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RETROSPECTIVE STUDY

Study of liver cirrhosis over ten consecutive years in Southern China

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Abstract

AIM: To investigate the etiology and complications of liver cirrhosis (LC) in Southern China.

METHODS: In this retrospective, cross-sectional study, we identified cases of liver cirrhosis admitted between January 2001 to December 2010 and reviewed the medical records. Patient demographics, etiologies and complications were collected, and etiological changes were illustrated by consecutive years and within two time periods (2001-2005 and 2006-2010). All results were expressed as the mean ± SD or as a percentage. The χ^2 test or Student's *t*-test was used to analyze the differences in age, gender, and etiological distribution, and one-way analysis of variance was applied to estimate the trends in etiological changes. We analyzed the relationship between the etiologies and complications using unconditioned logistic regression, and the risk of upper gastrointestinal bleeding (UGIB) and hepatocellular carcinoma (HCC) in the major etiological groups was evaluated as ORs. A *P* value less than 0.05 was considered significant. Statistical computation was performed using SPSS 17.0 software.

RESULTS: In this study, we identified 6719 (83.16%) male patients and 1361 (16.84%) female patients. The average age of all of the patients was 50.5 years at the time of diagnosis. The distribution of etiological agents was as follows: viral hepatitis, 80.62% [hepatitis B virus (HBV) 77.22%, hepatitis C virus (HCV) 2.80%, (HBV + HCV) 0.58%]; alcohol, 5.68%; mixed etiology, 4.95%; cryptogenic, 2.93%; and autoimmune hepatitis, 2.03%; whereas the other included etiologies accounted for less than 4% of the total. Infantile hepatitis syndrome LC patients were the youngest (2.5 years of age), followed by the metabolic LC group (27.2 years of age). Viral hepatitis, alcohol, and mixed etiology were more prevalent in the male group, whereas autoimmune diseases, cryptogenic cirrhosis, and metabolic diseases were more prevalent in the female group. When comparing the etiological distribution in 2001-2005 with that in 2006-2010, the proportion of viral hepatitis decreased from 84.7% to 78.3% ($P < 0.001$), and the proportion of HBV-induced LC also decreased from 81.9% to 74.6% ($P < 0.001$). The incidence of mixed etiology, cryptogenic cirrhosis, and autoimmune diseases increased by 3.1% ($P < 0.001$), 0.5% ($P = 0.158$), and 1.3% ($P < 0.001$), respectively. Alcohol-induced LC remained relatively steady over the 10-year period. The ORs of the development of UGIB between HBV and other major etiologies were as fol-

lows: HCV, 1.07; alcohol, 1.89; autoimmune, 0.90; mixed etiology, 0.83; and cryptogenic, 1.76. The ORs of the occurrence of HCC between HBV and other major etiologies were as follows: HCV, 0.54; alcohol, 0.16; autoimmune, 0.05; mixed etiology, 0.58; and cryptogenic, 0.60.

CONCLUSION: The major etiology of liver cirrhosis in Southern China is viral hepatitis. However, the proportions of viral hepatitis and HBV are gradually decreasing. Alcoholic LC patients exhibit a greater risk of experiencing UGIB, and HBV LC patients may have a greater risk of HCC.

Key words: Liver cirrhosis; Epidemiology; Etiology; Complication; Hepatocellular carcinoma; Southern China

Core tip: Liver cirrhosis (LC) is an important cause of death globally, and prevention and treatment based on etiology is fundamental. Large-sample epidemiology studies of the distribution and changes of etiology in the Southern China population are rare. This study illustrates that the major etiology of LC in Southern China is viral hepatitis, and the proportions of viral hepatitis and hepatitis B virus (HBV) are decreasing; whereas autoimmune, cryptogenic, and mixed etiology cases are increasing. Alcoholic LC patients exhibit a greater risk of suffering from upper gastrointestinal bleeding, and HBV LC patients exhibit greater risk of developing hepatocellular carcinoma.

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INTRODUCTION

Liver cirrhosis (LC) is a life-threatening worldwide health problem that is characterized by regenerated nodule development due to different liver diseases. Many patients can progress to upper gastrointestinal bleeding (UGIB), hepatic encephalopathy (HE), and hepatocellular carcinoma (HCC) in the decompensated stage. Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and alcohol consumption are considered to be the major global etiologies of LC[1-3].

The epidemiological distribution of the etiology of LC differs geographically and remains poorly described. Globally, approximately 57% of liver cirrhosis was due to HBV (30%) and HCV (27%) in 2006[2]. In the United States, most European countries, and Japan, HCV and alcohol are the most common causes, whereas HBV-related LC is predominant in most Asian-Pacific and African countries[2,4-8]. The epidemiology and etiology have changed dramatically because of socioeconomic development and hepatitis vaccination; however, the availability of detailed information is limited. Fleming *et al*[5] reported that the cirrhosis incidence increased from 12.05/100000 to 16.99/100000 person-years from 1992 to 2001 in the United Kingdom, and a nationwide survey of Japan reported that HCV infection accounted for 60.9% of LC in 2008, representing a decrease from 65.0% in 1998[4]. Moreover, studies have reported that different etiologies tend to result in different complications; for example, HCC occurs more often in viral hepatitis LC cases than in alcoholic and autoimmune LC cases, but the exact relationship between the LC etiology and complications has not been verified by clinical research on a large sample[2,9].

Based on this background, we designed this serial cross-sectional study to analyze the etiology, complications, and clinical features of 8080 patients with LC in our hospital and to determine an accurate etiological distribution, the proportional changes over 10 consecutive years, and the relationship between LC etiology and complications.

