ORIGINAL ARTICLE

Differentiation between alcohol-associated cirrhosis and hepatitis B-associated cirrhosis based on hepatic complications and psychological symptoms

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Background: The prognosis of and occurrence of complications in patients with different clinical features of cirrhosis differ, and cirrhosis with different etiologies has varying clinical characteristics. The aim of this study was to describe the liver function markers, hepatic complications, and psychological features differentiating patients with hepatitis B virus (HBV) infection-related and alcohol-related cirrhosis. **Materials and Methods:** This was a retrospective and observational study that analyzed the medical data of inpatients with alcohol-related or HBV infection-related cirrhosis from May 2014 to May 2020. Markers of liver function, portal hypertension, and psychological symptoms were compared between the two groups. **Results:** Patients with alcohol-related cirrhosis showed higher Self-Rating Anxiety Scale scores and prevalence of hypoproteinemia, fatty liver, and depression than those with HBV infection-related cirrhosis (all $P < 0.05$). After adjustment for potential confounders, patients with alcohol-related cirrhosis also showed higher risks of increased total cholesterol (odds ratio [OR] =2.671, 95% confidence interval [CI]: 1.160–6.151, $P = 0.021$), increased high-density lipoprotein-cholesterol (OR = 2.714, 95% CI: 1.009–7.299, $P = 0.048$), and fatty liver (OR = 2.713, 95% CI: 1.002–7.215, $P = 0.048$); however, splenomegaly and splenectomy were significantly associated with HBV infection-related cirrhosis (OR = 2.320, 95% CI: 1.066–5.050, $P = 0.034$). **Conclusion:** Patients with alcohol-related cirrhosis were more likely to develop hyperlipidemia, fatty liver, and psychological symptoms, whereas those with HBV-related cirrhosis had a higher risk of splenomegaly.

Key words: Alcohol-induced disorders, fatty liver, hepatitis B virus, liver cirrhosis

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INTRODUCTION

Cirrhosis, an end-stage liver disease, is characterized by liver dysfunction and portal hypertension, and leads to esophageal varices, splenomegaly, and ascites.[1] As the 14th most common cause of adult mortality worldwide, cirrhosis causes up to 1.16 million deaths per year.[2] In Western countries, alcohol abuse has become one of the main causes of cirrhosis.[2] In 2017, more than 26.0 million people had alcohol-related cirrhosis.[3] Besides, alcohol-related cirrhosis has been reported to contribute to 0.9% of all deaths worldwide and to 47.9% of all liver cirrhosis-related deaths.[4] However, in Asian countries (especially China and India), hepatitis B virus (HBV) infection is the leading cause of cirrhosis.[5] Cirrhosis-related deaths in countries in East Asia and the Pacific regions represented more than half of all cirrhosis-related deaths globally, and ~70% of global cirrhosis-related deaths are caused by HBV infection in 2015.[6] Nevertheless, the clinical features of these two types of cirrhosis are poorly understood.[6, 7]

The incidence of complications and disease prognosis differ among cirrhosis patients with different clinical features.[7] For example, those with severe portal hypertension and liver dysfunction carry a higher

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risk of variceal hemorrhage relative to those with mild portal hypertension and liver dysfunction.[8] Furthermore, hypoproteinemia is a predictor of hepatic decompensation and is associated with increased mortality.[9] Moreover, splenomegaly is associated with the development of decompensation, a higher prevalence of hepatocellular carcinoma, and poor outcome in patients with compensated liver disease.[10] Therefore, understanding the clinical features of cirrhosis is crucial, because it can help to direct treatment decisions and prevent cirrhosis-associated complications. Studies have shown that cases of cirrhosis with varying etiologies have different clinical characteristics.[11,12] This study was conducted to differentiate the liver function markers, hepatic complications, and psychological features of patients with HBV infection- and alcohol-related cirrhosis.

MATERIALS AND METHODS

Selection and description of participants

In this retrospective study, we included all patients with cirrhosis and referral to the First Affiliated Hospital of Guangdong Pharmaceutical University (Guangdong, China) from May 2014 to May 2020. After obtaining the code of ethics from the ethics committee of our hospital, eligible patients were included in the study by consensus. The inclusion criteria were patients diagnosed with alcohol-related or HBV infection-related cirrhosis. The exclusion criteria were: (i) autoimmune liver disease, cholestatic liver disease, drug-induced liver injury, other viral liver diseases, or Wilson disease-related liver diseases; (ii) severe cardiac or pulmonary diseases; (iii) carcinoma (excluding hepatocellular carcinoma); and (iv) infection with the human immunodeficiency virus. Patients who were hospitalized multiple times were included only once in our analyses. The present study protocol was reviewed and approved by the ethics committee of the First Affiliated Hospital of Guangdong Pharmaceutical University (approval number: 202110). Informed consent was waived because of the retrospective study design.

