

Manifestation of Hepatitis C Virus Infection Positively Associated with Gallstones in Patients with Diabetes Mellitus

Naimatullah Kalhoro¹, Asad Ali Zardari², Sajjad Qureshi², Mujeeb ur Rehman Sahito², Ameer Abbas² and Gunesh Kumar¹

ABSTRACT

Objective: To determine relationship between HCV infection and Gallstones (GS) in our adult population in Sindh Pakistan.

Study Design: Cross sectional and case control study.

Place and Duration of Study: This study was conducted at the Liaquat University of Medical and Health Sciences, Jamshoro from June 2016 to May 2018.

Materials and Methods: All adult HCV positive patients were included who visited our hospital. Stage of disease, weight, BMI, associated DM (Diabetes Mellitus), ethnicity was noted. We took control groups as well; who were attendants of patients visited our clinic. Those patients who had history of cholecystectomy were excluded. Data was analyzed using SPSS version 22.0.

Results: There were seven hundred and sixty-two (762) participants and controls were 295. HCV antibody was positive in 467(61.37%). Four hundred and twenty (55%) were males, of these, 270(64.28%) were HCV antibody positive and 150 (35.72%) were controls, of these 342 (45%) were females, 197 (57.60%) had HCV positive infection and 145 (42.4%) were control. There was a significant (p-value 0.007) difference in mean ages of both cohorts. There was no difference in mean weight and BMI of both groups. In HCV antibody positive (9.4 percent) gallstones was significantly higher (p- value 0.048) than controls (4.0 percent).

There were 2 positive HCV males (9.25%, n=270) and 25 positive HCV males (12.69%, n=177) in gallstones; 6 (4.13%), n=145) negatively HCV in males and 20 (13.3%), n=150) negative females.

However, hepatic disease severity, increased age, marital status and village residence were major factors in increase of prevalence of gallstones.

Conclusion: HCV infections with gallstones are closely correlated in males, while they are not related in females. Gallstones are also found with elevated age and incidence of liver disease.

Key Words: Gallstones, liver cirrhosis, Hepatitis C virus

Citation of article: Kalhoro N, Zardari AA, Qureshi S, Sahito MR, Abbas A, Kumar G. Manifestation of Hepatitis C Virus Infection Positively Associated with Gallstones in Patients with Diabetes Mellitus. Med Forum 2021;32(5):124-128.

INTRODUCTION

Gallstone formation is a very common issue in Pakistan¹ internationally as well as². Gallstones may grow due to several different factors, i.e. two major types of stones. Stones containing cholesterol and pigment.

¹. Liaquat University of Medical and Health Sciences, Jamshoro.

². People University of Medical and Health Sciences for Women, Shaheed Benazirabad.

Correspondence: Naimatullah Kalhoro, Resident, Liaquat University of Medical and Health Sciences, Jamshoro.

Contact No: 0333-2666019

Email: naimatkalh_20@yahoo.com

Received: November, 2020

Accepted: February, 2021

Printed: May, 2021

Different pathophysiological pathways for creation of these two major stone forms have been established.

The causative pathways have been established for cholesterol stones, hypersecretion, gallbladder hypomotility and mucin gel accrual and pigment stones.^{3,4}

Several risk factors have been investigated, which may contribute to physiological problems in general public, and gallstones are frequent in females than males, with different factors like age, genes, ethnicity, obesity, rapid weight loss, aldohexaemic aversion, susceptibility to hypoglycaemic agents, use of alcohol, hypertriglyceridemia, pregnancy and multiple medications.⁵

In patients with liver diseases and development of gallstones, a growing correlation has been found. A number of published research literature confirm that cirrhosis is one of most significant risk elements for gallstones if precise cause of liver disease could help improve gallstone occurrence and morbidity has not yet been thoroughly studied. Although hepatitis C virus

infection has been used as an independent risk factor for gallstone development in patients with chronic infections without cirrhosis.^{6,7,8} Since chronic hepatitis C infection is a serious public health issue in Pakistan and some 10 million people are infected with HCV in Pakistan. This research was performed to find out occurrence of gallstones among HCV patients in Pakistan and to verify it compared to control group Particularly if HCV virus has a greater incidence of gallstones than non-HCV viruses.