MATERIALS AND METHODS

Patient enrollment and data acquisition

We extracted the records of all patients admitted between January 1, 2001, and December 31, 2010, from the hospital-based electronic database of medical records. Any diagnostic or therapeutic code for cirrhosis, esophageal varices, or portal hypertension in the discharge diagnosis was included in the searching process. To minimize the potential of missing cases with underlying LC but lacking the above diagnostic codes, we performed a second search in the database with recorded non-malignant ascites, hepatic encephalopathy and hepatorenal syndrome. A final diagnosis of LC and a diagnosis of etiology were made according to the discharge diagnosis of the medical record; if no explicit etiology was mentioned, an additional etiological diagnosis was established based on the following criteria of etiology. Moreover, patients who had no clinical features of chronic liver disease but exhibited a positive pathologic diagnosis or did not undergo laboratory tests for evaluating liver function were excluded for this study. Each enrolled patient was assigned a date of diagnosis defined as the first record of liver cirrhosis over the 10-year span. For patients who had several admissions to our hospital during this period, we only collected the first record when the LC diagnosis was established. We collected clinical information for every patient, including age, gender, birth place, admission and discharge time, ID number, laboratory data, complications, and data indicating etiology diagnosis. Moreover, liver function status was evaluated by the Child-Pugh scoring system and the model for end-stage liver disease (MELD) scoring system. The ethics committees of the appropriate institutional review boards approved this study according to the Declaration of Helsinki 2000.

Table 1 Criteria for the etiological diagnosis of liver cirrhosis

Viral hepatitis
Hepatitis B virus (HBV): positive for HBsAg for at least 6 mo
Hepatitis C virus (HCV): positive for anti-HCV or HCV-RNA
HBV + HCV: HBV overlap with HCV
HBV + Hepatitis D virus (HDV): positive for HBsAg and anti-HDV
Alcoholic cirrhosis
The diagnosis was made by a history of alcohol use (⩾ 40 g/d for males and ⩾ 20 g/d for females or > 80 g/d within past 2 wk), physical examinations for signs of chronic liver disease, laboratory abnormalities [including elevation of aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase (GGT) and prothrombin time] or typical imaging features of fatty liver and cirrhosis and the exclusion of other causes of LC[10]
Autoimmune diseases
Autoimmune hepatitis (AIH)[11]
Primary biliary cirrhosis (PBC)[12]
AIH + PBC: AIH and PBC overlap syndrome
Primary sclerosing cholangitis[13]
Secondary biliary cirrhosis
Established when compatible with the diagnosis of liver cirrhosis, excluding some common causes of LC and indicated by cholestatic biomarkers (such as elevated alkaline phosphatase and GGT)
Metabolic diseases
Wilson's disease[14]
Hereditary hemochromatosis[15]
Non-alcoholic fatty liver disease[16]
Others (amyloidosis, glycogen storage disease, *etc.*)
Drugs
Established when the liver function test abnormalities related to drug intake and other causes of LC were excluded[17]
Vascular diseases
Budd-Chiari syndrome[18]
Cardiac[19]
Parasite cirrhosis
The diagnosis was based on clinical manifestations, epidemiologic features, and lab tests, excluding other types of LC; the diagnosis needed to be verified by a positive pathogenic finding
Infantile hepatitis syndrome
The diagnosis was based on criteria of Roberts[20]
Mixed etiology
HBV + Alcohol
HBV + HCV + Alcohol
Other known etiology
Cases with a definite known etiology but not listed above
Cryptogenic cirrhosis
Diagnosed only after an extensive evaluation excluded recognizable etiologies[21]

Criteria for the diagnosis of liver cirrhosis

The diagnosis of LC was made according to the discharge diagnosis of the medical record, and the diagnosis was made in accordance with the criteria below when no explicit etiology was mentioned. Patients with clinical features of esophageal varices, ascites, or hepatic encephalopathy were clinically diagnosed with LC. Moreover, LC could be confirmed by abdominal imaging (coarse parenchyma with enlargement or shrinkage of the liver; splenomegaly; ascites found by ultrasound, computed tomography, or magnetic resonance imaging) or surgical findings (laparoscopy, autopsy) combined with indicating laboratory findings (low platelet count and albumin, high level of serum bilirubin, and/or prolonged prothrombin time)[4]. The criteria for the etiological diagnosis of LC are listed in Table 1.

LC Complications

UGIB, HCC, HE, secondary infection, ascites, portal vein thrombosis, portal vein tumor thrombosis, cavernous transformation of the portal vein, hepatorenal syndrome, hepatopulmonary syndrome (HPS), and hepatic hydrothorax were included in our study as complications of liver cirrhosis. Complications were diagnosed in accordance with the complications listed in the medical record.

Statistical analysis

Data were analyzed using SPSS 17.0. All results were expressed as the mean ± SD or as a percentage. We used the χ^2 test or Student's *t*-test to analyze the differences in age, gender, and etiology distribution. One-way analysis of variance (ANOVA) was applied to estimate the changes in etiology over time. We analyzed the relationship between etiologies and complications using multivariate unconditioned logistic regression. All statistical tests were two-sided. *P*-values below 0.05 are considered significant.

