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Original Article

The Incidence of Gallstone Complications in Patients with Cirrhosis

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ABSTRACT

Background:
About one-third of patients with cirrhosis have gallstones. Gallstones in these patients are often asymptomatic and discovered incidentally, and only 1–2% per year will develop complications. We aimed to assess the frequency of gallstone complications in Egyptian patients with cirrhosis and compare them to gallstone complications in those without cirrhosis.

Materials and Methods:
Our study included 120 patients with first-time discovered gallstones. They were selected from patients admitted to the outpatient clinic or the Tropical Medicine Department of Zagazig University, Egypt. They were classified into two groups. The first group comprised 60 patients with cirrhosis with gallstones and the second group comprised 60 healthy individuals with gallstones. Risk factors of gallstones were assessed. Upon admission, all patients underwent a thorough history and clinical examination. Moreover, liver function tests and pelviabdominal ultrasound were done and triglyceride and amylase levels were measured to confirm the presence of gallstones. They were followed up for five years to assess the frequency of gallstone complications.

Results:
The group with cirrhosis had significantly lower gallstone complications than the non-cirrhotic group (8% vs. 41%, $p < 0.001$) as regard the overall complications after 5 years of follow-up. We found that there was a significant difference regarding each complication separately. Acute cholecystitis was (5% vs. 16.7%, $p = 0.03$). Acute pancreatitis was (1.6% vs. 13.3%, $p = 0.01$). Obstructive jaundice was (1.6% vs. 11.7%, $p = 0.02$).

Conclusion:
Our study revealed that the frequency of gallstones complications in patients with cirrhosis was much lower than patients without cirrhosis with gallstones after 5 years of follow-up.

Keywords: Gallstone, Cirrhosis, Complications

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INTRODUCTION

Gallstones are considered a common clinical finding in the general population. Gallstones disease (GSD) is one of the most prevalent and costly gastrointestinal tract disorders in the world (1). The prevalence of gallstones in the general population was 10-20% (2). They are cholesterol or pigment stones or mixed. Cholesterol stones occur mostly solitary, whereas pigment stones are commonly multiple in numbers (3).

Cirrhosis is considered a major health problem causing significant morbidity and mortality worldwide

especially in Egypt (4). About 1/3 of patients with cirrhosis have gallstones, and most of them have pigmented stones. The occurrence of gallstones in cirrhosis is around 23% with an annual incidence of 3.4% (5). The main risk factors for gallstone formation are female sex, obesity, alcohol use, diabetes mellitus, and hypertriglyceridemia, but these factors are less important in patients with cirrhosis who have gallstones. The main risk factors considered in these patients are severity, duration, and cause of the underlying liver disease (6).

Gallstones in patients with cirrhosis are often asymptomatic and discovered incidentally on ultrasound imaging, but about 1–2% per year will develop complications, mostly because of gall bladder stasis and autonomic neuropathy (1). Many national and international studies have assessed the frequency of GSD in patients with cirrhosis. We aimed to assess the frequency of GSD complications in Egyptian patients with cirrhosis and compared it to complications of patients without cirrhosis with gallstones.

MATERIALS AND METHODS

Our study was a prospective cohort study. The sample size was calculated according to the expected positive predictive value of 70, 85% power, and 95% confidence interval. Our study included 120 patients with first-time discovered gallstones. They were selected from patients admitted to the outpatient clinic or Tropical Medicine Department of Zagazig University. They were classified into two groups. The first group was comprised 60 patients with cirrhosis with gallstones and the second group comprised 60 age- and sex-matched healthy individuals with gallstones. This study was done from May 2015 to May 2020. The study was conducted according to the sound clinical practice guidelines and according to the declaration of Helsinki. A written informed consent was obtained from each patient.

Most of the patients admitted to the outpatient clinic were complaining of biliary colic, epigastric pain, or fatty dyspepsia. Only 20% of patients needed admission to the department for further care. Patients younger than 18 years, those who refused to give consent, had hepatocellular carcinoma, cholangiocarcinoma, or any abdominal tumors and cirrhotic patients with active variceal bleeding were excluded from the study.

On admission either to the department or outpatient clinic, gallstone risk factors such as sex, diabetes, body mass index (BMI), weight in kilograms divided by the square of height in meters, or hypertriglyceridemia were assessed in all patients. All patients underwent a thorough history and clinical examination. Moreover, liver function tests and pelviabdominal ultrasound were done and triglyceride and amylase levels were checked to confirm the presence of gallstones (by detection of an echogenic structure within the gallbladder lumen that caused a posterior acoustic shadow). All patients were followed up for five years. Patients without cirrhosis were followed up in the outpatient clinic regularly every six months or they were admitted to the department only if severe non-responding biliary colic or other complications were present. Patients with cirrhosis were followed up every two months mainly in the department because of frequent admission because of cirrhosis complications. The regular follow-up included ultrasound and full clinical examination. Lipase, amylase, and abdominal CT were done if acute pancreatitis were suspected. Bilirubin, alkaline phosphatase, gamma-glutamyl transferase (GGT) were measured and magnetic resonance cholangiopancreatogram (MRCP) or endoscopic retrograde cholangiogram (ERCP) were done if obstructive jaundice was suspected.