MATERIALS AND METHODS

This research was undertaken as a cross sectional and case control dependent on hospital. Two groups of population were introduced by us, one of those people with "C" chronic hepatitis and next. Patients attending our hepatology clinic were monitored and either HCV antibodies were negative or they do not recognize their HCV-antibodies.

The sample population aged from 18 to 80 years of age. The HCV antibody was first tested by ELISA process. All tests were completed. If reactive, they are classified as patients and if negative, they are kept under supervision.

After at least 4 hours of fasting, all patients received ultrasound from abdomen. Using 3.5 MHz transducers in supine and left decubitus positions, ultrasound experiments were performed on TOSHIBA system. A diagnosis of gallstone demands two views of gallbladder echoes. All people in background with a diagnosis of HCV cholecystemoy. Even HCV positive antibody was removed from RNA negative.

We have also received knowledge about association between HCV and gallstone disease regarding ultrasound pelvis and HCV examinations. some other variables are currently capable of confirmed (GSD). The possible covariations in both sexes include age, weight, body mass index, highest completed year of schooling, race (Sindhi, Urdu Punjabi, Pushto and others) alcohol drinking, habits seriousness of liver disease, presence or absence of diabetes, hypertension and babies in women's cases in these studies.

For two years from June 2016 to May 2018, this research was performed in Medicine and Pathology University of Jamshoro University of Medical and Health Sciences.

Statistical Analysis: In SPSS version 20.0, results were evaluated through descriptive analysis. General analyses of participants were carried out. In case of a complex sample, a continuous variable was comparable to "t" with a person-basic chi-square measure. The variables were compared. The multivariate logistic regression analysis was undertaken to classify risk and ration variable (OR).

RESULTS

A total of 762 participants were included. Out of them, 467 (61.3%) were HCV antibodies and 295 (38.7%) were control subjects.

Table No.1: Demographic Finding (n = 762)

Factors	n (%)
Gender	
Male	420 (55.1)
Female	342 (44.9)
Age (in years)	40.9 ± 13.1
Weight (in kg)	62.6 ± 14.6
Body Mass Index (kg/m ²)	25.5 ± 5.5
Age Group	
< 32 years	188 (24.7)
32 – 40 years	220 (28.9)
41 – 50 years	198 (26.0)
> 50 years	156 (20.5)
BMI Group	
< 18.5 kg/m ²	71 (9.3)
18.5 – 22.9 kg/m ²	178 (24.4)
23 & above kg/m ²	513 (67.3)
Marital Status	
Single	96 (12.6)
Married	666 (87.4)
Educational Status	
Illiterate	222 (29.1)
Literate	540 (70.9)
Smokin	
Smokers	78 (10.2)
Non-Smokers	684 (89.8)

Table 2. Clinical Finding (n = 762)

Factors	n (%)
Hepatitis C-Virus	467 (61.3)
Diabetic Mellitus	82 (10.8)
Ascites	63 (8.3)
Gall Stone	76 (10.0)
Bilirubin	
Normal (< 1.4 mg)	715 (93.8)
Mild / Sever (≥ 1.4mg)	47 (6.2)
Albumin	
Normal (> 3.5 mg/L)	614 (80.6)
Mild / Severe (≤ 3.5 mg/L)	148 (19.4)
Platelets	
Normal (≥ 150 10 ³ /cu.mm)	729 (95.7)
Mild (100 – 149 10 ³ /cu.mm)	21 (2.7)
Moderate / Severe (< 100 10 ³ /cu.mm)	12 (1.6)

In our study 420(55%) males and 342(45%) for females. Out of 420 Male patients, 270(64.28%) patients had HCV positive while 150(35.72%) were controls. However 342 females, 197(57.60%) had positive and 145(42.4%) were controls. Subjects Table Number 1 shows demographic details of patients. It was found that there was no significant difference between frequency of Hepatitis C with age, gender, BMI, and educational status. The marital status was found to be a

significant factor, which was seen in 426(91.2%, n=467) of married males and 240(81.4%, n = 295) of Married males and married females (P-value < 0.001), Moreover 420(55%) males and 342(45%) females out of 270 (64.28%) had positive infections and 150 (35.72%), were negative.