RESULTS

Demographic characteristics of LC patients

Of the 8080 patients with LC in this study, 6719 (83.2%) were male, 1361 (16.8%) were female, and the ratio of males to females was 4.9:1. The average age at the time of diagnosis was 50.5 ± 13.0 years. Demographic characteristics of the LC patients are presented in Figure 1; the age distribution of LC patients is delineated as a pyramid depending on gender, and 93.5% of male patients and 89.7% of female patients were between 30-74 years old. The overall liver function stages are listed in Table 2. In our study population, 6728 (83.3%) patients were Cantonese, and 1300 (16.1%) were from other provinces. Moreover, we also collected data on 52 (0.6%) foreign patients who mostly came from southeastern Asian countries.

Etiology distribution

The etiology distribution of all LC cases is presented in Table 3. The top five LC causes were viral hepatitis (80.62%), alcohol (5.68%), mixed etiology (4.95%), cryptogenic cirrhosis (2.93%), and autoimmune diseases (2.03%). Among the remaining > 4.00% of patients, metabolic diseases and other known etiologies were identified in 1.40% and 0.73%, respectively. In addition to 106 cases of Wilson's disease, 4 cases of non-alcoholic fatty liver disease (NAFLD), and 2 cases of hereditary hemochromatosis, we also observed 1 case of amyloidosis and 1 case of glycogen storage disease. Moreover, we identified 46 (0.57%) cases caused by vascular diseases, which included Budd-Chiari syndrome (n = 31) and cardiac congestion (n = 15). In the 38 (0.47%) cases of secondary biliary liver cirrhosis, 30 involved biliary tract constructions, and the other 8 were congenital biliary atresia cases. Among the 33 (0.41%) cases of parasites, 30 were caused by *Clonorchis sinensis*, and 3 were caused by *Schistosoma japonicum*. In this study, we also identified 9 (0.11%) drug-induced LC cases, and the toxic drugs included

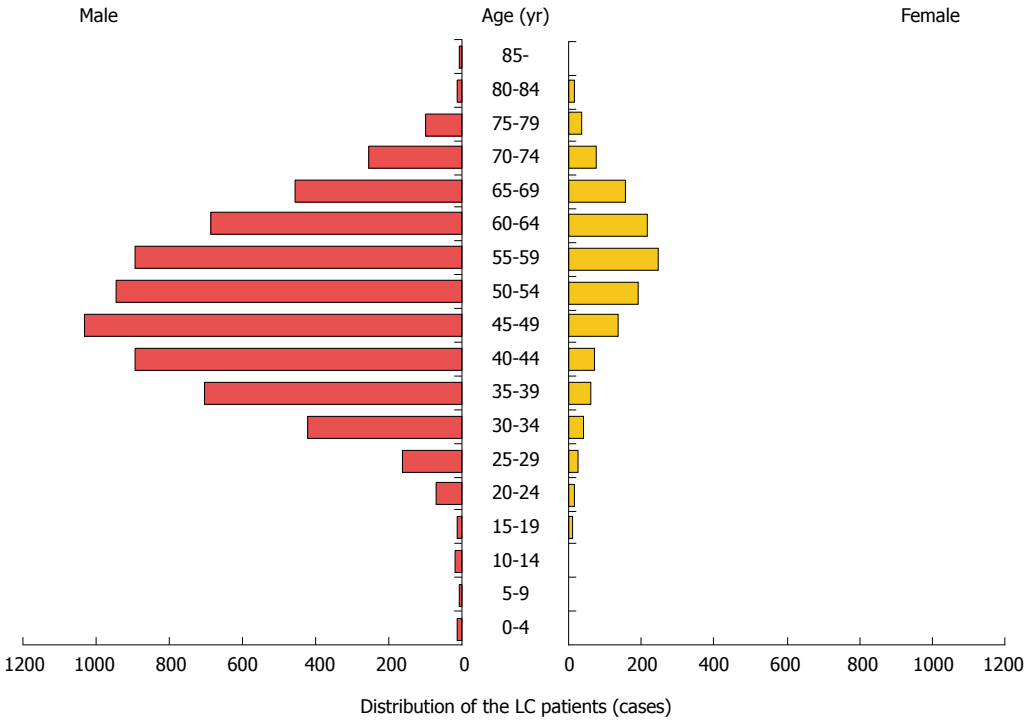

Figure 1 Demographic characteristics of the 8080 enrolled liver cirrhosis patients. Age distribution of the liver cirrhosis patients is delineated as a population pyramid depending on gender, and 93.5% of male patients and 89.7% of female patients are between 30-74 years old. Male cases are presented as red bars, and female cases are presented as yellow bars.

Table 2 Liver function characteristics of the study population *n* (%)

Male	6719 (83.2)
Mean age (yr)	50.5 ± 13.0
Child-Pugh score	
A	2521 (31.2)
B	3369 (41.7)
C	2190 (27.1)
Mean ± SD	8.0 ± 2.3
MELD score (mean ± SD)	15.3 ± 7.2
MELD: median (extreme)	13.6 (6-65)

The MELD score was calculated from 7145 cases in the study population because the creatinine value was not available from the others. MELD: Model for end-stage liver disease.

Chinese herbs, chemotherapy drugs, antipsychotic drugs, and arsenic agents. Eight cases of infantile hepatitis syndrome (IHS)-induced LC were also included in our study; the patients were neonates or infants exhibiting jaundice, light-colored feces, pathological hepatic signs, and ALT elevation with proof of liver cirrhosis.

Among the 6514 LC patients with viral hepatitis, HBV was the most common cause; HBV accounted for nearly 96% of all viral hepatitis cases and 77.2% of the study population. HCV was the second major cause of viral hepatitis LC, but the proportion was only 2.8%. In contrast, overlapping viral hepatitis involved 47 cases of HBV plus HCV and 2 cases of HBV plus HDV. The proportions were both less than 1.0% of all cases.

