Original Article Muhammad Med Coll; April 2018-Oct 2018 vol 9, (1)

Risk assessment of gallstone among indoor patients of chronic liver diseases secondary to Hepatitis C.

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Abstract

Introduction: Gallstones (GS) are widely reported as the major cause of mortality and morbidity globally.[1] The frequency of GS in patients with chronic liver disease (CLD) is considerably higher than in the general population.[1-7] Moreover, prevailing risk of gallstone is associated with disease frequency and severity in advance stages of CLD.[1,3] The predictable local incidence of gallstones in CLD patients is approximately 24-31%.6-7 HCV is presumed to be the major cause of CLD in the local settings6-7. Despite high prevalence of GS and HCV CLD in our population, the occurrence of GS in HCV CLD cases has not been assessed so far.

Objective: To assess gallstone disease in indoor patients of chronic liver diseases secondary to Hepatitis-C.

Methodology: This cross-sectional study was carried out at Department of Gastroenterology, Liaquat National Hospital (LNH), Institute for postgraduate medical studies and health sciences, Karachi from January 2013 to July 2013. Totalof145 patients of chronic liver disease (CLD) secondary to Hepatitis C Virus (HCV) of either gender, regardless of duration of disease, having age more than 30 years were selected purposively. Structured questionnaire used for data collection. Ultrasonography was done to diagnose gallstones. The routine investigations such as platelet count, anti HCV antibodies, and prothrombin time (PT) were performed. SPSS version 20 was used to analyze data. Variables like gallstone was presented through percentages and frequencies, age as mean and SD. After stratification of age, gender and severity of liver disease, chi-square test was applied and p-value less than 0.05 was considered statistically significant.

Results: The mean age of patients (n=145) was 54.8±9.4 years, whereas mean of males was 53.9±9.3 years and females were 56.2±9.5years. Among total cases86(59.3%) were males and59(40.7%) were females. The gallstones in male patients (n= 30, 58.8%) was higher than female patients (n=21, 41.2%). However, this difference with regards to gender, was not statistically significant (p-value=0.9). The Child-Pugh score with gallstones patients was (10.0±2.1) slightly higher than patients without gallstone (10.7±2.1). In patients with gallstone, Child'sPughclass-Cwasfoundin51(54.3%) patients, class-Bin37(39.4, %) and class-A in 6 (6.3%) patients.

Conclusion: HCV infection is independent risk factor for gallstones in cirrhotic patients. Laparoscopic cholecystectomy in Child-Pugh A and B patients with symptomatic gallstone disease is a safe procedure.

Keywords: Gallstones, HCVCLD, Child-Turcotte-Pugh, Cholecystectomy

Introduction:

Gallstones (GS) are widely reported as the major cause of mortality and morbidity globally.1 The frequency of GS in patients with chronic liver disease (CLD) is considerably higher than in the general population.[1-7] Moreover, prevailing risk of gallstone is associated with disease frequency and severity in advance stages of CLD.[1,3] Additionally, the risk also differ according to the cause (etiology) of CLD, reported higher in cirrhosis of viral etiology (HCV and HBV related) than non -viral origins i.e. alcoholic.[6,8] Hepatitis-C virus infection is presumed to be independent risk factor for GS.[3,4] The, etiology is multi-factorial, diminished gallbladder (GB) emptying is considered as major factor accountable for surge in prevalence of GS among CLD patients.[2-3] The prevalence of 22-54% have been stated in various studies using ultrasonography.1GS are mostly found asymptomatic in CLD and discovered on ultrasound parenthetically while assessing liver disease and require elective intervention when symptomatic.[4,6-7] Whenthereisanindicationofcholecystectomy,regardlessoftype(openorlaparoscopic)linkedwithhigh morbidity in CLD cases especially in advanced stages of disease.[2,8-11].A total morbidity of 21 percent described in CLD cases going through laparoscopic cholecystectomy, as compared to 8% in non-cirrhotic cases.[3] While cirrhosis has usually been considered a contraindication for laparoscopic cholecystectomy (L.C), few studies recently report the safety of L.C in selected cases.[9-11] laparoscopic cholecystectomy can be done in Child-Pugh A and B cases with acceptable conversion rates, complication and morbidity and mortality.[11-10] However, compared with compensated liver illness, child C cases presented with more complications[1-3].Thus, a conservative approach seems preferable for symptomatic GS in Child-Pugh class C patients.[9] Gallbladder disease is common in Pakistan.[11] The predictable local incidence of gallstones in CLDpatientsisapproximately24-31%.[6-7]HCV is presumed to be the major cause of CLD in the local settings[6-7]. Despite high prevalence of GS and HCV CLD in our population, the occurrence of GS in HCV CLD cases has not been assessed so far. The present study aimed to estimate the frequency of GS in HCV CLD patients. The purpose of the study is to find cases at risk who needs urgent attention and management. These cases benefit from prophylactic procedures, together with earlier cholecystectomy when symptomatic in child class A & B. This is to cope up in an emergency condition in advanced liver disease when surgery carries significantly high risk.