Table No.3: Characteristics of patients with hepatitis C virus (n = 762)

Factors	Hepatitis C Virus		P-value
	Positive (n = 467)%	Negative (n = 295)%	
Age (in years)	41.9 ± 11.9	39.2 ± 14.6	0.007
Gender			0.060
Female	197	145	
Male	(57.60) 270 (64.28)	(42.4) 150 (35.72)	
Marital Status			< 0.001
Single	41 (8.8)	55 (18.6)	
Married	426 (91.2)	240 (81.4)	
Body Mass Index (kg/m ²)	25.7 ± 5.2	25.2 ± 5.8	0.239
Body mass index			0.199
<18.5 kg/m ²	37 (7.9)	34 (11.5)	
18.5-22.9 kg/m ²	107 (22.9)	71 (24.1)	
23 and above kg/m ²	323 (69.2)	190 (64.4)	
Education Level			0.877
Literate	330 (70.7)	210 (71.2)	
Illiterate	137 (29.3)	85 (28.8)	
Smoking Habit			0.433
No	416 (89.1)	268 (90.8)	
Yes	51 (10.9)	27 (9.2)	
Diabetes Mellitus			0.168
No	411 (88.0)	269 (91.2)	
Yes	56 (12.0)	26 (8.8)	
Ascites			0.011
No	419 (89.7)	280 (94.9)	
Yes	48 (10.3)	15 (5.1)	
Gall Stones			0.699
No	417 (89.3)	266	

Yes	50 (10.7)	(90.2) 29 (9.8)	
Bilirubin			< 0.001
Normal (< 1.4 mg)		295 (100.0)	
Mild / Severe (≥ 1.4 mg)	420 (89.9) 47 (10.1)	0	
Albumin			< 0.001
Normal (> 3.5 mg/L)		262 (88.8)	
Mild / Severe (≤ 3.5 mg/L)	352 (75.4) 115 (24.6)	33 (11.2)	
Platelets			0.001
Normal (≥ 150x10 ³ /cu.mm)		292 (99.0)	
Abnormal (< 150x10 ³ /cu.mm)	437 (93.6) 30 (6.4)	3 (1.0)	

In chronic Hepatitis C frequency, we found that age, gender, BMI, ethnicity, and educational status were not significantly associated but in married males 426 and 420 married women per impacted by marital status in HCV (P-value < 0.002). In 467(61.2%) HCV positive patients cal stones were seen in 50(10.7%) patients and 295 (38.3%) HCV negative patients gallstones were seen in 26(8.81%) patients prevalence of gallstone was significantly higher in HCV positive than controls. Frequency of gallstones was seen in 25(9.25%, n = 270) HCV positive male patients and 25(12.69%, n = 197) HCV positive female patients however frequency of gallstone was observed in 6 HCV negative Mel patients and 20 (13.3%, n = 150). HCV negative females.

In our study most of patients with HCV positive infection present with gallstones.

In this study, most of females with HCV positive patients were observed in age group 51 to 60 years and it was not significantly associated with prevalence of gallstones and HIV positive.

Moreover, with regards to severity of liver disease, we assessed that serum total bilirubin level, serum albumin level, and platelet count was associated with gallstones. Analysis of logistic regression revealed that serum total bilirubin levels, lower serum albumin level, and lower platelet count were increased.

Table No.4: Logistic regression analysis showing risk of gallstones HCV pateints in gender

Variable	Crude Prevalence (95% CI)		Odds Ratios (95% CI)		
	HCV Positive (n = 467)	HCV Negative (n = 295)	Unadjusted	Age-Adjusted	Age and Race Adjusted
Males (n=420) Gallstones	9.3% (5.8, 12.8%)	4.0% (0.9, 7.1%)	2.5 (1.0, 6.1)	2.2 (0.9, 5.5)	2.2 (0.9, 5.4)
Females (n =342) Gallstones	12.7% (8.1, 17.3)	15.9% (9.9, 21.9%)	0.8 (0.4, 1.4)	0.7 (0.4, 1.3)	0.8 (0.4, 1.5)

DISCUSSION

Liver cirrhosis is one of common risks for gallstones, and incidence of gallstones is seen to rise with increased cirrhosis severity⁽¹⁰⁻¹²⁾

Recently Stroffolini et al⁽¹³⁾ had a study to figure out whether etiology of cirrhosis had played a part in occurrence of gallstone development and he noted high prevalence of HCV-induced cirrhosis of gallstones relative to HBV-induced and alcoholic cirrhosis. Very few studies have been performed that HCV infection is an independent risk factor for development of gallstones without cirrhosis, thus, a review was conducted to see association between chronic hepatitis C and gallstones.