Etiology in different ages and genders

The etiology distribution among different ages and genders is listed in Table 3 and Table 4. With respect to the etiology in different genders, we observed that the leading etiology was viral hepatitis in both genders. However, the prevalence of viral hepatitis, alcohol, and mixed etiology was higher among men, whereas that of autoimmune disease, cryptogenic cirrhosis, and metabolic disease was higher among women ($P < 0.001$).

In all cases, IHS-induced LC patients were youngest, and the average age was 2.5 ± 3.9 years, followed by the metabolic disease group (27.2 ± 14.1 years). The parasite group had the maximum average age (58.1 ± 14.9 years), followed by the drug-induced LC group (56.0 ± 18.2 years).

Changes in the constituent ratio of etiologies from 2001 to 2010

To determine the changes in etiology from 2001 to 2010, we divided the study population into two groups. One group was defined as subjects admitted from 2001 to 2005, and the other group involved subjects admitted from 2006 to 2010. The constituent ratio of etiologies is presented in Table 5. We noticed that the top five categories did not change over the decade, but the ratio changed dramatically. The top five etiologies were viral hepatitis, alcohol, mixed etiology, cryptogenic cirrhosis, and autoimmune disease. Viral hepatitis decreased from 84.7% to 78.3% ($P < 0.001$, P-trend < 0.001); meanwhile, mixed etiology, cryptogenic cirrhosis, and autoimmune

Table 3 Etiology of the 8080 enrolled liver cirrhosis patients *n* (%)

Etiology	Total (*n* = 8080)	Male (*n* = 6719)	Female (*n* = 1361)	*P* value
Viral hepatitis	6514 (80.62)	5489 (81.69)	1025 (75.31)	< 0.001
HBV	6239 (77.22)	5316 (79.12)	923 (67.82)	
HCV	226 (2.80)	135 (2.01)	91 (6.69)	
HBV + HDV	2 (0.02)	2 (0.03)	0 (0.00)	
HBV + HCV	47 (0.58)	36 (0.54)	11 (0.81)	
Alcohol	459 (5.68)	451 (6.71)	8 (0.59)	< 0.001
Autoimmune	163 (2.03)	30 (0.43)	133 (9.77)	< 0.001
AIH	54 (0.67)	13 (0.19)	41 (3.01)	
PBC	87 (1.08)	15 (0.22)	72 (5.29)	
AIH + PBC	19 (0.24)	1 (0.01)	18 (1.32)	
PSC	3 (0.04)	1 (0.01)	2 (0.15)	
Secondary biliary	38 (0.47)	22 (0.33)	16 (1.18)	< 0.001
Metabolic diseases	114 (1.40)	73 (1.09)	41 (3.02)	< 0.001
WD	106 (1.31)	67 (1.00)	39 (2.87)	
HH	2 (0.02)	2 (0.03)	0 (0.00)	
NAFLD	4 (0.05)	2 (0.03)	2 (0.15)	
Others	2 (0.02)	2 (0.03)	0 (0.00)	
Drugs	9 (0.11)	6 (0.09)	3 (0.22)	0.186
Vascular diseases	46 (0.57)	30 (0.44)	16 (1.17)	0.001
BCS	31 (0.38)	21 (0.31)	10 (0.73)	
Cardiac	15 (0.19)	9 (0.13)	6 (0.44)	
Parasites	33 (0.41)	26 (0.39)	7 (0.51)	0.502
IHS	8 (0.10)	7 (0.10)	1 (0.07)	1.000
Mixed etiology	400 (4.95)	399 (5.93)	1 (0.07)	< 0.001
HBV + Alcohol	389 (4.81)	388 (5.77)	1 (0.07)	
HBV + HCV + Alcohol	11 (0.14)	11 (0.16)	0 (0.00)	
Other known etiology	59 (0.73)	51 (0.76)	8 (0.58)	0.499
Cryptogenic cirrhosis	237 (2.93)	135 (2.01)	102 (7.49)	< 0.001

The differences in gender proportion were determined using the χ^2 test. HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis D virus; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis; WD: Wilson's disease; HH: Hereditary hemochromatosis; NAFLD: Non-alcoholic fatty liver disease; BCS: Budd-Chiari syndrome; IHS: Infantile hepatitis syndrome.

disease increased by 3.1% (both *P* value and *P*-trend < 0.001), 0.5% (*P* value = 0.158; *P*-trend = 0.011), and 1.3% (both *P* value and *P*-trend < 0.001), respectively. The incidence of alcohol-induced LC was relatively stable over the 10-year period, although there was a slight increase from 5.3% to 5.9% in the constituent ratio (both *P* value and *P*-trend > 0.05, Figure 2). As the major cause of viral hepatitis-induced LC, the proportion of HBV-induced LC also decreased from 81.9% to 74.6% (*P* < 0.001, *P*-trend < 0.001). Compared with the decreasing proportion of HBV-induced LC, the proportion of HCV-induced LC slightly increased from 2.3% to 3.1% (*P* = 0.044; *P*-trend = 0.263, Figure 3).

LC complication distribution

Among all of the patients, we found that ascites, HCC, secondary infection, and UGIB were the most frequent complications, and the numbers of cases were 4493 (55.6%), 2399 (29.7%), 2177 (26.9%), and 1006 (12.5%), respectively. The other complications were relatively less common, and HPS was rare in our study group (6 cases). The distribution of complications classified by gender is presented in Table 6.