Methodology:

A cross-sectional study was carried out from January through July 2013 in the department of Gastroenterology,

Liaquat National Hospital (LNH), Institute for postgraduate medical studies and health sciences, Karachi. The sample size was calculated using OpenEPI software. We estimated local prevalence of gallstones in CLD patients was about 24.3 – 31%1. Considering prevalence of 24.3%, the required sample size found to be 145 with 95% confidence interval (CI) and 5% margin of error. Non-probability consecutive sampling was used to recruit patients. The inclusion criteria included, indoor patients of either sex, admitted with HCV CLD of any duration, aged more than 30 years. We excluded patients with other causes of CLD (alcohol, cryptogenic etc.), diabetes mellitus, hyperlipidemia, gallbladder polyp, any biliary pathology, patients with BMI > 30%, and patients with history of cholecystectomy. The diagnosis for chronic liver disease was established based on "clinical features" (encephalopathy, ascites), hematology findings (thrombocytopenia, prolong prothrombin time) and ultrasonography findings (coarse echotexture& irregular margins of liver, increased portal vein diameter > 13mm, splenomegaly).

Our study aimed to estimate the prevalence of gallstones in patients with chronic liver disease secondary to hepatitis C virus admitted in tertiary healthcare facility in Karachi, Pakistan. The written permission from Hospital Ethical Review Committee was sought prior to data collection. The HCV CLD patients meeting inclusion criteria admitted in LNH gastroenterology ward were considered in the stud y. Informed written consent was taken from every patient before including them in study. The data was collected on pre-design ed, pre-structured questionnaire by researcher himself. Routine clinical biochemistry was performed at LNH hospital laboratory on Roche diagnostic automatic analyzer, prothrombin time (PT) on coagulation auto analyzer Sysmex-CA 1500, platelet count on Sysmex auto analyzer, and Anti HCV antibodies on third generation ELISA micro enzyme immune essay by single pathologist having more than ten years working experience. Toshiba xario ultrasound machine was used by consultant radiologist to diagnose gallstones. All reports were collected and documented by researcher himself.

Statistical package of social sciences (SPSS.15) for windows was used to analyze data. Continuous variables like age were measured as mean values and standard deviation (SD), and categorical variables like gallstone were determined through percentages and frequencies. Stratification of the age and gender were done, and chi-Square test was applied to see the effect of these on outcome variables. Results were adjusted according to liver disease severity. Diabetes, hyperlipidemia and obesity has been excluded. p-value less than 0.05 was considered statistically significant.

Results:

A total of 145 patients meeting inclusion criteria were investigated to determine frequency of gallstones and its associated factors. Out of 145 patients, 86 (59.3%) were males and 59 (40.7%) were females with maletofemaleratio1.4:1(table-I). Mean age of all patientswas54.8±9.4years, while mean of males was 53.9±9.3 years and females were 56.2±9.5 yrs. This difference in age of male and female patients age was insignificant on independent t-test (p= 0.1).

The number of male patients with gallstones (n=30, 58.8%) was higher than female patients (n=21, 41.2%). However, difference was statistically insignificant (p=0.9). The mean-average Child-Pugh Score was 10.2±2.1. In addition, the Child-Pugh score in patients with gallstone swasfound10.0±2.1whichwasmarginallyhigherthanpatientswithoutgallstone10.7±2.1. The mean of Child-Pugh Score in patients with and without GS was insignificantly in each group when analyzed by t- test (*p*-value = 0.05). In patients with gallstone, Child's Pugh class-A was found in 6 (6.3%) patients, class-B in 37 (39.4%) and class-C in 51 (54.3%) patients(table-II).

