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Gallstones in liver transplant recipients: A single-center study in China

LIVER/BILIARY

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Original Article

ABSTRACT

Background/Aims: Liver transplant recipients include patients who present with almost all kinds of end-stage liver disease. Studying the relationship between gallstones and end-stage liver disease among liver transplant recipients is becoming important.

Materials and Methods: Multiple logistic regression analysis was applied to assess 1640 liver transplant recipients. Multiple factors were involved in the analysis, including age, sex, total bilirubin and total cholesterol levels, Child score, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcoholic cirrhosis, and hepatocellular carcinoma (HCC).

Results: Age and Child score are independent risk factors for the development of gallstone disease (GD). The average age of the recipients in the GD group was 49.22±9.96 years, which was significantly higher than that in the GD-free group (48.23±9.79 years). The Child score of the recipients in the GD group was 9.21±2.47, which was significantly lower than that of the recipients in the GD-free group, which was 8.79±2.48 ($t=3.23$, $p<0.001$). We also found that hepatitis B is an influential factor in GD.

Conclusion: The prevalence of gallstones among liver transplant recipients is related to the Child score and patient age. The prevalence of GD is lower in patients with HCC and in those who are HBV positive and is relatively higher in HCV-positive patients and in those with alcoholic cirrhosis, although no significant differences were found.

Keywords: Gallstone, GD, liver transplant, prevalence, Child score, hepatitis B, hepatitis C, alcoholic cirrhosis, hepatocellular carcinoma

INTRODUCTION

Hepatitis, cirrhosis, liver cancer, and other liver diseases influence the metabolic functions of the liver and affect the development of gallstones.

Liver transplantation is the only effective treatment for end-stage liver disease. Candidates for liver transplantation include patients that present with almost all kinds of end-stage liver disease. The relationship of gallstones with end-stage liver disease needs to be evaluated among candidates for liver transplantation. We investigated the prevalence of gallstones in 1640 liver transplant recipients in our transplant center. Multivariate analysis was applied to determine the causes of gallstones in patients with end-stage liver disease.

MATERIALS AND METHODS

Patients

We selected Chinese liver transplant recipients from Tianjin First Center Hospital (from May 1994 to July 2011) who registered in the Chinese Liver Transplant Registry. A total of 1640 cases were selected, including 1411 male patients and 229 female patients, with ages ranging from 16 to 77 years. Patients who underwent retransplantation and who had congenital liver disease were excluded. Total bilirubin, serum albumin, and total cholesterol levels, hepatic encephalopathy, ascites, coagulation conditions, Child score, and the etiology of all patients were investigated and assessed. All patients underwent ultrasonography (HD11 XE ultrasound ma-

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Table 1. The etiology of 1640 liver transplant recipients, and the incidence of gallstone disease (GD)

Entity	Case (n)	Ratio (%)	GD present	GD prevalence (%)
HBV	1343	81.77	420	31.27
HCV	100	6.10	40	40.00
Alcoholic cirrhosis	64	3.90	28	43.75
PBC	56	3.41	15	26.79
PSC	7	0.43	2	28.57
AIH	6	0.37	4	66.67
Wilson's disease	7	0.43	4	57.14
Budd–Chiari Syndrome	3	0.18	2	66.67
Multiple hepatic cyst	3	0.18	1	33.33
Drug-induced liver disease	5	0.30	2	40
Cancer (without virus)	12	0.73	2	16.67
Cryptogenic cirrhosis	34	2.07	14	41.18

HBV: hepatitis B virus; HCV: hepatitis C virus; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; AIH: autoimmune hepatitis

chine; Philips Healthcare, Amsterdam, Holland), abdominal computer tomography (CT) (SOMATOM Spirit CT scanner; Siemens AG, Munich, Germany), and abdominal magnetic resonance imaging (MRI) (MAGNETOM MRI systems; Siemens AG, Munich, Germany) before operation, and their postoperative pathology reports were reviewed to confirm the presence of gallstones (Table 1). This study was conducted in accordance with the declaration of Helsinki and with approval from the ethics committee of Tianjin Medical University. Signed consent forms were obtained from all participants.

Statistical analysis

All patients were divided into two groups, namely, the gallstone disease (GD) group and the GD-free group. First, we compared the two groups using single-factor analysis. Single mean data were obtained using a t-test, and non-normally distributed data were evaluated using a rank sum test. The frequency data were analyzed using a chi-square test. Multivariate analysis was then applied using SPSS 16.0 statistical software (SPSS, Inc., Chicago, IL, USA). Multiple logistic regressions were used to analyze whether the gallstones were related to age, sex, total bilirubin and total cholesterol levels, Child score, liver cancer, hepatitis B, hepatitis C, and alcoholic cirrhosis.