Table 4 Etiology of the 8080 liver cirrhosis patients by age

Etiology	Age, yr		
LC classification	mean ± SD	*t* value	*P* value
Viral hepatitis	50.7 ± 12.4		
Alcohol	52.2 ± 11.0	-1.48	0.308
Autoimmune	54.3 ± 12.9	-3.66	0.029
Secondary biliary	46.3 ± 25.1	4.33	1.000
Metabolic diseases	27.2 ± 14.1	23.49	< 0.001
Drugs	56.0 ± 18.2	-5.33	1.000
Vascular diseases	42.8 ± 17.6	7.87	0.212
Parasites	58.1 ± 14.9	-7.42	0.319
IHS	2.5 ± 3.9	48.18	< 0.001
Mixed etiology	51.2 ± 9.7	-0.52	1.000
Other known etiology	44.7 ± 13.6	5.98	0.079
Cryptogenic cirrhosis	55.0 ± 17.5	-4.29	0.015

The *P* values were determined using the independent samples *t*-test. The viral hepatitis patients were used as the reference group when comparing differences in age for different etiologies. LC: Liver cirrhosis; IHS: Infantile hepatitis syndrome.

Relationship between etiology and complications

To determine whether various etiologies might cause a variance in complications, the ORs of different etiologies for UGIB and HCC are presented in Table 7 and Table 8, respectively. We found that alcoholic LC patients exhibited a higher risk of developing UGIB compared with other major etiologies, whereas HBV infection was the most important cause of HCC in LC patients. The ORs of UGIB in all major etiologies were as follows: HBV, 1.00; HCV, 1.07; alcohol, 1.89; autoimmune, 0.90; mixed etiology, 0.83; and cryptogenic cirrhosis, 1.76. The ORs of HCC in all major etiologies were as follows: HBV, 1.00; HCV, 0.54; alcohol, 0.16; autoimmune, 0.05; mixed etiology, 0.58; and cryptogenic cirrhosis, 0.60.

DISCUSSION

In this large sample and medical center-based study, we found that viral hepatitis is the most prevalent cause of LC in our hospital, accounting for more than 80% of all LC patients. In addition, most of the viral hepatitis LC was caused by HBV (nearly 96% of all viral hepatitis LC cases). However, because of the admission of a large number of patients from other provinces of Southern China and the considerable local influence of our hospital, our single-center based findings may reflect the changing trend of etiologies in Southern China to some extent.

In the study group, the ratio of males to females is 4.9:1 (6719 males *vs* 1361 females), which is remarkably

Table 5 Etiologic analysis for the years 2001-2005 and the years 2006-2010 *n* (%)

Etiology	2001-2005 (*n* = 2907)	2006-2010 (*n* = 5173)	χ^2-value	*P* value	*P*-trend
Viral hepatitis	2462 (84.7)	4052 (78.3)	48.22	< 0.001	< 0.001
HBV	2381 (81.9)	3858 (74.6)	56.78	< 0.001	< 0.001
HCV	67 (2.3)	159 (3.1)	4.05	0.044	0.263
HBV + HCV	12 (0.4)	35 (0.7)	2.24	0.135	0.267
HBV + HDV	2 (0.1)	0 (0.0)	-	0.129	-
Alcohol	155 (5.3)	304 (5.9)	1.031	0.31	0.919
Autoimmune	34 (1.2)	129 (2.5)	16.509	< 0.001	< 0.001
Secondary biliary	12 (0.4)	26 (0.5)	0.321	0.571	0.369
Metabolic diseases	32 (1.1)	82 (1.6)	3.139	0.076	0.07
Drugs	1 (0.0)	8 (0.2)	1.459	0.227	0.161
Vascular diseases	17 (0.6)	29 (0.6)	0.019	0.89	0.551
Parasites	14 (0.5)	19 (0.4)	0.598	0.439	0.154
IHS	2 (0.1)	6 (0.1)	0.078	0.78	0.696
Mixed etiology	87 (3.0)	313 (6.1)	36.984	< 0.001	< 0.001
Other known etiology	16 (0.5)	43 (0.8)	2.95	0.086	0.285
Cryptogenic cirrhosis	75 (2.6)	162 (3.1)	1.989	0.158	0.011

The *P* values were determined using the χ^2 test by comparing the proportion of 2001-2005 with that of 2006-2010. The *P*-trend values were determined using ANOVA by comparing proportions of separated years and reflected the general trend of the etiology proportion in the 10 consecutive years.

