

ORIGINAL ARTICLE

Hepatitis C Virus Infection, A Risk Factor for Gallstone Disease: A Cross Sectional SurveySamia Kausar¹, Fazeela Farid², Shamaila Burney³, Kiran Fatima⁴, Muhammad Farooq⁵, Amina Shahzad⁶**ABSTRACT****Objective:** To study the frequency of gallstone disease in patients with hepatitis C virus infection.**Study Design:** Descriptive cross sectional study design.**Place and Duration of Study:** From 1st March 2019 to, 31st December 2019 at Department of Medicine and Radiology of Pakistan Railway Hospital Rawalpindi**Materials and Methods:** A total of 200 subjects were selected through non probability consecutive sampling from medical In-patient and Out-patient Department. They were screened for hepatitis C virus (HCV) infection by anti-HCV antibodies test by enzyme linked immunosorbant assay (ELISA). They were divided into two groups. HCV positive and HCV negative groups with 100 participants in each group. The study subjects were sent to Radiology Department for detection of gall stones by abdominal ultrasound. The data was obtained from each participant regarding demographic and clinical variables and analyzed using SPSS version 21.**Results:** HCV positive patients had significantly higher frequency of gallstones (12.5%) compared with HCV negative patients (4.5%). Higher percentage of males had gallstones in HCV positive group. Cirrhosis was present in 52% of HCV infected patients.**Conclusion:** The HCV infection is associated with increased risk of gallstone disease.**Key Words:** *Cirrhosis, Cholelithiasis, Gallstones, HCV.***Introduction**

Gallstone disease affects almost 20% of adults, two to three times more common in females with peak incidence at more than forty years of age. Majority patients are asymptomatic but more than 20% present with biliary symptoms and complications.¹ Cholelithiasis highly prevalent because of rising trend in obesity and modifiable life style factors. Factors increasing the risk are: infection, high body mass index, pregnancy, birth control pills, hereditary, diabetes, liver disease, rapid weight loss, smoking, lack of exercise, diet rich in red meat and hydrogenated fat.² Factors decreasing the risk are: Intake of fruits and vegetables.³

Worldwide HCV has infected almost 3% population,⁴

transmitted mostly through unsterile medical equipment and injections. HCV infection is more prevalent in intravenous (IV) drug abuser and human immunodeficiency virus (HIV) positive patients.⁵ Hepatitis C virus, a major cause of chronic liver disease increases the risk of gall stone formation,⁶ and several explanations have been suggested for the possible link between the two. HCV impairs gallbladder motility and mucosal function that might contribute to gallstone formation.^{7,8} It may be due to direct HCV infection of gallbladder as HCV ribonucleic acid (RNA) has been traced in gallbladder epithelium on autopsy.⁹ HCV nonstructural protein leads to fatty liver by altering lipid metabolism thus promoting cholesterol lithogenesis.¹⁰ Evidence in the current literature states that HCV infected patients develop gallstone even without cirrhosis and at a younger age.^{6,11} They are more prone to have multiple gallstones and bile duct stones.^{11,12}

So dissimilarity exists in clinical pattern of gallstone disease with or without HCV infection. The correlation between HCV infection and cholelithiasis should be explored further. The prevalence of HCV is high in Pakistan, almost 5%.¹³ This will build up further if we do not put forward efforts on modes of transmission and virus behavior. There is added

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financial burden on hospitals due to gallstones and related complications. The beneficial effect of prevention of transmission and eradication of HCV infection by effective drugs lowers the risk and reduces associated morbidity and mortality. Community based epidemiological data from Pakistan is scarce on this association. Studying the link between gallstones formation and hepatitis C infection will create awareness about magnitude of problem in our population. So early recognition will accomplish better outcome.

Our study aimed to compare the frequency of gallstones in patients with hepatitis C virus infection to patients who are HCV negative.

