Frequency of Cholelithiasis in Patients with Chronic Liver Disease: A Hospital-Based Study

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Background and study aim: Liver Cirrhosis is a strong and a common known risk factor for Cholelithiasis. Cholelithiasis is a multifactorial disease, based on a complex interaction of environmental and genetic factors. The primary aim of this study is to determine the frequency of cholelithiasis in chronic liver disease (CLD) patients admitted to Zagazig university hospitals. The secondary aim is to determine the risk factors and their association with the underlying etiology and severity of liver disease.

Patients and Methods: We conducted a hospital based study including 131 patients with chronic liver disease based on clinical, laboratory and Ultrasonographic findings. Demographic, clinical and etiological data were recorded, using a pre-coded questionnaire. A number of laboratory tests as fasting plasma glucose, total cholesterol, triglyceride, aspartate aminotransferase (AST), alanine amino-transferase (ALT), alkaline phosphatase (ALP), hepatitis B surface antigen (HBsAg), and antibody to hepatitis C virus (HCV-Ab) were analyzed.

Results: The number of registered cases was 131 with age (52.9±11.7).There were 55 (42%) males and 76 (58%) females. Hepatitis C (HCV) was present in 101 (77%) cases. The prevalence of cholelithiasis was 50.4%% (66 of 131 patients). Most of cholelithiasis patients presented with child C stage (68.2%), followed by child B (21.2%) and the least one was Child A. Hepatitis C (10.6%) was found to be associated with cholelithiasis (75.8%), followed by hepatitis B (13.6%). Auto-immune disease, diabetes mellitus, contra-ceptive pills and obesity are considered risk factors for cholelithiasis.

Conclusion: Cholelithiasis tends to occur more frequently in patients with decompensated CLD. The higher incidence of cholelithiasis in CLD appears to be associated with HCV infection. This is an important parameter to be considered in a country with high prevalence of HCV as Egypt.

INTRODUCTION

Gallstones (GS) are a major cause of morbidity and mortality throughout the world **[1]**. Gallstone disease (GSD) is responsible for about 10,000 deaths per year in the United States. About 7000 deaths are attributed to acute GS complications, such as acute pancreatitis. About 2000-3000 deaths are caused by gallbladder cancers (80% of which occur in the setting of gallstone disease with chronic cholecystitis) **[2]**. The prevalence of GS in patients with chronic liver disease (CLD) is 20-40%, while it is 10-15% among the general population **[3]**. Moreover, the incidence of gallstones increased significantly with the progression of liver disease **[4]**. In Eygpt, it was found that the prevalence of GSD in patients with CLD was 21.8% **[5]**. GSD is a multifactorial disease based on a complexinteraction of environmental and genetic factors. Gallstones are principally formed due to abnormal bileconstituents (eg, cholesterol, phospholipids and bilesalts) **[6]**. When bile is concentrated in the gallbladder, it can become supersaturated with such substances, which then precipitate as microscopic

crystals. The crystals are trapped in gallbladder mucus, producing gallbladder sludge. Over time, the crystals grow, aggregate, and fuse to form macroscopic stones **[7]**. Moreover, the increase in gall bladder wall thickness by hyperemia, edema, decreased contractility or impaired gallbladder emptying contributes to gallstone formation **[8]**. The most accurate and non-invasivemethod of predicting gallstone disease was achieved with the advent of the ultrasound, which has a sensitivity and a specificity of greater than 95%. However, the true prevalence of the disease remains hard toderive as the majority of patients remain asymptomatic.

According to the NIH guidelines, removal of thegallbladder is the treatment of choice for symptomatic GSD **[9]**. However, less focus has been directed on patient selection and typical or common symptom characteristics of this disease.

The primary aim of this study is to determine the frequency of cholelithiasis in CLD patients admitted to Zagazig university hospitals. The secondary aim is to determine the risk factors and their association with the underlying etiology and severity of liver disease.

PATIENTS AND METHODS

The study included 131 patients with CLD who were selected from Zagazig University hospitals from May to December, 2013. The study was approved by the local institutional review board. Informed consent was provided by all participants.