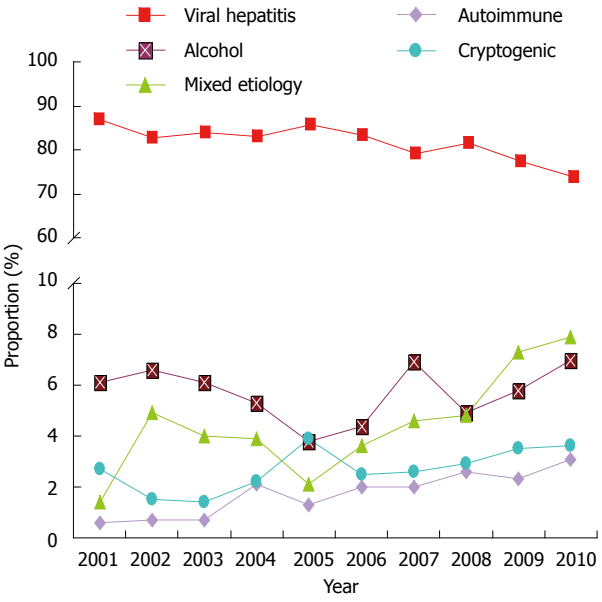

Figure 2 Changing trends in the proportion of major etiologies over 10 consecutive years. The proportion of viral hepatitis-induced liver cirrhosis (LC) has decreased gradually in the past 10 years and that of alcoholic, mixed etiology, autoimmune and cryptogenic-induced LC have increased to some extent. Every marker illustrates the proportion of LC due to a different cause, and the changing trend is simulated by lining up the markers for each etiology as different colored lines. Viral hepatitis: LC caused by viral hepatitis, $P < 0.001$ in 10 years comparison; Alcohol: LC caused by alcohol consumption, $P = 0.919$ in 10 years comparison; Mixed etiology: LC caused by mixed etiology, $P < 0.001$ in 10 years comparison; Autoimmune: LC caused by autoimmune diseases, $P < 0.001$ in 10 years comparison; Cryptogenic: LC of unknown reason, $P = 0.011$ in 10 years comparison.

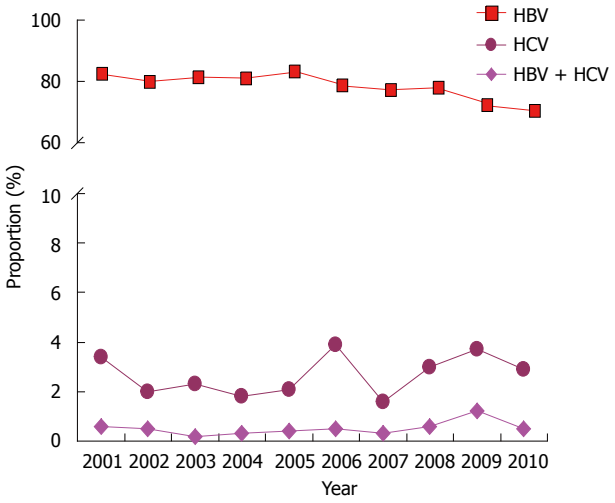

Figure 3 Changing trends in the proportion of subgroups of viral hepatitis over 10 consecutive years. The proportion of HBV-induced LC has decreased gradually over the 10 years, and those of HCV- and (HBV + HCV)-induced LC have not exhibited explicit trends. Every marker illustrates the proportion of LC due to a different cause, and the changing trend is simulated by lining up the markers for each etiology as different colored lines. HBV: LC caused by hepatitis B virus, $P < 0.001$ in 10 years comparison; HCV: LC caused by hepatitis C virus, $P = 0.263$ in 10 years comparison; HBV + HCV: LC caused by hepatitis B virus combined with hepatitis C virus, $P = 0.267$ in 10 years comparison. LC: Liver cirrhosis; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

higher than what is reported in some other countries[4,5]. The gender difference may be explained by the higher prevalence of HBV infection (male to female 5.8:1) in LC patients.

The HBV-predominant etiology pattern was consistent with some former studies of mainland China[22,23], Hong Kong[24], and Taiwan[25]. China is a highly endemic area of HBV infection. According to an epidemiological survey of HBV infection conducted in 2006, the hepatitis B surface antigen (HBsAg) carrier rate was 7.18% in the overall population, meaning that there was an estimated 93 million HBV carriers, 30 million of whom developed chronic hepatitis B in China[26].

In this study, we divided our research population into two groups based on admission time, before 2006 and after 2006, for a comparison of the etiology changes during the decade studied. We noticed that the ratio of viral hepatitis LC decreased slightly in the two periods (from 84.7% to 78.3%) and decreased gradually over the 10

Table 6 Complications in the 8080 liver cirrhosis patients by gender *n* (%)

Complication	Total (*n* = 8080)	Male (*n* = 6719)	Female (*n* = 1361)	χ^2 value	*P* value
UGIB	1006 (12.5)	875 (13.0)	131 (9.6)	12.00	0.001
Infection	2177 (26.9)	1806 (26.9)	371 (27.3)	0.08	0.773
Ascites	4493 (55.6)	3739 (55.6)	754 (55.4)	0.03	0.867
HCC	2399 (29.7)	2157 (32.1)	242 (17.8)	111.21	< 0.001
HE	544 (6.7)	464 (6.9)	80 (5.9)	1.90	0.168
PVT	405 (5.0)	342 (5.1)	63 (4.6)	0.51	0.477
PVTT	783 (9.7)	733 (10.9)	50 (3.7)	67.7	< 0.001
CTPV	250 (3.1)	229 (3.4)	21 (1.5)	13.13	< 0.001
HRS	293 (3.6)	252 (3.8)	41 (3.0)	1.76	0.184
HPS	6 (0.1)	4 (0.1)	2 (0.1)	1.17	0.280
HHT	398 (4.9)	337 (5.0)	61 (4.5)	0.69	0.407

Because some patients have more than one complication, number is greater than 8080; The *P* values were determined using the χ^2 test. UGIB: Upper gastrointestinal bleeding; HCC: Hepatocellular carcinoma; HE: Hepatic encephalopathy; PVT: Portal vein thrombosis; PVTT: Portal vein tumor thrombosis; CTPV: Cavernous transformation of the portal vein; HRS: Hepatorenal syndrome; HPS: Hepatopulmonary syndrome; HHT: Hepatic hydrothorax.

consecutive years (as shown in Figure 2). For the HBV group, as the leading agent of viral hepatitis, we observed a similar trend (Figure 3). Our observation was confirmed by another domestic study[23]. We also observed that more patients were captured from 2006-2010 (4052) compared with 2001-2005 (2462), consistent with what was observed in the number of HBV patients (3858 in 2006-2010 and 2381 in 2001-2005). Because of the rapid development and expanding influence of our hospital, admitted patients increased each year; thus, the increase in the number of viral hepatitis cases may be due to the increase in patient enrollment rather than increased incidence, whereas the proportion was not affected by the number of hospitalized patients. The decreasing tendency should be attributed to the widespread application of HBV vaccination starting from 1996 in our nation. The HBsAg carrier rate has decreased from 10.1% in 2001 to 7.18% in 2006 in adolescents, and in children less than 5 years of age, the rate was only 0.96% overall in Chinese people and 4.91% in children from Guangdong[27,28]. Moreover, with the development of better diagnosis options and improved management of chronic liver diseases, more and more cases of rare causes of LC are being identified, which may also have played a role in reducing the ratio.