RESULTS

Incidence of GD in liver transplant recipients

Gallstone disease was diagnosed in 534 of the 1640 liver transplant recipients; the incidence was 32.56%. We divided the liver transplant recipients into GD-free group and GD group and then analyzed their results (Table 2). The two groups exhibited a significant age difference. The average age of the recipients in the GD group was 49.22±9.96 years, which was significantly higher than that of the recipients in the GD-free group, which was 48.23±9.79 years (t=3.30, p<0.001). There was no significant difference in the prevalence of gallstones between the male (1411 cases) and female (229 cases; p=2.0) recipients. However, the prevalence was higher in females (36.24%) than in males (31.96%). The Child score of the recipients in the GD group (9.21±2.47) was significantly higher than that of the recipients in the GD-free group (8.79±2.48; t=3.23, p<0.001). Total bilirubin data exhibited a non-statistical distribution. The rank sum test was applied to compare the two groups. In the recipients in the GD-free group, the median was 43.48, with an interquartile range of 21.92 to 100.20. In the recipients in the GD group, the median was 44.90, with an interquartile range of 23.32 to 112.92. A two-sided test Z-value was 0.52 (p=0.601). These results suggest no significant differences between the recipients in the two groups. No significant difference in the total cholesterol level was observed between the recipients in the GD (3.21±1.47) and GD-free (3.28±1.55) groups.

Incidence of GD in different diseases

Hepatitis C virus (HCV) infection was positive in 100 liver transplant recipients and was negative in the remaining 1540 recipients. The incidence of gallstones was 40.00% in the HCV-positive group and 32.08% in the HCV-negative group (p=0.101), but the difference was not statistically significant. Up to 1343 liver transplant recipients were hepatitis B surface antigen (HBsAg) positive, and the incidence of gallstones was 31.27%, which is significantly lower than that in the remaining 297 HBsAg-negative recipients (38.38%, p=0.018). We also compared the effects of alcoholic cirrhosis. The incidence of gallstones in 64 alcoholic cirrhosis recipients was 43.75%, whereas that in the 1576 non-alcoholic cirrhosis recipients was 32.11% (p=0.051); this difference is not significant. The incidence of gallstones among the 873 hepatocellular carcinoma (HCC) liver transplant recipients was 30.24%, which is not significantly from that of the 767 non-HCC recipients (35.2%) (Table 2).

Relationship of end-stage liver disease with gallstones

Two-dimensional multivariate logistic regression analysis revealed the relationship between end-stage liver disease and gallstones. Recipient age and Child score were independent risk factors for developing gallstones among liver transplant recipients. Other factors such as recipient sex, total bilirubin and total serum cholesterol levels, hepatitis B and C, alcoholic cirrhosis, and liver cancer are not independent risk factors for developing GD among patients who underwent liver transplantation (Table 3).

DISCUSSION

The prevalence of cholelithiasis is 3.5% to 7.3% in the ethnic Chinese population (1-3). Our study showed that the incidence of gallstones was 32.56% in liver transplant recipients. This result is approximately 5 to 10 times higher than that of the general population and is even higher than the incidence in patients with liver cirrhosis in China (2).

Table 2. Factors impacting the formation of gallstones in 1640 liver transplant recipients

Factors	GD present (n=534)	GD absent (n=1106)	T=	Z=	X2=	p=
Age	49.22±9.96	48.23±9.79	3.30			<0.001
Gender					1.65	0.20
Male	451	960				
Female	82	146				
Child score	9.21±2.47	8.79±2.48	3.23			<0.001
TBIL (μmol/L)	44.90	43.48		0.52		0.601
Total cholesterol (mmol/L)	3.21±1.47	3.28±1.55	0.83			0.41
HCV infection					2.68	0.101
Positive	40	60				
Negative	494	1046				
HBV infection					5.60	0.018
Positive	420	923				
Negative	114	183				
Alcoholic cirrhosis					3.80	0.051
Present	28	36				
Absent	506	1070				
HCC					4.58	0.032
Present	264	609				
Absent	270	497				

TBIL: total bilirubin; HCV: hepatitis C virus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma.

