one-year death rate of 5.04%. In contrast, 17 cases died within one year after diagnosis in infection group of 105 LCHD with one-year death rate of 16.19%. The one-year mortality between the two groups were significantly different (P=0.006<0.05). These data indicate that the one-year mortality of infection group was significantly higher than that of non-infection group of LCHD patients.

The infection site and frequency distribution analysis

There were totally 111 infections occurring in the 105 infection group, with one time infection in 100 cases and two times infection in 5 cases. The most common infection site was respiratory tract (37 cases times), followed by intraperitoneal (31 cases times), gastrointestinal (16 cases times), urinary tract (17 cases times), biliary tract (3 cases times), septicemia (3 cases times), unknown sites (3 cases times), and skin infections (1 case time) (**Table 1**). The nosocomial infections occurred mainly in intraperitoneal, gastrointestinal, and respiratory tract; the community-acquired infection occu-

Table 4. The relationship between gastrointestinal bleeding and infection rate

Infection status	n	Without gastrointestinal bleeding	With gastrointestinal bleeding	χ^2	P
		n	n		
Non-infection	119	99	20		
Infection	105	68	37		
Total	224	167	57	9.989	0.002

Table 5. The gender distribution in infection and non-infection groups

Infection status	n	Female		Male		χ^2	P
		n	%	n	%		
Non-infection	119	43	36.13	76	63.87		
Infection	105	37	35.24	68	64.76		
Total	224	80	35.71	144	64.29	0.020	0.889

Table 6. The age distribution in infection and non-infection groups

Infection status	n	Ages ($\bar{x}$ ± sd)	*t*	*P*
Non-infection	119	55.28 ± 11.55		
Infection	105	58.26 ± 12.09		
Total	224	56.67 ± 11.87	1.886	0.061

rred mainly in respiratory tract, gastrointestinal and gastrointestinal.

The isolation and characterization of pathogens from 42 LCHD patients

Forty-two clinical samples of the 105 infection group were subjected to pathogen isolation by bacterial culturing and 28 pathogen strains were isolated, including 12 from sputum culture, 5 from urine culture, one from blood culture, 9 from ascites culture, and one from stool. The strains included 16 Gram-negative and 7 Gram-positive bacteria, and 5 fungi. The pathogenic pathogens were mainly E. coli, followed by Streptococcus pneumoniae, fungi, Klebsiella, Pseudomonas aeruginosa and Staphylococcus aureus.

Fever situation and leukocyte changes

In the 41 patients with nosocomial infection, 19 had fever (46.34%). Compared with that prior to hospital admission, the number of white blood cell (WBC) increased in 14 cases (34.15%), including 8 fever cases; WBC had no significant change in 18 cases (43.90%), including 9 fever cases; WBC reduced in 9 cases (21.95%), including 2 cases of fever. However, there was no statistical difference among the three groups (P>0.05).

The infection rate distribution in different Child classification grades

Among the 224 LCHD patients, 112 cases were Child grade A, including 3 deaths and 32 cases of infection with infection rate was 28.57%; 83 cases were Child grade B, including 13 deaths and 49 cases of infection with infection rate was 59.04%; 29 cases were Child grade C, including 7 deaths and 24 cases of infection with infection rate was 82.76% (**Table 2**). The infection rates among Child grades were statistically different (χ^2= 34.992, P<0.001). Among the 64 cases of community-infected patients, 27 cases were Child grade A, 23 cases were Child grade B, 14 cases were Child grade C. Among the 56 cases of hospital infection patients, 5 cases were Child grade A, 26 cases were Child grade B and 10 cases were Child grade C (**Table 2**).

The hospital stay between the infected and non-infected groups

The average hospital stays of 119 non-infected and 105 cases of infection were 15.19 ± 10.29 and 12.61 ± 7.89 days, respectively. The average hospital stay of the infection group were significantly longer than that of non-infection group (P<0.05, **Table 3**).