Autoimmune liver disease is composed of autoimmune hepatitis (AIH), primary biliary cirrhosis, primary sclerosing cholangitis, and overlapping syndromes. As a relatively rare disease, the proportion of autoimmune liver disease increased from 1.2% in 2001-2005 to 2.5% in 2006-2010 and increased each year in the 10-year span (Figure 2). Song *et al*[23] also found a similar increasing trend in autoimmune LC in North China. The epidemiology of AIH remains poorly characterized in China, and the exact incidence and prevalence of AIH is not known. Our research data may suggest a possible increase in the incidence and prevalence of AIH, but some large-scale nationwide epidemiology studies from Japan, Israel, Norway, and Sweden did not report a rise in the incidence and prevalence of AIH and autoimmune LC[4,29-32]. We presumed that the rapid development and wide application of diagnostic methods for detecting autoantibodies, immunoglobulin, and other hepatitis markers may be strongly correlated with the increasing rate of the disease in our study.

For LC of unknown etiology, also known as cryptogenic LC, the etiology ratio increased from 2.6% in 2001-2005 to 3.1% in 2006-2010, and the point proportion was 2.7% in 2001 and 3.6% in 2010. Since the discovery of HCV and the established diagnosis of AIH, cholestatic liver disease, and metabolic liver disease, the etiology proportion has decreased from approximately 40% to 5%[32]. Caldwell *et al*[21] found that the majority of cryptogenic cirrhosis patients were older females with Type 2 diabetes mellitus, hyperlipidemia, and obesity. Therefore, they assumed that some of these patients may have unrecognized AIH or may have progressed from nonalcoholic steatohepatitis (NASH) to LC. Similar results were observed in a Japanese study, which found that age, body mass index (BMI), serum triglyceride level, and prevalence of HCC were higher in females than in males[4]. Our data for cryptogenic cirrhosis were complicated; cryptogenic cirrhosis is more common in females (7.5% *vs* 2.0%), and the mean age is older than that for viral hepatitis (55.0 years *vs* 50.7 years) and very close to that for autoimmune diseases (54.3 years). Moreover, these cases exhibited a lower incidence of HCC compared with HBV cases (31.7% *vs* 51.4%). Because most of NASH or NAFLD cases were treated as outpatients in the clinic and few of them were admitted, we only collected 4 cases of NAFLD LC in our study group, and little is known about the prevalence of this disease in hospitalized patients. Therefore, we cannot compare cryptogenic cirrhosis with NAFLD LC. We assumed that some of these cases may bear occult AIH or viral hepatitis due to the scarcity of liver biopsy and the absence of viral hepatitis serum markers. Further studies are necessary to confirm our observations and reveal the possible mechanisms.

It is reported that UGIB is the leading cause of death for patients with alcoholic liver cirrhosis[33]. Among the major causes of LC, the OR of alcoholic LC is highest (OR = 1.89), indicating that alcoholic LC patients may have the highest risk of developing UGIB. Risk factors for UGIB include Child-Pugh classification (C > B > A), the size of varices (large > medium > small, defined as > 10 mm, 5-10 mm, and < 5 mm in diameter, respectively), and the endoscopic presence of red wale marks. In addition, alcoholic cirrhosis is one of the main factors associated with the progression from small to large varices[34]. Luca *et al*[35] have demonstrated that minor alcohol consumption will increase hepatic venous pressure gradient (HVPG) and blood flow in the collateral portal vein. Although it is controversial whether alcohol consumption increases the incidence of gastroduodenal ulcer, research by Auroux *et al*[36] suggests that recent alcohol intake favors the development of gastroduodenal erosions. Above

Table 7 Odds ratios of the different etiologies with respect to the complications of upper gastrointestinal bleeding

Complication	HBV cirrhosis (n = 6239)	HCV cirrhosis (n = 226)	Alcoholic cirrhosis (n = 459)	Autoimmune cirrhosis (n = 163)	Mixed etiology (n = 400)	Cryptogenic cirrhosis (n = 237)	Others (n = 356)
UGIB (Y/N)	739/5500	24/202	98/361	16/147	47/353	41/196	41/315
OR	1.00	1.07	1.89	0.90	0.83	1.76	1.01
95%CI		0.68-1.69	1.48-2.41	0.50-1.60	0.60-1.16	1.21-2.52	0.72-1.44
P value		0.759	< 0.001	0.713	0.282	0.002	0.938

Others: cases excluding the six previous etiologies; OR (95%CI) was calculated with a multivariate logistic model adjusted for age, gender, year, birthplace (Cantonese, Other Chinese, Foreigner), and Child-Pugh value using the stepwise forward method, and the *P* values were determined by unconditioned logistic regression. HBV: Hepatitis B virus; HCV: Hepatitis C virus; UGIB: Upper gastrointestinal bleeding.