Table 3. Logistic regression results

		B	S.E.	Wald	Df	Sig.	Exp (B)	95.0% C.I. for Exp (B)
Step 8a	Age	0.019	0.006	12.302	1	0.000	1.019	1.009-1.031
	Child score	0.074	0.021	11.935	1	0.001	1.007	1.033-1.123
	Constant	−2.344	0.351	44.553	1	0.000	0.096	

a. Variable(s) entered on step 1: recipient's age, Child score, sex, total bilirubin and total cholesterol levels, hepatitis B, hepatitis C, alcoholic cirrhosis, carcinoma

Treating GD in patients with end-stage liver disease is difficult because of their poor general health and poor hemostasis. Cholecystitis is likely to cause abdominal adhesion, which would make liver transplantation difficult. Peritonitis, which is caused by cholecystitis, can be life-threatening to patients with end-stage liver disease. Therefore, investigating the prevalence of cholelithiasis is very important in patients with end-stage liver disease who are undergoing liver transplantation.

Liver cirrhosis is an independent risk factor for GD. Patients with liver cirrhosis have weak gallbladder contractility, which delays bile emptying. Therefore, bile cannot be fully secreted from the gallbladder, and large amounts of oversaturated unconjugated bilirubin are deposited in the gallbladder, thereby contributing to gallstone formation (3,4). The prevalence of gallstones gradually increases with the progression of liver cirrhosis (5).

The current study concludes that the Child score is an independent risk factor for GD among liver transplant recipients. Considering the Child score is a common indicator for evaluating the severity of liver damage, this result suggests that the incidence of GD is positively associated with the severity of liver damage. This finding is consistent with findings of previous studies (2,6,7). In our present study, the prevalence of gallstones was 27.81% in the 338 Child A patients, 30.32% in the 597 Child B patients, and 36.60% in the 705 Child C patients (p=0.007). The results indicate that GD is more likely with an increasing severity of liver disease (8). A study on Child classification showed that cirrhosis severity and decreased liver function are precipitating factors for gallstone formation. Our data revealed the same conclusion. Liver function is decreased by the inactivation of various substances such as estrogen, glucagon, vasoactive intestinal peptide, histamine, and somatostatin in end-stage liver disease. These substances relax the gallblad-

der smooth muscle, which contributes to the formation of gallstones. A study on patients with cirrhosis revealed that the severity of cirrhosis is an independent risk factor for gallstone formation and that the incidence of cholelithiasis is positively correlated with the severity of liver damage (9-11). The results of our study showed significant differences in gallstone incidence and Child classification ($p<0.01$) among the three different groups. The incidence of gallstones among patients with end-stage liver disease was positively associated with the severity of liver damage.

The incidence of gallstones in the general population increases with age (1,2,7,12-15). Our study also concluded that the incidence of gallstones increases with age in patients with end-stage liver disease. Age is an independent risk factor for GD. The prevalence of cholelithiasis is estimated to be between 0.13% and 2% in children less than 19 years and is lower than that in adolescents (16-18). Therefore, we excluded patients under 15 years. We found a significant relationship between age and gallstone formation in end-stage liver disease. Furthermore, the multivariate analysis revealed that hepatitis B is an independent risk factor for gallstone formation. However, our findings are different from those of Coelho et al. (19). They did not find any relationship between age and gallstone formation among liver transplant recipients.

Numerous studies have investigated gallstones among patients with different genders (20). Most studies suggest that women are more prone to suffer from gallstone formation and that the incidence of gallstones is increased in pregnant women and in patients taking hormone supplements (1,21). Studies on patients with liver cirrhosis also found that the prevalence is higher in females than in males (2). However, the incidence of gallstones did not significantly differ between male and female patients with end-stage liver disease. The high incidence of GD in female patients is estrogen-related because estrogen plays a key role in gallstone formation. Furthermore, patients with end-stage liver disease often suffer from estrogen-related metabolic disorders (22,23). Estrogen inactivation is often reduced, and the conversion of progesterone to estradiol is increased among patients with liver cirrhosis. In addition, the levels of sex hormone-binding globulin and other factors are also elevated. Therefore, estradiol levels are elevated in patients with liver cirrhosis. Estradiol significantly reduces diphosphate UDP-glucose acid transferase activity in liver microsomes. Intrahepatic glucuronide during bilirubin formation is also reduced. Therefore, elevated unconjugated bilirubin levels contribute to the formation of pigment gallstones. Elevated estrogen levels also affect bilirubin emptying, which contributes to gallstone formation. Estrogen inactivation is weakened in male and female patients with liver cirrhosis; therefore, the risk of gallstone formation has no gender difference (13,24,25).