Both hepatitis C patients have been tested and compared to controls. Both participants were investigated by ultrasonography for gallstones since gallbladder is a fast and non-invasive imaging technique.¹⁴

Our research further shows that incidence of gallstones is more prevalent in females (13.15%) than in males (7.38%). However, since prevalence was measured based on sex, gallstones are significantly more common in females than in HCV+Ve patients (10.7%) than in males (8.81%). (OR 0.8).

Edmund J Bini EJ and McGready J¹⁵ performed same form of analysis, with a substantial rise in prevalence of gallstones in HCV-positive males than HCV-negative (OR=3.57) in male positives. On other hand, gallstones were not substantially higher in HCV-positive women (OR=2.55).

Acalovschi M et al.¹⁶ also performed this form of analysis and found that 88 of 453 HCV patients (19.4%) had gallstones compared with 158 out of 879 patients (17.9%) in control group, but that in HCV patients there was a greater incidence of gallstones in both men and women than in controls. In a trial at Lahore for gallstones in liver cirrhosis, Naheed et al¹¹ observed that 31% of cirrhotic gallstones and 70% of those have HCV are again heavy in relation to chronic hepatitis C. Gallstones and hepatitis are closely correlated. Gallstones have a strong correlation.

In our research, we also revealed that occurrence of gallstones raises incidence of liver disease, as determined by level of serum, serum albumin and platelet levels (Table 5). The comparative chances of gallstones improved with increased levels of serum bilirubin overall, lower level of serum albumin and lower levels of platelets Edmund JBini and John MC Gready¹⁵ have observed.

The findings listed here and several other studies indicate that patients with hepatitis C have an elevated risk of gallstone formation and that different clinical studies have examined impact of development of gallstones in HCV+Ve patients. Shi S et al¹⁷ had

indicated that only risk factor for development of gallstones may be liver steatosis.

HCV NS5A was present in combination with lipid droplets and APoA, which indicates that NS5A and core protein may be associated with liver steatosis and gallstone formation.

Loria P¹⁸ et al also observed that steatosis (fatty liver disease) is related to an elevated risk of obese gallstones. Liver steatosis has also been shown to develop increased tolerance of insulin¹⁹, and increased insulin resistance can be linked with development of gallstones in patients with chronic hepatitis C virus by increasing bile saturation of cholesterol.

Additionally, overt disruption to bile duct by HCV infection was noted of these indirect pathways contributing to gallstone development. The involvement of HCVRNA in gallbladder cells by gallbladder culture has been shown by Lorient MA et al.²⁰ Further, in patients with chronic C hepatitis WilzelTM et al²¹ were previous damage to bile duct. All these studies have shown that infection by HCV may affect function of Gallbladder and Gallbladder epithel and encourage production of Gallstones.

Finally, all evidence and our analysis favours facilitation of gallstone development through infection with hepatitis C virus.

CONCLUSION

Chronic HCV infections with gallstones are strongly correlated in adults, but in female patients there is no correlation. In our adult patients with a growing age and heaviness of liver disease gallstones are also observed.

Author's Contribution:

Concept & Design of Study:	Naimatullah Kalhoro
Drafting:	Asad Ali Zardari, Sajjad Qureshi
Data Analysis:	Mujeeb ur Rehman Sahito, Ameer Abbas, Gunesh Kumar
Revisiting Critically:	Naimatullah Kalhoro, Asad Ali Zardari
Final Approval of version:	Naimatullah Kalhoro

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Channa NA. Gallstone disease: a review. Pak Armed Forces Med J 2008;58(2):197-208.
2. Stinton LM, Myers RP, Shaffer EA. Epidemiology of gallstones. Gastroenterol Clin North Am 2010; 39(2):157-69.
3. Acalovschi M. Cholesterol gallstones: from epidemiology to prevention. Postgrad Med J 2001; 77(906):221-9.