Study variables

The following data of study participants were collected retrospectively: demographic information; smoking status or alcoholism; medical history (hypertension, type-2 diabetes mellitus, and liver disease); clinical presentations of cirrhosis; radiological imaging tests; and laboratory data, including transaminase, serum albumin (ALB), serum lipids, routine examination of blood, bilirubin, and prothrombin time (PT).

Definitions

Patients with chronic HBV infection were positive for hepatitis B surface antigen for ≥6 months. Liver cirrhosis was diagnosed based on liver biopsy, clinical examination, imaging findings, and laboratory test. The diagnosis of alcohol-related cirrhosis was based on imaging studies, and an equivalent of ≥ 40 g/day alcohol consumption for >5 years as reported by the patient was considered chronic alcohol abuse, with the exclusion of other liver diseases.

According to the international standards, aspartate transaminase (AST) >40 U/L, alanine transaminase (ALT) >56 U/L, and bilirubin >1.2 mg/dL were defined as an increased level of these compounds.[13] Dyslipidemia was defined[14] as (i) total cholesterol (TC) ≥5.20 mmol/L; (ii) triglyceride (TG) ≥1.70 mmol/L; (iii) low-density lipoprotein-cholesterol (LDL-C) ≥3.12 mmol/L; or (iv) high-density lipoprotein-cholesterol (HDL-C) ≤0.91 mmol/L in fasting blood samples. Fatty liver was defined as the presence of fatty infiltration on ultrasonography or computed tomography (CT). Hypoproteinemia was defined as ALB <35 g/L. Leukopenia was defined as a white blood cell (WBC) count of $< 4.0 \times 10^9$/L; erythropenia was defined as a red blood cell (RBC) count of $<4.0 \times 10^{12}$/L for male or 3.5×10^{12}/L for female patients; and thrombocytopenia was defined as a platelet count of $<100 \times 10^9$/L. Indications for splenectomy were hypersplenism as characterized by splenomegaly and hematocytopenia.[15] Smokers were defined as those who had smoked ≥100 cigarettes during their lifetime. The portal-vein diameter was assessed using ultrasonography or computed tomography.[16]

The Zung Self-Rating Depression Scale (SDS) and Zung Self-Rating Anxiety Scale (SAS) were used by nursing staff to assess levels of depression and anxiety during patients' hospitalization.[17,18] In accordance with standard practice in China, a score of ≥53 on the SDS categorized individuals as having depression, and a score of >50 on the SAS was indicative of anxiety.[19]

Statistical analyses

Statistical analyses were undertaken using SPSS 22 (IBM Corporation, Armonk, NY, USA). Categorical variables were described as frequencies (percentages). Continuous variables with a normal distribution were presented as the mean ± standard deviation. Continuous variables with a nonnormal distribution were presented as medians (interquartile ranges). Independent samples *t*-test, Mann–Whitney *U*-test, Chi-square test, or Fisher's exact test were used, where appropriate. To assess the association of cirrhosis etiology with portal-vein diameter, multiple linear regression analysis was undertaken to adjust for confounders. Logistic regression analysis was used to assess whether the risk of fatty liver, ascites, splenomegaly, esophageal varices, or gastric varices differed between patients with HBV-related cirrhosis and those with alcohol-related cirrhosis. Results are presented

as odds ratios (ORs) with 95% confidence intervals (CIs). P <0.05 (two-tailed) was considered to indicate statistically significant differences.

RESULTS

Demographic characteristics

Based on their electronic medical records, 408 patients with HBV infection-related cirrhosis and 62 patients with alcohol-related cirrhosis were enrolled. Their demographic characteristics are presented in Table 1. In patients with HBV infection-related cirrhosis, 90.20% (368/408) were undergoing antiviral medication, and 61.83% (162/262) had low HBV DNA level (≤2000 IU/mL).