For each patient; demographic, clinical and etiological data were recorded by using a pre-coded questionnaire. A number of laboratory tests as fasting plasma glucose, total cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phos-phatase (ALP), hepatitis B surface antigen (HBsAg), and antibody to hepatitis C virus (HCV-Ab) were analyzed. All patients underwent ultrasound abdominal scanning.Ultrasonographic findings suggesting cirrhosis include; hypertrophy of the caudate lobe with concomitant atrophy of the posterior segments of the right lobe, coarse and heterogeneous echo texture, portal vein diameter> 13 mm, splenomegaly, and ascites **[10]**. Gallstones appear as echogenic foci in the gallbladder. They move freely with positional changes and cast an acoustic shadow **[11,12]**. Cirrhosis of the liver was diagnosed based on typical clinical features and sonographic findings according to the following criteria; (a)surface nodularity of the liver (b) coarsening and nodularity of the liver parenchyma with ascites (c)evidance of splenomegaly, and (d) evident collateral circulation shown in US. The severity of cirrhosis was categorized according to the Child– Pugh classification.

Patients were subsequently classified into compensated group (N=22 patients) and decompensated group (N= 109 patients). Decompensation means cirrhosis complicated by one or more of the following features; jaundice, ascites, hepatic encephalopathy, bleeding varices, hepatorenal syndrome, hyponatremia and spontaneous bacterial peritonitis.

Statistical analysis:

The Sample size was calculated using Epi info version 6.04. According to the statistical data, the average total number of registered patients was 1500 patient per year, and the prevalence of cholelithiasis was 40 %in CLD patients in the study of Acalovschi et al.[8] at confidence interval 95%, and the power was 80%. Our study included 131patients. We used SPSS (Statistical package for social science) version 21 to obtain descriptive statistics that were calculated in the form of: A) Mean ± Standard deviation (SD) for quantitative parametric data, B) Median and range for quantitative non-parametric data, C) Frequency (Number and percent) for qualitative data. Significance level for all statistical tests has a threshold of significance is fixed at 5% level (p-value).

RESULTS

This study included 131 patients with CLD; Their mean age was 52.9, SD (±11.7) years. There were 55 (42%) males and 76 (58%) females. Chronic HCV infection was found in 101 (77%) patients and 21 (16%) had chronic HBV infection. Table (1) summarizes the demographic and clinical characteristics of patients included in the study. The clinical presentation of the patients included in the study was summarized in Table (2).

The prevalence of cholelithiasis in the examined patients was 50.4% (66 of 131 patients). Our study showed that Cholelithiasis is more associatied with decompensated than compensated liver diseases (54.1% Vs 30.4%; p value <0.05).

In compensated patients with cholelithiasis; the mean serum Direct bilirubin level was significantly lower than in patients without cholelithiasis

(3.5mg/dL vs 0.5mg/dL, p value = 0.031).Other factors including AST, ALT, GGT, cholesterol and TG were not significantly associated with cholelithiasis.

In decompensated patients with cholelithiasis; the mean serum cholesterol and TG level was significantly lower than in patients without cholelithiasis (179mg/dL vs 155mg/dL, p value <0.001) and (109mg/dL vs 91mg/dL, p value = 0.017) retrospectivly. There was no statistically significant difference between ultrasonographic finding of cholelithiasis in compensated and decompensated patients in term of CBD, number and size of gallbladder stones (p value > 0.05) (Table 3).

There was no statistically significant difference between patients with or without cholelithiasis in term of spontaneous bacterial peritonitis, hepatic encephalopathy, hematemesis and melena (p value > 0.005) (Table 4).

The etiology of liver disease did not differ significantly between theose patient with or without cholelithiasis. Common causes included HCV infection, HBV infection and autoimmune disease (p value > 0.05) (Table 5).

The prevalence of cholelithiasis increased with the severity of the disease according to Child-Pough classification as the fellowing; In Child-Pugh A (10.6%), Child-Pugh B (21.2%), and in Child-Pugh C (68.2%). For all child-pugh grades, the difference between patients with or without cholelithiasis was statistically significant (p value = 0.004) as shown in Table (6).

The risk of cholelithiasis increased in patients with liver disease who were smokers, diabetic or have a history of contraceptive pills intake (OR= 0.86, 4.71 and 18.69 retrospectively. Diabetis mellitus and history of contraceptive pills intake have a significant association with cholelithiasis (p value > 0.001) (Table 7).