Table-1 Frequency of Gallstone by Gender and age

		Gallstone recoded		Total
		No	Yes	
Sex	Male	56	30	86
		59.6%	58.8%	59.3%
	Female	38	21	59
		40.4%	41.2%	40.7%
Total		94	51	145
Age Group	<40	9 9.6%	2 3.9%	11 7.6%
	41-50	30 31.9%	11 21.6%	41 28.3%
	51-60	35 37.2%	23 45.1%	58 40.0%
	61-70	14 14.9%	14 27.5%	28 19.3%
	>85	6 6.4%	1 2.0%	7 4.8%
Total		94	51	145

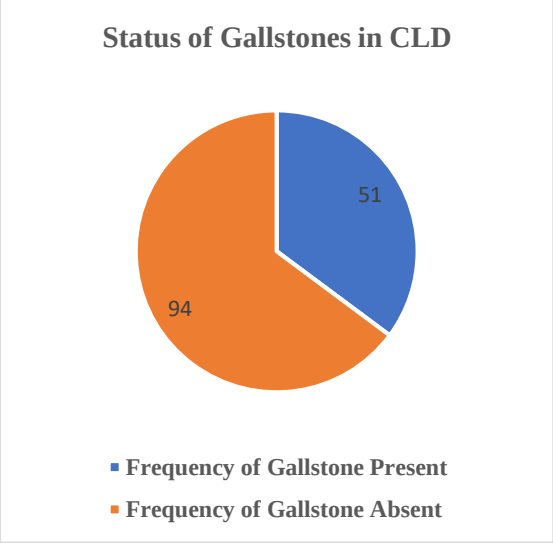
Table-II: Distribution of patients by Child-Pugh Class

		Gallstone recoded		Total
		Yes	No	
class	A	6	2	8
		6.4%	3.9%	5.5%
	B	37	13	50
		39.4%	25.5%	34.5%
	C	51	36	87
		54.3%	70.6%	60.0%
Total		94	51	145

The ascites was common in cases with gallstone 29 (31%) than those without gallstone 4 (8%). With regards to encephalopathy, 16 (31%) patients with gallstones developed encephalopathy whereas, 35 (37%) patients found without gallstones. Mean prothrombin time of the patients with GS was 10.7±2.1, while it was slightly higher than the patients without GS (10.1±2.1 seconds). On t-test the difference between the mean of PT in patients with and without GS was found to have significant difference (*p*=

0.05). Mean serum bilirubin in patients with GS was 3.0±2.0. The mean serum bilirubin was slightly higher than patients without GS (2.0±2.2). However, mean serum albumin levels were not significantly different on t-test (p = 0.3).

Figure: 1 Frequency of Gallstones in patients with chronic liver disease secondary to Hepatitis C



Discussion:

The prevalence of gallstone in our study was 11.7% in anti-HCV-positive patients, whereas the corresponding figures in HbsAg positive persons and in those without hepatitis viral markers were 6.0% and 5.4%, respectively.[8] Furthermore, almost similar study in the USA has shown that anti-HCV-positive subjects compared with those negative had an increased risk of gallstones, after adjusting for possible confounders.[9] Our findings endorse that subjects with HCV-related chronic infection show increased prevalence rate of GS. Literature review revealed several reasons in subjects with GS chronically infected by HCV. Furthermore, chronic hepatic infection found in about70–80%of individuals infected by HCV[10] is one of the causes that could lead to GS development. Moreover, an HCV can effectively infect gallbladder epithelial cells11 it may possibly damage or modify gallbladder mucosal function and add to the formation of GS. Additionally, HCV could bind to apolipoprotein A-11 [1-14] resulting liver steatosis in HCV-infected patients, and may leads to increased cholesterol lithogenesis[1, 4,15].