Comparison of indices of liver function between patients with hepatitis B virus infection- and alcohol-related cirrhosis

The prevalence of hypoproteinemia (62.90% vs. 48.89%, P = 0.042), fatty liver (14.52% vs. 4.20%, P = 0.003), and the percentage of patients with Child–Pugh B/C (67.21% vs. 52.07%, P = 0.037) were higher in patients with alcohol-related cirrhosis than in those with HBV infection-related cirrhosis [Table 2]. However, the prevalence of increased levels of ALT, AST, bilirubin, PT or International Normalized Ratio (INR), and dyslipidemia did not differ significantly between the two groups [all P > 0.05; Table 2].

Comparison of features of portal hypertension between patients with hepatitis B virus infection- and alcohol-related cirrhosis

The prevalence of ascites was significantly higher (53.23% vs. 38.48%, P = 0.037) in patients with alcohol-related cirrhosis than in those with HBV infection-related cirrhosis, although no differences were detected in portal-vein diameter or the prevalence of esophageal varices, gastric varices, splenomegaly, or splenectomy [all P > 0.05; Table 3].

Multiple linear and logistic regression analyses

After adjustment for confounders, linear regression analysis showed that patients with HBV-related cirrhosis presented a significantly higher portal-vein diameter than those with alcohol-related cirrhosis (β =1.287, Standard error = 0.647, P = 0.048).

Logistic regression analysis revealed that patients with alcohol-related cirrhosis had significantly higher risks of increased TG (OR = 2.671, 95% CI: 1.160–6.151, P = 0.021). increased LDL-C (OR = 2.714, 95% CI: 1.009–7.299, P = 0.048), and fatty liver (OR = 2.713, 95% CI: 1.002–7.215, P = 0.045) than patients with HBV infection-related cirrhosis, after adjustment for confounders [Table 4]. By contrast, patients with alcohol-related cirrhosis had a lower risk of splenomegaly and splenectomy than those with HBV infection-related cirrhosis (OR = 0.431, 95% CI: 0.198–0.938, P = 0.034) [Table 4].

Comparison of depression and anxiety between patients with hepatitis B virus infection- and alcohol-related cirrhosis

Patients with alcohol-related cirrhosis showed higher SAS scores (65.00 [53.13–71.25] vs. 57.50 [51.25–63.75], P = 0.002) than those with HBV infection-related cirrhosis, whereas the prevalence of anxiety did not differ significantly between the two groups [79.31% vs. 75.45%, P = 0.818, Table 5]. Furthermore, the prevalence of depression was higher (72.41% vs. 50.00%, P = 0.029) in patients with alcohol-related cirrhosis than in those with hepatitis B-related cirrhosis, although the SDS score did not differ significantly [58.92 ± 10.49 vs. 53.66 ± 14.16, P = 0.055, Table 5] between the two groups.

Table 1: Characteristics of the patient cohort

	HBV infection-related cirrhosis (n=408), n (%)	Alcohol-related cirrhosis (n=62), n (%)	P
Age (years)	58.96±13.66	58.44±12.45	0.777
Sex/male	334 (81.86)	62 (100)	<0.001
BMI (kg/m^2)	22.66 (20.58–24.98) (n=348)	21.61 (19.60–25.01) (n=47)	0.140
Diabetes mellitus	86 (21.10)	17 (27.42)	0.322
Hypertension	127 (31.13)	23 (37.10)	0.381
Smoking	117 (28.68)	46 (74.19)	<0.001

Data are presented as the mean ± SD; median (IQR) or n (%). Comparison was determined by independent sample t-test, Mann-Whitney U-test, or Chi-square test. BMI=Body mass index; HBV=Hepatitis B virus; SD=Standard deviation; IQR=Interquartile range

DISCUSSION

In the present study, patients with alcohol-related cirrhosis had higher SAS scores and a higher prevalence of hypoproteinemia, fatty liver, and depression, as well as a more severe Child–Pugh classification than patients with HBV infection-related cirrhosis. Furthermore, patients with alcohol-related cirrhosis carried higher risks of increased TG, increased LDL-C, and fatty liver after adjustment for potential confounders. However, the risk of splenomegaly and splenectomy was significantly higher in patients with HBV infection-related cirrhosis than in those with alcohol-related cirrhosis. To our knowledge, this is the first study to delineate differences in the liver function markers, portal hypertension features, and psychological symptoms between HBV infection- and alcohol-related cirrhosis.