In the compensated group; we found three patients with cholecystitis. Two of them developed obstructive jaundice and one patient had Cholangitis. While, in decompensated group; we found seven patients with cholecystitis. Two of them developed obstructive jaundiceand onepatient had Cholangitis. Obstructive jaundice and cholecystitis showed a statistically significant increase in the compensated group (p value >0.008).

Table (1): Baseline characteristics of enrolled patients

Variables	Compensated group		Decompensated group	
	Patients with cholelithiasis N=7	Patients without Cholelithiasis N=15	Patients with Cholelithiasis N=59	Patients without Cholelithiasis N=50
Age (Mean±SD)	48.1±12.9	51.6±7.3	55.9±7.6	53.3±8.9
Sex Female (%)	6(85.7)	4(25.0)	36 (61)	30(60)
DM No.(%)	5(28.6)	3(18.8)	35(59.3)	13(26.0)
Smoking No. (%)	1(14.3)	9(56.3)	25(42.4)	19(38.0)
RBS (Mean ± SD)	203.3±79.3	136.5±34.6	178.6±11	157.5±10
Cholesterol(mg/dl)	186.2±44.4	138.3±43.7	179.1±41.2	155±23.1
TG (mg/dl)	114.8±52.8	62±39.3	109±42.6	91.3±20.3
WBC (cells/L)	5.5±4.1	5.6±1.4	7.6±4.7	7±5.1
HB(g/dl)	11.7±1.8	10.3±3.9	11.9±12.4	10.1±2
Platelet (cells/L)	80.5±56.5	117±112.7	86.9±49.1	107.9±83
T. bilirubin (mg/dl)	7.5±3	0.8±0.1	5.7±6.9	5.5±7.1
D.bilirubin (mg/dl)	3.5±1	0.5±0.1	3.3±5.2	4.2±5.3
T. protein (gm/L)	7.7±1.1	7.6±0.6	6.3±1.5	6.4±0.8
Albumin (gm/L)	3.3±0.5	3.2±0.5	2.4±1.2	2.3±0.9
Creatinine (mg/L)	0.9±0.3	0.6±0.2	1.1±0.7	1.7±3.1
INR	1.2±0.2	1.3±0.1	1.7±0.5	1.8±0.5
PT(seconds)	53.7±26.5	44.4±15.2	46.6±17.7	41.3±19.3
AST(IU/L)	57±15	49.4±14.8	66.8±62.4	74.4±90.4
ALT(IU/L)	55.5±17.8	47.2±14	80.2±119.1	64±42.8

Table (2): Clinical presentation of patients with chronic liver disease

Variables	Decompensated group			Compensated group		
	Patients with cholelithiasis N=59	Patients without cholelithiasis N=50	P value	Patients with cholelithiasis N=7	Patients without cholelithiasis N=15	P value
Abdominal pain	**42(71.2)**	**31(62.0)**	**0.309**	**7(100.0)**	**4(25.0)**	**<0.001****
Nausea	**30(50.8)**	**27(54.0)**	**0.743**	**3(42.9)**	**9(56.3)**	**0.554**
Vomiting	**18(30.5)**	**20(40.0)**	**0.3**	**1(14.3)**	**6(37.5)**	**0.265**
Anorexia	**54(91.5)**	**38(76.0)**	**0.026***	**7(100.0)**	**11(68.8)**	**0.094**
Heart burn	**46(78.0)**	**36(72.0)**	**0.472**	**3(42.9)**	**9(56.3)**	**0.554**
Dyspepsia	**58(98.3)**	**49(98.0)**	**0.906**	**5(71.4)**	**12(75.0)**	**0.857**
Rt. Hypo-chondrium pain	**29(49.2)**	**9(18.0)**	**<0.001****	**7(100.0)**	**12(75.0)**	**0.146**
Fever	**39(66.1)**	**24(48.0)**	**0.06**	**3(42.9)**	**0(0.0)**	**0.004***
LL edema	**40(67.8)**	**25(50.0)**	**0.06**	**6(85.7)**	**5(31.3)**	**0.016***
Bleeding tendency	**30(50.8)**	**22(44.0)**	**0.475**	**5(71.4)**	**0(0.0)**	**<0.001****
Jaundice	**33(55.9)**	**33(66.0)**	**0.284**	**7(100.0)**	**4(25.0)**	**<0.001****
HE	**45(76.3)**	**32(64.0)**	**0.161**	**3(42.9)**	**9(56.3)**	**0.554**