Statistical Analysis

All data were collected and statistically analyzed using SPSS software, version 19. Continuous quantitative variables were expressed as the mean ± SD and median (range), and categorical qualitative variables were expressed as absolute (number) and relative frequencies (percentage). Continuous data were checked for normality using the Shapiro-Wilk test. Independent samples Student's *t*-test was used to compare two groups of normally distributed data and the Mann-Whitney test was used to compare two groups of not-normally distributed data. Categorical data were compared using the Chi-square test. All tests were two-sided. $p < 0.05$ was considered statistically significant (S), $p < 0.001$ was considered highly statistically significant (HS), and $p \geq 0.05$ was considered statistically insignificant (NS).

Table 1: Relationship between presence of cirrhosis and baseline characteristics among the studied groups

Variables	Patients with cirrhosis (n = 60)	Patients without cirrhosis (n = 60)	*t* test	*p* value
Age				
Mean ± SD (yrs)	53.80 ± 4.25	53.50 ± 4.10	0.394	0.694
Range	47-62	48-61		
BMI				
Mean ± SD (kg/m^2)	22.80 ± 1.25	23.10 ± 1.89	-1.074	0.284
Range	18-26	22-33		
Sex				
Female	33 (55%)	35 (58.3%)	0.135*	0.712
Male	27 (45%)	25 (41.7%)		
Diabetes mellitus				
No	39 (65%)	29 (48.3%)	3.394*	0.065
Yes	21 (35%)	31 (51.6%)		

*: Chi-square test

Table 2: Relationship between presence of cirrhosis and laboratory characteristics among the studied groups

Variables	Patients with cirrhosis (n = 60)	Patients without cirrhosis (n =6 0)	*t* test	*p* value
ALT (U/l)				
Mean ± SD	53.10 ± 11.70	44 ± 12.90	4.407	< 0.001
Range	18-74	18-79		
AST (U/l)				
Median	41	30	-4.544*	< 0.001
Range	28-72	17-72		
Albumin (g/dl)				
Mean ± SD	3.18 ± 0.56	3.59 ± 0.13	-5.445	< 0.001
Range	1.8-4	3 - 4		
Bilirubin (mg/dl)				
Mean ± SD	1.26 ± 0.70	0.60 ± 0.21	6.703	< 0.001
Range	0.2–2.30	0.2–1.30		
Triglycerides (mg/dl)				
Mean ± SD	136.90 ± 9.60	137.40 ± 8.90	-0.266	0.791
Range	120-159	120-159		
Amylase (units/l)				
Mean ± SD	34.60 ± 8.50	35.50 ± 6.85	-0.571	0.569
Range	20-65	20-48		

*: Mann-Whitney test

RESULTS

As shown in table 1, there was no significant difference between both groups regarding baseline data.

We found no significant difference was seen between the groups concerning serum triglyceride and amylase levels as risk factors for gallstone formation (table 2).

We found a highly significant difference between the groups regarding the overall complications with a significant difference regarding each complication separately (table 3).

DISCUSSION

GSD represents a prime public health problem worldwide. GSD can be taken into consideration as a high prevalence hepatobiliary disease, with a prevalence of 10-20%. Approximately 6.3 million men and 14.2 million women aged 20–74 withinside the USA have GSD (1). GSD is one of the maximum pricey digestive diseases in western countries, and fees for treating gallstones increase significantly (approximately 4–6.2 billion dollars) if surgical complications occur (7).

Gallstones present in patients with cirrhosis in a higher percentage than the normal population. The high incidence of gallstones in these patients has been attributed to metabolic changes including elevated unconjugated bilirubin in bile secondary to hemolysis

Table 3: **Frequency of gallstones complications among the studied groups**

Variables	Patients with cirrhosis (n = 60)	Patients without cirrhosis (n = 60)	*t* test	*p* value
Complications	5(8%)	25 (41.6%)	17.78	< 0.001
Acute cholecystitis	3(5%)	10 (16.7%)	4.227	0.03
Acute pancreatitis	1(1.6%)	8 (13.3%)	5.886	0.01
Obstructive jaundice	1(1.6%)	7 (11.7%)	4.821	0.02

and hypersplenism, reduced cholesterol secretion, diminished bile acid pool, reduced apolipoprotein (apoAI and apoAII) secretions. Gallbladder contractility was also observed in some studies to be impaired in liver cirrhosis (5). Grassi and colleagues suggested that biliary calculus does not worsen the course of liver cirrhosis (8).