Table 8 Odds ratios of different etiologies with respect to the complications of hepatocellular carcinoma

Complication	HBV cirrhosis (n = 6239)	HCV cirrhosis (n = 226)	Alcoholic cirrhosis (n = 459)	Autoimmune cirrhosis (n = 163)	Mixed etiology (n = 400)	Cryptogenic cirrhosis (n = 237)	Others (n = 356)
HCC (Y/N)	2118/4121	51/175	41/418	4/159	97/303	57/180	325/31
OR	1.00	0.54	0.16	0.05	0.58	0.60	0.20
95%CI		0.38-0.75	0.11-0.22	0.02-0.17	0.45-0.74	0.44-0.83	0.13-0.31
P value		< 0.001	< 0.001	< 0.001	< 0.001	0.002	< 0.001

Others: cases excluding the six previous etiologies. The OR (95%CI) was calculated with a multivariate logistic model adjusted for age, gender, year, birthplace (Cantonese, Other Chinese, Foreigner), and Child-Pugh value using the stepwise forward method, and the *P* values were determined by unconditioned logistic regression. HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

all, the cases of alcoholic LC may have more serious varices, higher HVPG, and more gastroduodenal erosions, resulting in a higher prevalence of UGIB.

HCC is the most common form of liver cancer and has become the sixth-most common neoplasm and leading cause of death among patients with cirrhosis[37,38]. Chronic HBV infection accounts for more than 50% of all cases of HCC globally and 70% in Asia and Africa[37]. In this study, HBV LC exhibited the highest OR compared with all other major etiologies. Our observation has been confirmed by the other large-scale study conducted in the same city, in which the OR of primary liver cancer in HBV was highest for HBV, HCV, family history, aflatoxin B1, and alcohol consumption[39]. Data from other nations and regions also suggests that HBV LC is an independent risk factor for HCC development[40,41]. Although the exact mechanism of HBV infection resulting in HCC has not been well described, a large number of experiments *in vitro* and *in vivo* have demonstrated the important role of HBV infection in HCC occurrence[42,43].

In conclusion, viral hepatitis remains a major cause of LC, but the ratio has decreased to less than 80%. Meanwhile, cases of autoimmune, cryptogenic, and mixed etiology are increasing gradually, from which an increase in incidence and prevalence can be expected in the future. LC caused by alcohol consumption accounted for significantly more patients with upper gastrointestinal hemorrhage. HBV has long been considered a strong carcinogenic agent in LC patients, and our study confirmed this point of view, suggesting that more measures should be taken to prevent and manage viral hepatitis cirrhosis.

As this is a retrospective, cross-sectional study, and although we have searched cases by all means, there are still possibilities of missing cases of LC due to the lack of clinical data; furthermore, some cases had the potential of being falsely defined as "cryptogenic" because of the absence of some laboratory tests, and the epidemiologic conclusion based on a single center clinical practice is limited. Prospective, multi-center studies need to be conducted to reveal the exact incidence and prevalence of liver cirrhosis in China.

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COMMENTS

Background

Liver cirrhosis can cause gastrointestinal bleeding, liver cancer and other severe clinical complications; therefore, it is very important to prevent and treat the disease. The epidemiology and etiology have changed dynamically in the past decade, but to date, limited information about the epidemiological distribution of the etiology in China is available. It is reported that approximately 57% of liver cirrhosis is due to hepatitis B virus (HBV) (30%) and hepatitis C virus (HCV) (27%) globally, and the etiologies differ geographically. Many studies have reported that different etiologies tend to result in different complications; for example, hepatocellular carcinoma (HCC) occurs more often in viral hepatitis liver cirrhosis (LC) cases. However, the exact relationship between the LC etiology and complications has not been verified in large sample studies.

Research frontiers

The research hotspot in liver cirrhosis epidemiology is to describe the etiology distribution in different areas, to reveal the exact incidence and prevalence and to explore the prognostic factors affecting mortality.

Innovations and breakthroughs

Clinical research concerning the etiology and complications of LC in Southern China are rare and typically involve a small sample population. We investigated the etiology distribution based on a cross-sectional, 8080-patient study and

found that viral hepatitis remained the major cause of LC in Southern China. Furthermore, we observed a continuous decrease in the constitutional ratio of HBV cirrhosis as well as a slight increase of autoimmune, cryptogenic and mixed etiology over 10 years. Moreover, the authors observed that alcohol consumption is the most important risk factor for upper gastrointestinal bleeding and confirmed that HBV is a strong carcinogenic agent in LC patients using unconditioned, multivariate logistic regression incorporating age, gender and liver function status.

Applications

The study results suggest that the major etiology of LC in Southern China is viral hepatitis. However, the proportions of viral hepatitis and HBV are gradually decreasing. Alcoholic LC patients had a greater risk of experiencing upper gastrointestinal bleeding, and HBV LC patients may have more hepatocellular carcinoma.

Terminology

LC is a chronic and progressive disorder caused by varying liver diseases and characterized by regenerated nodule development. Cirrhosis can progress to upper gastrointestinal bleeding, hepatic encephalopathy, HCC and other severe clinical complications in the decompensated stage. HCC is one of the most common malignancies worldwide and is usually caused by HCV, HBV and chronic alcohol consumption. HCC is the leading cause of death among patients with cirrhosis.

Peer review

This is an interesting cross-sectional study aimed at evaluating the etiology and complications of LC in Southern China. The manuscript is generally well written and has scientific value because it discusses a relevant subject (etiology of LC) and includes a large cohort of patients.

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