The relationship between gastrointestinal bleeding and infection rate

In the 224 LCHD patients, there were 57 cases with gastrointestinal bleeding, including 37 cases of infection. Thus, the infection rate was 64.91% in LCHD with gastrointestinal bleeding. In the rest 167 patients with no gastrointestinal bleeding, 68 cases had infection with infection rate of 40.72%. The infection rate of the cases

Table 7. Univariate analysis of risk factors of infection in LCHD patients

Infection status		n	Non-infection group		Infection group		χ^2	P
			n	%	n	%		
ALB	0	94	33	35.11	61	64.89	21.117	<0.001
	1	130	86	66.15	44	33.85		
TBIl	0	132	76	57.58	56	42.42	2.557	0.110
	1	92	43	46.74	49	53.26		
Bile acids	0	88	44	50.00	44	50.00	0.568	0.451
	1	136	75	55.15	61	44.85		
WBC	0	85	60	70.59	25	29.41	16.775	<0.001
	1	139	59	42.45	80	57.55		
PLT	0	125	69	55.20	56	44.80	0.489	0.484
	1	99	50	50.51	49	49.49		
Prothrombin	0	94	64	68.09	30	31.91	14.587	<0.001
	1	130	55	42.31	75	57.69		
Cholesterol	0	58	30	51.72	28	48.28	1.331	0.514
	1	8	5	62.50	3	37.50		
	2	107	65	60.75	42	39.25		

Table 8. Logistic regression analysis of risk factors of infection in LCHD patients

Index	β	Wald	P	OR
Gastrointestinal bleeding	1.041	6.299	0.012	2.833
Liver function grade C	1.978	9.208	0.002	2.659
Hospitalized time	1.048	5.343	0.021	1.049
Age grouping (<65, ≥65)	1.390	16.967	<0.001	4.014

with gastrointestinal bleeding were significantly higher than that of the cases without gastrointestinal bleeding (P<0.05, **Table 4**).

Univariate analysis of risk factors of infection in LCHD patients

There were no significant differences of gender (**Table 5**) and age (**Table 6**) between the infection group and non-infected group.Further analyses found that ALB in infection group was significantly lower than non-infected group; the WBC number in infection group was significantly higher than non-infected group; prothrombin time in infection group was significantly longer than the non-infected group (**Table 7**). However, there was no significant difference of serum total bilirubin (TBil), bile acids, platelets (PLT) and cholesterol between the infection group and non-infected group.

Logistic regression analysis of risk factors of infection in LCHD patients

Finally, we performed a Logistic regression model analysis of the association of infection with dependent variables (**Table 8**). Five risk factors were found significantly associated with infection. According to OR descending order, they were age (OR 4.014, P<0.001), gastrointestinal bleeding (OR 2.833, P: 0.012<0.05), liver function grade C (OR 2.659, P: 0.002<0.05), hospitalization time (OR 1.049, P: 0.021<0.05).

Discussion

Infection is closely associated with decompensated liver function in liver cirrhosis. With the broad-spectrum antibiotic prophylaxis, the infection-mediated death rate of liver cirrhosis with hepatic decompensation (LCHD) has decreased, but its incidence rate is still high (20-60%) [4]. In this study of 224 LCHD, the infection rate was 46.88%, including 34.27% of community infection and 18.30% of nosocomial infection, indicating that infection of LCHD mainly results from community infection. Our data were consistent with previous studies [5-7].

It has been reported that the risk of infection in older patients, particularly in patients aged ≥65 years, is higher, but the data from different geographic populations are inconsistent [3, 12]. We found the infection rate in patients aged ≥65 years (64.86%) was significantly higher than those <65 years (29.20%). Among the rest 113 cases whose ages were less than 65 years, 33 had amalgamative infection with infection rate of 29.2%. The infection rates between these two groups were significantly different (P<0.05). Non-conditional Logistic regression analysis showed that age was an independent risk factor for infection of LCHD.

Infection is an important factor for the death of LCHD patients. We found the one-year mortali-

ty of infection group (16.19%) was significantly higher than that of non-infection group (5.04%) of LCHD patients. Our results suggest the importance of early diagnosis, and proper application of antibiotics for the treatment of LCHD patients.

In the present study, we found that respiratory tract and intraperitoneal were the most common infection sites for LCHD patients, followed by urinary tract, gastrointestinal tract, biliary tract and skin soft tissue infection. The majority hospital infection was intraperitoneal infection and the main community-acquired infection was respiratory tract infection, which is consistent with previous reports. Furthermore, we isolated 28 pathogen strains for the 42 clinical samples of the 105 infection group. The strains included 16 Gram-negative and 7 Gram-positive bacteria, and 5 fungi. The higher isolation rate of Gram-negative strains may be to the widely combinatorial application of the third generation cephalosporins and quinolones [16]. Antibiotics have been reported to inhibit or kill the normal flora but increase the risk of fungal infection. Fungal infection can aggravate the patient's condition and difficult to isolate. This study showed a high proportion of fungi infection within a limited number of cases, suggesting that we should pay attention to the etiology and drug sensitivity in order to improve diagnosis and treatment.