People without cirrhosis with gallstones are asymptomatic. Symptoms may arise within five years in approximately 10% and within 20 years in 20% of patients. However, when typical symptoms appear, there is a high possibility that they become recurrent or are accompanied by complications as approximately two-thirds of symptomatic patients display recurrent symptoms within 24 months (9). The most common symptom is biliary colic (steady right upper quadrant abdominal pain lasting more than half an hour) in the absence of fever. Other common symptoms related to gallstones include epigastric pain and intolerance to fried or fatty foods, nausea, bloating, and flatulence, frothy and foul-smelling stools (10).

Complications over 5 years are relatively uncommon in asymptomatic patients, and the overall risk rates for complications are very low (annual incidence of 0.3%) (10). The most common complications include acute cholecystitis, obstructive jaundice, and acute pancreatitis. Incidence of gallstone causing biliary obstruction is approximately 5 in 1000 people and 10-15% of the adult US population will develop gallstones in their lifetime. Other rare complications include Mirizzi syndrome, gallstone ileus, and gallbladder cancer (10). In most patients with cirrhosis, gallstones are asymptomatic. The risk of developing symptoms and complications is also low in patients with liver cirrhosis, but it was evaluated only in a few studies (9).

In our study, we found that there was no significant difference between both groups regarding age, sex, BMI, and diabetes mellitus. Concerning age, consistent with Coelho and colleagues, who did not observe the linear trend of increasing prevalence with increasing age in patients with chronic liver disease (11). Our results were not consistent with one study reporting that gallstone prevalence elevated with age in patients with chronic liver disease (12).

Age, sex, diabetes mellitus, and BMI, relevant factors for gallstone development in the general population, are much less important in patients affected by cirrhosis, where the main factors to be considered are the degree of impairment, and the cause and duration of underlying liver disease (13).

In our study, there was a highly significant difference between both groups regarding gallstone complications with a significant difference regarding acute cholecystitis, obstructive jaundice, and acute pancreatitis. These results are consistent with Gurusamy and Davidson (14).

Acute cholecystitis is the most frequent complication of symptomatic cholelithiasis (with an annual incidence of 0.3-0.4%) and is characterized by inflammation of the gallbladder wall. The risk of this is increased in patients with larger gallstones that are more likely to be trapped within the gallbladder. Gangrenous cholecystitis and perforation of the gallbladder are serious complications of acute cholecystitis. In severe cases, acute cholecystitis can be fatal (15). In our study, only three patients with cirrhosis developed acute cholecystitis with a frequency of 5%, consistent with one other study (16). They were hospitalized and relieved by intravenous hydration, correction of electrolyte disorders, pain control by ketorolac, and empirical antibiotics. 10 (16.7%) patients without cirrhosis developed acute cholecystitis; six were relieved by supportive care while four patients did not respond and required cholecystectomy. On follow-up, four of the six patients had already done cholecystectomy.

Acute pancreatitis (with an annual incidence of

0.04-1.5%), is caused by temporary obstruction to the pancreatic duct during the passage of a bile duct stone through the ampulla of Vater into the duodenum. It can range in severity from mild and transient to life-threatening (17). In our study, only one (1.6%) patient with cirrhosis developed acute pancreatitis, inconsistent with another study that reported an incidence of 21.1% for acute pancreatitis in patients with cirrhosis (18). This patient was hospitalized and received intravenous fluids, pain control by morphine and imipenem and required no further therapy, and recovered and ate after six days. In our study, eight (13.3%) patients without cirrhosis developed acute pancreatitis, consistent with Lindkvist and co-workers who found an incidence of 13.3% in patients without cirrhosis (19). Our results were inconsistent with a study reporting an incidence of 21.72% for acute pancreatitis in patients with cirrhosis and 14.28% in those without cirrhosis (20). All of them were completely relieved by hospitalization and supportive care and they started to eat within five to seven days. On follow-up, five of the eight mentioned patients had done cholecystectomy.

Obstructive jaundice (with an annual incidence of 0.1-0.4%) occurs when a bile duct stone obstructs the flow of bile into the duodenum. Patients will typically present with biliary colic accompanied by jaundice, dark urine, pale stools, and pruritus. In our study, only one (1.6%) patient with cirrhosis developed obstructive jaundice, which was inconsistent with a study reporting a rate of 26.2% in these patients (18) and required ERCP and stone extraction. Seven (11.7%) patients without cirrhosis developed obstructive jaundice, consistent with another study reporting the frequency of acute pancreatitis to be 7-20% in patients without cirrhosis (21). All of them required ERCP and stone extraction. On follow-up, all seven patients had done cholecystectomy. The limitation of this study was its small sample size. Other studies with more patients must be done.

CONCLUSION

We found that the frequency of gallstones complication in patients with cirrhosis was much lower than patients without cirrhosis who had gallstones after five years of follow-up.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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