China has a high prevalence of hepatitis B, and majority of liver transplant recipients are HBV positive. Many Chinese studies have investigated the relationship between hepatitis B and gallstone formation, and majority of the articles concluded that hepatitis B increases the risk of developing gallstones (26,27). Our study compared the incidence of gallstones among patients with hepatitis B with that of other patients. However, many patients with liver cirrhosis and fibrosis were included from the hepatitis B group. By contrast, patients without hepatitis B seldom had liver disease. Consequently, these studies cannot rule out the influence of liver cirrhosis on gallstone formation. In our present study, the incidence of gallstone among HBV-positive patients with end-stage liver disease was lower than that of the other patients. The univariate analysis showed that the incidence of cholelithiasis among patients with hepatitis B was significantly lower than that of other patients ($p<0.05$). Furthermore, the multivariate analysis indicated that hepatitis B was not an independent risk factor for gallstone formation. Similar results were obtained from other foreign studies (28). Hepatitis B may slightly affect gallstone formation in patients with end-stage liver disease, but it is not an independent risk factor.

The prevalence of gallstones was 23.3% among HCV-positive patients with cirrhosis, which is significantly higher than 12.4%, which was its prevalence among HBV-positive patients with cirrhosis. Our current study also had a similar result. The incidence of gallstones was 40% among HCV-positive liver transplant recipients, higher than 31.27%, which was its incidence among HBV-positive patients. However, majority of the participants had end-stage liver disease. Thus, the incidence of gallstones among the HCV- and HBV-infected patients was significantly higher than that in other patients with stable cirrhosis, with no significant difference between the patients infected with HBV and those infected with HCV. Therefore, HCV infection is not an independent risk factor for gallstone formation among liver transplant recipients. HCV can directly infect the gallbladder and may contribute to the development of gallstones (29). Other researchers also found HCV RNA and HCV antigen in gallbladder specimens from the autopsy of hepatitis C patients (28). This may increase the infection risk among patients with gallstones by changing the function of the gallbladder and gallbladder mucosa. We found a relatively higher incidence of gallstones among hepatitis C patients with end-stage liver disease. Further research is needed to determine the relationship between HCV and gallstones.

Buchner et al. (7) studied the relationship between gallstone occurrence and alcoholic cirrhosis in 3000 American patients with alcoholic cirrhosis. They found that patients with alcoholic cirrhosis are relatively resistant to gallstone formation. However, our results show that patients with alcohol-induced cirrhosis who underwent liver transplantation had a relatively higher incidence of gallstone formation than those with other liver diseases but that alcoholic cirrhosis was not an independent risk factor. These results differ from those of studies conducted in the United States. Other studies involving Chinese populations have similar results to our study. Alcohol abuse in-

creases the risk of gallstone formation because of liver damage and reduced bile salt synthesis; therefore, alcoholic cirrhosis is a strong independent risk factor for gallstone formation in the general population (30-32). Bile salt synthesis is reduced in transplant recipients because of liver failure; thus, the gap between alcoholism and other factors is reduced. Ethnic differences and the type of alcohol consumed may contribute to gallstone formation.

Many studies investigated biochemical markers for the liver and gallbladder, including albumin, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, and other markers (2,3,33-36). A study involving 1000 cases (33) failed to find a single biochemical marker that was associated with the occurrence of gallstones. We selected total bilirubin to analyze its relationship with gallbladder stones; however, our study also failed to obtain a positive result.

Total serum cholesterol level is not a risk factor for GD. We obtained the same result in our study among liver transplant recipients. The secretion of cholesterol from bile affects gallstone formation. Increased total serum cholesterol level increases the liver uptake and secretion of biliary cholesterol. Elevated total cholesterol levels in bile promote gallstone formation. In patients with end-stage liver disease, cholesterol synthesis, uptake, secretion, and conversion are somehow disturbed by damaged liver function. Therefore, total serum cholesterol is not necessarily associated with gallstone formation. Consequently, the close relationship between cholesterol secretion in bile and total serum cholesterol has not been found.

We discussed the relationship between HCC and gallstone formation in liver transplant recipients, and no significant association was found. However, the prevalence of the capsule stone in liver cancer recipients was lower than that in non-tumor liver transplant recipients (37,38). We need to study further whether gallstones decrease the risk of developing liver tumors.

The current study is the first to evaluate the prevalence of gallstones among Chinese patients with end-stage liver disease who underwent liver transplantation. We concluded that the incidence of gallstones among liver transplant recipients is associated with the Child score and patient age. The analysis of the relationship between the etiology of liver disease and the formation of gallstones revealed no independent risk factors. The incidence of gallstones was relatively low among patients with hepatitis B and liver cancer but was relatively high among patients with hepatitis C and alcoholic cirrhosis.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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