4. Ostrow JD. The etiology of pigment gallstones. *Hepatology* 1984;4(5 Suppl):215S-222S.
5. Shaffer EA. Gallstone disease: Epidemiology of gallbladder stone disease. *Best Pract Res Clin Gastroenterol* 2006;20(6):981-96.
6. Conte D, Fraquelli M, Fornari F, Lodi L, Bodini P, Buscarini L. Close relation between cirrhosis and gallstones: cross-sectional and longitudinal survey. *Arch Intern Med* 1999;159(1):49-52.
7. Fornari F, Imberti D, Squillante MM, Squassante L, Civardi G, Buscarini E, et al. Incidence of gallstones in a population of patients with cirrhosis. *J Hepatol* 1994;20(6):797-801.
8. Acalovschi M, Buzas C, Radu C, Grigorescu M. Hepatitis C virus infection is a risk factor for gallstone disease: a prospective hospital-based study of patients with chronic viral C hepatitis. *J Viral Hepat* 2009;16(12):860-6.
9. Raja NS, Janjua KA. Epidemiology of hepatitis C virus infection in Pakistan. *J Microbiol Immunol Infect* 2008;41(1):4-8.
10. Li CP, Hwang SJ, Lee FY, Chang FY, Lin HC, Lu RH, et al. Evaluation of gallbladder motility in patients with liver cirrhosis: relationship to gallstone formation. *Dig Dis Sci* 2000;45(6):1109-14.
11. Naheed T, Akbar N, Akbar N. Frequency of Gallstones in patients of liver cirrhosis - a study in Lahore. *Pak J Med Sci* ;20(3):215-8.
12. Fornari F, Imberti D, Squillante MM, Squassante L, Civardi G, Buscarini E, et al. Incidence of gallstones in a population of patients with cirrhosis. *J Hepatol* 1994;20(6):797-801.
13. Stroffolini T, Sagnelli E, Mele A, Cottone C, Almasio PL. Italian Hospitals' Collaborating Group. HCV infection is a risk factor for gallstone disease in liver cirrhosis: an Italian epidemiological survey. *J Viral Hepat* 2007;14(9):618-23.
14. Kratzer W, Mason RA, Kächele V. Prevalence of gallstones in sonographic surveys worldwide. *J Clin Ultrasound* 1999;27(1):1-7.
15. Bini EJ, McGready J. Prevalence of gallbladder disease among persons with hepatitis C virus infection in the United States. *Hepatology* 2005;41(5):1029-36.
16. Acalovschi M, Buzas C, Radu C, Grigorescu M. Hepatitis C virus infection is a risk factor for gallstone disease: a prospective hospital-based study of patients with chronic viral C hepatitis. *J Viral Hepat* 2009;16(12):860-6.
17. Shi ST, Polyak SJ, Tu H, Taylor DR, Gretch DR, Lai MM. Hepatitis C virus NS5A colocalizes with the core protein on lipid droplets and interacts with apolipoproteins. *Virology* 2002;292(2):198-210.
18. Loria P, Lonardo A, Lombardini S, Carulli L, Verrone A, Ganazzi D, et al. Gallstone disease in non-alcoholic fatty liver: prevalence and associated factors. *J Gastroenterol Hepatol* 2005;20(8):1176-84.
19. Eguchi Y, Mizuta T, Ishibashi E, Kitajima Y, Oza N, Nakashita S, et al. Hepatitis C virus infection enhances insulin resistance induced by visceral fat accumulation. *Liver Int* 2009;29(2):213-20.
20. Lorient MA, Bronowicki JP, Lagorce D, Lakehal F, Persico T, Barba G, et al. Permissiveness of human biliary epithelial cells to infection by hepatitis C virus. *Hepatology* 1999;29(5):1587-95.
21. Welzel TM, Graubard BI, El-Serag HB, Shaib YH, Hsing AW, Davila JA, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. *Clin Gastroenterol Hepatol* 2007;5(10):1221-8.