Fat deposition is a common pathological feature of cirrhosis. Here, we found that the prevalence of fatty liver in patients with alcoholic cirrhosis was higher than in those with HBV infection-related cirrhosis. Similarly, one study demonstrated that around 90–95% of heavy drinkers will develop fatty liver,[20] whereas only ~30% of those

Table 2: Comparison of indices of liver function between patients with hepatitis B virus infection and alcohol-related cirrhosis

	HBV infection-related cirrhosis (*n*=408), *n* (%)	Alcohol-related cirrhosis (*n*=62), *n* (%)	*P*
Liver function parameters	*n*=405	*n*=62	
Increased ALT >56 U/L	88 (21.73)	12 (19.35)	0.742
Increased AST >40 U/L	190 (46.91)	37 (59.68)	0.076
Increased bilirubin (>1.2 mg/dL)	116 (40.99)	34 (54.84)	0.053
Hypoproteinemia (albumin <35 g/L)	198 (48.89)	39 (62.90)	0.042
Coagulation parameters	*n*=387	*n*=61	
Increased PT (>15 s)	173 (44.70)	29 (47.54)	0.782
Increased INR (>1.5)	50 (12.92)	8 (13.11)	1.000
Blood lipid parameters	*n*=226	*n*=45	
Increased TC (≥5.20 mmol/L)	27 (11.89)	8 (17.78)	0.328
Increased TG (s1.70 mmol/L)	29 (12.83)	10 (22.22)	0.107
Increased LDL-C (.5) rsimmol/L)	38 (16.81)	12 (26.67)	0.140
Reduced HDL-C ((.5) rmmol/L)	77 (34.07)	18 (40.00)	0.495
Fatty liver	17 (4.20)	9 (14.52)	0.003
Child-Pugh classification	*n*=386	*n*=61	
A	185 (47.93)	20 (32.79)	0.037
B/C	201 (52.07)	41 (67.21)	

Data are presented as the *n* (%). Comparison was determined using the Chi-square test. ALT=Alanine transaminase; AST=Aspartate transaminase; HBV=Hepatitis B virus; HDL-C=High-density lipoprotein-cholesterol; INR=International Normalized Ratio; LDL-C=Low-density lipoprotein-cholesterol; PT=Prothrombin time; TC=Total cholesterol; TG=Triglyceride

Table 3: Comparison of features of portal hypertension between patients with hepatitis B virus infection and alcohol-related cirrhosis

	HBV infection -related cirrhosis (*n*=408), *n* (%)	Alcohol-related cirrhosis (*n*=62), *n* (%)	*P*
Portal-vein diameter (mm)	13.00 (11.00–15.00) (*n*=265)	13.00 (11.50–15.00) (*n*=41)	0.471
Ascites	157 (38.48)	33 (53.23)	0.037
Esophageal varices and gastric varices	193 (47.30)	31 (50.00)	0.785
Splenomegaly/ splenectomy	320 (78.43)	43 (69.35)	0.142

Data are presented as the median (IQR) and *n* (%). Comparison was determined by Mann-Whitney *U*-test or Chi-square test. HBV=Hepatitis B virus; IQR=Interquartile range

with HBV infection had fatty liver.[21] After adjustment for confounders, logistic regression analysis suggested that patients with alcohol-related cirrhosis had an increased risk of fatty liver. Moreover, our results also showed that patients with alcohol-related cirrhosis had a higher risk of hyperlipidemia than those with HBV infection-related cirrhosis. Therefore, it is necessary to improve screening for fatty liver and blood lipids in patients with alcohol-related cirrhosis.

Although univariate analysis did not find differences in portal-vein diameter between the two groups, the results from multiple linear regression showed that patients with HBV-related cirrhosis presented a significantly higher portal-vein diameter than those with alcohol-related cirrhosis. This result indicated that patients with HBV-related cirrhosis might have higher portal vein pressure and were more likely to present portal hypertension-related complications.

As a common complications of portal hypertension, splenomegaly is usually asymptomatic, but often causes hypersplenism.[22] The present study found that patients with HBV infection-related cirrhosis presented an increased risk of splenomegaly relative to those with alcohol-related cirrhosis, after adjustment for confounders. Similarly, Gibson *et al*.[23] indicated that the prevalence of splenomegaly in patients with nonalcohol-related cirrhosis (61%) was higher than that in patients with alcohol-related cirrhosis (41%). Soper and Rikkers found that patients with nonalcoholic cirrhosis also had a higher prevalence and more severe hypersplenism than those with alcohol-related cirrhosis.[24] Splenomegaly can be a sub-fatal complication in cirrhosis patients.[25] Thus, more attention should be paid to these patients to avoid potentially lethal complications such as infections, anemia, and bleeding.