Borzio *et al.* [3] reported that 46% of liver cirrhosis patients with infection had no apparent symptoms. Similarly, we did not find significant alteration of fever and WBC when compared to non-infection LCH patients. The absence of apparent clinical symptoms is probably due to the decline of body immune system. Thus, we should pay attention to early diagnosis such as patient's medical history, patient's temperature, and ascites etiological analysis [17].

Dysfunction of liver leads to significantly reduced cellular and humoral immune response of the body, resulting in declined ability to process toxins, eliminate intestinal pathogenic microorganisms and antigens. This in turn promotes intestinal bacterial translocation and proliferation. In this study, non-conditional Logistic regression analysis showed that liver function grade C was an independent risk factor for infection in cirrhosis liver with decompensated function, which is consistent with previous report [3].

It is well known that prolonged hospitalization increase the possibility of infection of LCHD patients. Consistent with previous studies, our multivariate Logistic regression analysis showed that hospitalization time was an independent risk factor for LCHD patient infection.

Gastrointestinal bleeding decreases the effective circulating blood volume, resulting in the body stress response, intestinal vasoconstriction, intestinal mucosal ischemia, hypoxia, and impairment of intestinal barrier function. These may increase the risk of infection. Indeed, it was reported that the infection rate (45%) was significantly higher in LCHD patients with upper gastrointestinal bleeding than those without gastrointestinal bleeding [6]. It was also reported that bacterial infection is closely associated with the second time gastrointestinal bleeding and the failure of hemostatic within 5 days. Thus, prevention and control of infection is the key for the successful management of LCHD patients.

Bernard *et al*. [18] reported that the prophylactic use of antibiotics in the short-term could effectively reduce the incidence of infection and improve the patient's prognosis and survival of LCHD patients. Similar results were obtained in a study with Chinese population, but it did not analyze the risk factors for infection of those patients [19]. Moreover, it was reported that prophylactic use of antibiotics may lead to increase in bacterial drug-resistant and fungi infection [20, 21]. In this study, we found that gastrointestinal bleeding was an independent risk factor for the infection of LCHD patients. Whether the use of prophylactic antibiotics to reduce the incidence of infection and improve the quality of life of patients need to be further explored.

Currently, it is controversial about low protein in the infection of LCHD. Wang *et al.* [22] showed that low serum albumin is an independent risk factor for cirrhosis coinfection. Similar conclusion was obtained from Japanese studies [23-27]. However, Borzio *et al*. [3] demonstrated that low serum albumin is associated with cirrhosis coinfection. In the present study, we found low serum albumin was not an independent risk factor for infection of LCHD patients,

which is consistent with finding from Borzio *et al.* [3].

The liver is an important organ involved in glucose metabolism and up to 80% of cirrhotic patients have impaired glucose tolerance, of which 10-20% have clinical diabetes; however, the mechanism of the correlation of diabetes with liver cirrhosis is largely unknown. In the present study, we found 43 of the 224 LCHD cases had diabetes mellitus. Whether such diabetes belongs to primary diabetes or hepatic diabetes remains to be determined. Wang *et al.* [22] reported that diabetes is not an risk factor for the infection of liver cirrhosis, however, contradictory conclusion was obtained from other studies [24]. Our multivariate Logistic regression analysis showed diabetes was not an no risk factor for the infection of LCHD. These inconsistent results may be due to the differences of the severity of the objects, methods and sample size.

It remains unknown whether primary hepatocellular carcinoma contributes to the infection of LCHD. In this study, 49 of 224 LCHD cases had hepatocellular carcinoma with the incidence rate of 21.9%. Nevertheless, multivariate Logistic regression analysis results showed there was no statistical significance, suggesting that liver cancer is not a risk factor for the infection of LCHD, which is contradictory to the results from Borzio *et al.* [3]. These different inconsistent results may be due to the differences of the severity of the objects and sample size. Further studies are needed to clarify the correlation of hepatocellular carcinoma with the infection of LCHD.

In this study, we found that community infection is the main source for the infection of LCHD patients; the majority infection sites are respiratory tract and intraperitoneal; and one year mortality rate of LCHD patients with infection was 16.19%, which is significantly higher than those without infection. Moreover, we found that the main pathogens are Gram-negative bacteria; however, fungi also occupy a certain proportion. Furthermore, fever and WBC was not associated with nosocomial infection. Finally, age (≥65 years), gastrointestinal bleeding, Child grade C and prolonged hospitalization are independent risk factors for infection of LCHD patients.

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Disclosure of conflict of interest

None.

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