Table (3a): Ultrasonographic characteristic of cholelithiasis in compensated versus decompensated group

Variables	Compensated group N=7	Decompensated group N=59	P value
Number of GS			
single	4(57.1)	25(42.4)	
multiple	2(28.6)	11(18.6)	0.735
mud	1(14.3)	14(23.7)	
Size of GS			
Small	3(42.9)	25(42.4)	
Moderate	2(28.6)	5(8.5)	0.229
Large	2(28.6)	29(49.1)	
CBD			
Normal	5(71.4)	57(96.6)	0.191
Dilated	2(28.6)	2(3.4)	

Table (3b): Ultrasonographic presentation of enrolled patients

Variables	Decompensated group			Compensated group		
U/S Presentation	**Patients with cholelithiasis N=59**	**Patients without Cholelithiasis N=50**	**P value**	**Patients with cholelithiasis N=7**	**Patients without Cholelithiasis N=15**	**P value**
Spleen						
Removed	3(5.1)	1(2.0)	0.393	3(42.9)	1(6.3)	0. 32
Average	0(0.0)	0(0.0)		0(0.0)	6(43.7)	
Enlarged	56(94.9)	49(98.0)		4(57.1)	8(50.0)	
Liver (cirrhotic)						
Shrunken	43(72.9)	36(72.0)	0.97	3(42.9)	4(25.0)	0.315
Average	12(20.3)	10(20.0)		4(57.1)	7(50.0)	
Enlarged	4(6.8)	4(8.0)		0(0.0)	4(25.0)	
Gall bladder						
Shape						
Pear	57(96.6)	48(96.0)	0.132	6(85.7)	15(100.0)	0.122
Distended	2(4.0)	0(0.0)		1(14.3)	0(0.0)	
Contracted	0(0.0)	2(3.4)		0(0.0)	0(0.0)	
Wall						
Normal	0(0.0)	2(4.0)	0.121	1(14.3)	3(18.8)	0.795
Thick wall	59(100.0)	48(96.0)		6(85.7)	12(81.2)	
Ascitis						
Mild	2(3.4)	13(26.0)	0.003			
Moderate	40(67.8)	27(54.0)				
Marked	17(28.8)	10(20.0)				
Focal lesion	6(10.2)	15(30.0)	0.009			
IHBRRID	1(1.7)	0(0.0)	0.355			
PV	Mean±SD	Mean±SD	P value	Mean±SD	Mean±SD	P value
	1.8±0.2	1.4±0.3	<0.001**	1.3±0.2	1.4±0.3	0.605

Table (4): Complications in decompensated group

Variables	Patients with cholelithiasis N=59	Patients without cholelithiasis N=50	P value
Spontaneous bacterial peritonitis	32(54.2)	26(52.0)	0.816
Hepatic encephalopathy	45(76.3)	32(64.0)	0.161
Hematemesis and melena	25(42.4)	15(30.0)	0.182

Table (5): The etiology of liver disease

Etiology of liver disease	Patients with cholelithiasis N= 66(%)	Patients without cholelithiasis N=65(%)	P value
HCV	50(75.8)	51(78.5)	**0.713**
HBV	9(13.6)	12(18.5)	0.451
HCV+HBV	6(9.1)	2(3.0)	2(3.0)
Autoimmune	1(1.5)	0(0.0)	0.319

Table (6): Child Pugh classification of cirrhosis in patients with and without cholelithiasis

Variables	Patients with cholelithiasis N=66(%)	Patients without cholelithiasis N=65	Odds ratio (95%CI)	P Value
Child A	7(10.6)	15(23.1)	0.4(0.13-1.14)	0.06
Child B	14(21.2)	22(33.8)	0.53(0.22-1.23)	0.105
Child C	45(68.2)	28(43.1)	2.83(1.31-6.17)	0.004

Table (7): Frequencies of risk factors for patients with chronic liver disease

Variables	Patients with cholelithiasis N=66	Patients without cholelithiasis N=65	Odds ratio (95%CI)	P Value
Smoking	26(39.4)	28 (43.1)	0.86(0.4-1.83)	0.669
DM	40(60.6)	16(24.6)	4.71(2.09-10.74)	<0.001**
history of CCP intake	38(57.6)	4(6.2)	18.69(5.67-68.21)	<0.001**

DISCUSSION

Gallstone disease is a multifactorial disease based on a complexinteraction of environmental and genetic factors. The incidence rate of gallstones in the general populationwas found to be 0.60% per year. The current systematic review of Shabanzadeh et al. additionally identified some dietary factors,comorbidities, and parity to be positively associated and consumptionof coffee, fish, and whole meal bread to haveinverse associations to incident gallstones **[13]**. Impaired gallbladder contractility as in cirrhosis was found to be in direct relation with the severity of liver disease.