Anxiety and depression are common psychological problems that substantially impact the quality of life in cirrhosis patients.[26] We showed that the prevalence of depression was higher in patients with alcohol-related cirrhosis relative to those with HBV infection-related cirrhosis. Similarly, Di Florio *et al*.[27] showed that alcohol use disorder and psychiatric disorders frequently co-occur, thereby impacting treatment adherence and outcomes.[28] Furthermore, alcohol abuse can lead to psychiatric disorders and inferior mental health by increasing nerve damage in the brain through immune inflammation and multiple intestinal-axis pathways.[29] Patients with depression and

Table 4: Logistic regression analysis of hepatic features and portal-hypertension features in patients with hepatitis B virus infection versus alcohol-related cirrhosis

	OR	95% CI	*P*
Liver function parameters			
Increased ALT (>56 U/L)	0.692	0.312–1.535	0.365
Increased AST (>40 U/L)	0.467	0.229–0.950	0.036
Increased bilirubin (>1.2 mg/dL)	1.023	0.504–2.078	0.949
Hypoproteinemia (albumin <35 g/L)	1.064	0.455–2.489	0.887
Coagulation parameters			
Increased PT (>15 s)	0.533	0.242–1.174	0.119
Increased INR (>1.5)	0.772	0.295–2.019	0.598
Blood lipid parameters			
Increased TC (≥5.20 mmol/L)	2.183	0.659–7.229	0.201
Increased TG (≥1.70 mmol/L)	2.671	1.160–6.151	0.021
Increased LDL-C (≥3.12 mmol/L)	2.714	1.009–7.299	0.048
Reduced HDL-C (≤0.91 mmol/L)	1.055	0.451–2.471	0.901
Fatty liver	2.713	1.002–7.215	0.045
Portal-hypertension features			
Ascites	1.789	0.838–3.822	0.133
Splenomegaly/splenectomy	0.431	0.198–0.938	0.034
Esophageal varices and gastric varices	0.729	0.377–1.412	0.349

Adjusted for sex; smoking; Child–Pugh classification; hypoproteinemia; fatty liver and ascites. ALT=Alanine transaminase; AST=Aspartate transaminase; CI=Confidence interval; HBV=Hepatitis B virus; HDL-C=High-density lipoprotein-cholesterol; INR=International Normalized Ratio; LDL-C=Low-density lipoprotein-cholesterol; OR=Odds ratio; PT=Prothrombin time; TC=Total cholesterol; TG=Triglyceride

Table 5: Comparison of depression and anxiety between patients with hepatitis B virus infection and alcohol-related cirrhosis

	HBV infection-related cirrhosis (*n*=220)	Alcohol-related cirrhosis (*n*=29)	*P*
SAS score	57.50 (51.25-63.75)	65.00 (53.13–71.25)	0.002
SDS score	53.66±14.16	58.92±10.49	0.055
Anxiety, *n* (%)	116 (75.45)	23 (79.31)	0.818
Depression, *n* (%)	110 (50.00)	21 (72.41)	0.029

Data are presented as the mean±SD; median (IQR) or *n* (%). Comparison was determined by independent sample *t*-test; Mann-Whitney *U*-test; or Chi-square test. HBV=Hepatitis B virus; SAS=Self-Rating Anxiety Scale; SDS=Self-rating depression; SD=Standard deviation; IQR=Interquartile range

anxiety are more likely to report alcohol abuse.[30] Clinically, there should be a focus on the psychological problems of patients with cirrhosis and provision of psychological interventions.

This study has some limitations. First, because of the low economic status and lack of medical resources in some areas of China, patients with cirrhosis often receive a delayed diagnosis; hence, the duration from disease onset to cirrhosis diagnosis was not documented. Second, the severity of cirrhosis could not be assessed appropriately, because liver biopsies were not routinely performed. Third, the current study was limited by the small sample size. Therefore, further studies with large sample sizes are needed to validate our findings.

CONCLUSION

Patients with alcohol-related cirrhosis were more likely to develop hyperlipidemia, fatty liver, and psychological symptoms, whereas those with HBV infection-related cirrhosis had an increased risk of splenomegaly. These findings provide evidence that cirrhosis is not a single disease, and that further classification is needed to inform treatment decisions. Therefore, there should be a greater focus on regular screening for blood lipid levels, fatty liver, and mental disturbances in patients with alcohol-related cirrhosis and for splenomegaly in patients with HBV-related cirrhosis.

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Conflicts of interest

There are no conflicts of interest.

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