In our research, after adjusting for effect modifier such as BMI and age, compared with less severe liver disease cases, the HCV-related cirrhosis of either gender was twice at a risk of developing GS, whereas those patients with alcohol related cirrhosis were no longer at an increased risk of developing GS. It is widely accepted that the Liver cirrhosis carries significant risk factor for gallstones, largely of the pigment type. Pathogenesis of GS in cirrhosis is multi-factorial and includes a process such as reduced bile acid production and transport12-14reduced cholesterol synthesis, chronic hemolysis because of hyper-splenism[16-19] decreased apo-AI and apo-AII formation resulting reduced gallbladder motility[20-21]. Some studies discovered that the frequency of gallstones was greater in the advanced cirrhosis stage [9,14,22]. In recent times, are search showed that GS occurrence was significantly higher in subjects with HCV-related cirrhosis compared to those with HBV-related or alcoholic cirrhosis[23]. Few other studies [24-26] found significant risk of GS in cases with HCV infection mainly in the presence of liver cirrhosis.

Age proved to be one of the most major cause in our study, in consistent with many other studies[21, 27-28]. Frequency of GBS showed a positive direct trend with aging. Our study showed two age periods (31–40 yearsand61–70 years) with greater incidence of GBS. The peaks in either age groups possibly associated to the timing of HCV infection. In age group between 31 to 40 may be linked with early HCV infection through vertical transmission (maternal to fetal exchange), close family history or high syringes (injectable) rate in children with some diseases[29-30]. The second age group (61-70) seems more than one decade after the common appearance age of acute hepatitis-C acquisition[22, 31]. The incidence of GBS was not considerably higher among those aged 41–60 years or >70 years. It is likely that HCV infection and aging may share a similar trend in GBS occurrence, thus HCV may contribute but not inevitably increase the chance of GBS development. The mean age of HCV cases with GD was considerably younger. In all age groups up to 60 years, the percentage of GD patients was higher in HCV patients, suggesting that GS occurs earlier in patients with chronic HCV infection. With growing age, the exposure to the diet, hormones, and other factors that causes gallstones get increase. This indicates that cholelithiasis is an acquired disease, developed by chronic environmental factors with significant aging effect. Additionally, the studies recommended that portal vein diameter of greater than 13 mm point out portal hypertension [32, 33]. Greater frequency of cholelithiasis in cases with a portal vein diameter off higher than 13 mm was discovered in our study. Looking cholecystectomy as a proxy marker for symptomatic disease, our findings are in contrast to those indicating that symptoms follow more frequently in patients with viral cirrhosis16-18. Our study settings comprised of patients with earlier stages of HCV infection and probably with a shorter duration of GD. However, we could not find either the length of HCV infection or of GD, or their temporal relationship. Cholelithiasis in our patients aged above 50 years supports the recommendation by Zhang et al that advanced age is linked with the formation of gallstones in CLD. It is widely considered that the gallstone disease impact women frequently compare to men. Our research findings showed, prevalence of gallstones in female was comparable to other population-based surveys conducted on different races [13-15]. Gallbladder Ultrasound is the most precise diagnostic investigation in patient, with gallbladder wall thickness of 4 mm or more and peri-cholecystic fluid being the two most standard criteria. A thickened gallbladder wall is frequently seen with ultra-sound in patients with liver cirrhosis. In some studies, the contractility in gallbladder was also reported impaired in cases with liver cirrhosis[24–26]. We also discovered that, besides increase in gallbladder wall

thickness caused by edema and hyperemia, the gallbladder contractility was declined, signifies that impaired gallbladder emptying is a main factor in the increased frequency of gallstones in cases with cirrhosis [26]. Gallbladder wall thickening may result due to direct inflammation and edema seem to be of great importance, as shown in our study and previous other studies.[1, 5, 20]. The limitation of current study includes a weak study design; however, this was due to resource constraint that allow us only to take cirrhotic patients seeking medical care for liver disease or for gallstone symptoms/ complications. However, identifying the patient at risk is important for a close follow-up to perform cholecystectomy in the initial stages of liver cirrhosis, when the surgical risk is reduced.

Conclusion: The prevalence of GS in patients with CLD is higher than that in non-cirrhotic patients and the risk further increases with disease severity. Age and sex are the most important risk factors for developing gallstone disease in liver cirrhosis, and gallbladder wall thickness could be an additional risk factor. We recommended that laparoscopic-cholecystectomy can be performed safely in Child-Pugh A and B patients with symptomatic gallstone disease, with acceptable morbidity, mortality and complication rate.

Conflict of Interest:

All the authors declare no conflict of interest

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