The current study revealed 66 patients with cholelithiasis out of 131 patients with chronic liver disease with a proportion 50.4%. This prevalence is higher than the previously reported in an Egyptian study by Eljaky et al. **(**21.8 %) **[5]**. Also, many studies confirmed the relation between liver cirrhosis and GSD with varying percentage (23-40%) **[4,8,14].** This variability in the frequency may be explained by the different sample size, patients' characters and the stage of liver disease.

Our study revealed 22 compensated patients and 109 decompensated patients. Of them, 30.4% and 54% had cholelithiasis respectively. This result is consistent with the study of Naheed et al. which reported a higher incidence of cholelithiasis with cirrhosis **[15]**. Furthermore, Acalovschi et al., reported that the incidence of gallstones is five times higher in decompensated patients **[8]**.

In this study, female predominance among patients with cholelithiasis was statistically significant in the compensated group (p=0.006). The high frequency of cholelithiasis in compensated females may be due to childbearing age of these females which explain excessive secretion of cholesterol into bile under the influence of estrogen. Therefore, the incidence of gallstones in women is significantly reduced after menopause due to decline in estrogen levels **[16]**.

Our result revealed that 28.6% compensated patients with cholelithiasis had diabetes mellitus versus 18.8% without cholelithiasis. Also, 59.3% of decompensated patients with cholelithiasis had diabetes mellitus versus 26% without cholelithiasis. This results is consistent with the study of Shizuka et al., which proved a higher incidence of GSD in diabetics and explained that by the disturbed lipid profile and diminished gall bladder motility in diabetic patients **[17]**. Moreover, advanced liver disease may add to the disturbed lipid profile and also associated with disturbed glucose homeostasis **[18]**.

The body mass index of compensated patients with cholelithiasis showed a statistically significance increase in comparison with patients without cholelithiasis, suggesting that obesity is a risk factor for cholelithiasis. This result is consistent with the study of Sahi et al. which reported that obese subjects (BMI >30 kg/m2) are at twice the risk of gallbladder disease than those with a normal BMI **[19]**.

The history of contraceptive pills usage was frequently reported among female patients with cholelithiasis in decompensated group with a statistically significant pattern when compared to females with no history of contraceptive pills usage (p<0.001). This result was consistent with the study of Cirillo et al. which proved that women on long term oral contraceptives have a two folds increased incidence of cholelithiasis over controls and postmenopausal women taking estrogen-containing drugs have a significant increase frequency (around 1.8 times) of cholelithiasis **[20]**.

It was reported that gallstones are twice as common in CLD with portal hypertension due to prolonged congestion and increase in venous hydrostatic pressure, which results in edema of the gallbladder and reduce gallbladder contractility **[21]**.

As regard complication of cholelithiasis among our compensated and decompensated patients. Obstructive jaundice and cholecystitis showed statistically significant increase in compensated group. This finding is consistent with Acalovschi et al. suggesting that hypo-contractility could promote gallstone formation in advanced stage of liver disease.

Regarding to the etiology of CLD in patients with and without cholelithiasis, out result showed that hepatitis C in the most common cause for cholelithiasis (75.8%) followed by hepatitis B (13.6%) and autoimmune disease(1.5%).This result is consistent with the study of Eljaky et al., which proved that the prevalence of GSD in patients with chronic HCV infection was 24.7% versus 10.4% in patients with chronic hepatitis B infection **[5]**. The high prevalence of gall stones in patients with chronic HCV infection may be attributed to HCV which was detected in the biliary epithelium and it may potentially impair gall bladder function and contribute to gall stone formation **[22]**.

CONCLUSION

The higher incidence of cholelithiasis in CLD appears to be associated with HCV infection, portal hypertension, gallbladder stasis, and obesity. The risk is increased with the severity of CLD. This is an important parameter to be considered in a country with high prevalence of HCV as Egypt.

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Competing interests:
All authors have no competing interests to declare.

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