Materials and Methods

A descriptive cross sectional study was carried out involving 200 patients. It was performed at Medicine and Radiology departments of Pakistan Railway Hospital Rawalpindi from March 2019 to December 2019. All patients were included from outdoor and in patients department of Hospital using consecutive non-probability sampling. They were split into two equal groups (100 each) depending on the presence of anti-HCV antibodies. Both HCV positive and negative individuals were referred for ultrasound abdomen for detection of gall stones. The patients who were HIV, Hepatitis B surface Antigen positive, having sickle cell disease, alcoholic liver disease, chronic liver disease other than HCV, thalassemia and malignancy were excluded. The Institutional Ethical Review Committee of Riphah University permitted to study. We took informed consent from all participants before enrollment.

A brief history and examination was done. Information about age, sex, parity, oral contraceptive use/ estrogen replacement therapy, heredity, diabetes, hypertension, hyperlipidemia and voluntary weight loss in last one year was recorded on structured performa. All participants were investigated for blood sugar, serum cholesterol levels and body mass index (BMI) was calculated. The HCV-positive group was further investigated for bilirubin, prothrombin time, serum albumin levels. Cirrhosis was diagnosed on aggregate of clinical, radiological (surface nodularity, coarse echo texture, enlarged portal vein splenomegaly and ascites¹⁴) and biochemical criteria. Child-pugh score was calculated for assessment of cirrhosis severity.

Ultrasound (US) was done by single trained radiologist. US machine with 5.0M HZ transducer was used. Gall stones were diagnosed when it showed dense reflection from gallstone along with posterior acoustic shadow. Moreover gallstone mobility was seen on repositioning of patient.¹⁵ Anti-HCV antibodies were tested using ELISA method.

Data (parametric) was recorded on SPSS 21. Statistical variables like patient's age, gender and BMI were listed. Mean and frequencies were calculated. Independent sample t-test was used for group comparison.

Results

Out of 200 patients, 100 patients were HCV positive. The age range was 25 to 85 years. The mean age in HCV positive group was 54.90 ±8.93 and 56.14±9.23 in HCV negative group. The frequency of gall stones in HCV positive group was 12.5% and 4.5% in HCV negative group. Overall prevalence of gall stones in both groups was 17%.

Gender distribution with gallstones in HCV negative group was 79% female and 21% male while in HCV positive group 45% female and 55% male.

In HCV positive group with gallstones 48% did not have cirrhosis while 52% had cirrhosis. 15.38% patients belonged to child class A while 38.46% in child class B and 46.15% were in child class C.

Mean body mass index (BMI) was similar in both groups 27.31±0.6 and 26.99±0.5 in HCV negative and HCV positive group respectively. Mean fasting blood sugar and serum cholesterol were also comparable in both groups. There were 39% diabetics in HCV positive group and 35% diabetics in HCV negative groups. Almost 50% patients were found hypertensive in both groups. Regarding positive family history of gallstones it was present in 40% vs.35% in HCV negative group compared with HCV positive group.

Table I: Age and Gender of Study Population. (Total Subjects=200)

Age (Years)	HCV-Negative Group		HCV-Positive Group		Total
	Male	Female	Male	Female	
25-45	14	12	14	09	50
46-65	14	22	13	21	69
66-86	12	26	18	25	82
Total	40	60	45	55	200

Table II: Frequency of Gallstones in Study Patients

Study Groups	Gallstones Present	Gallstones Absent	Total	P Value
HCV-Positive Group	25	75	100	0.001
Percentage of Total	12.5	37.5	50	
HCV-Negative Group	9	91	100	
Percentage of Total	4.5	45.5	50	
Total	34	166	200	
Percent	17%	83%	100	

Discussion

The results of our study showed that HCV infection was associated with high frequency of gallstones (12.5%) compared with patients without HCV infection (4.5%). Moreover, for patients with HCV infection and cirrhosis, the frequency of gallstones increased further with worsening of liver dysfunction.

Worldwide it has been observed that HCV is associated with increased prevalence of gallstones. Initially Chang et al. found gallstones were present in 11.7% of HCV positive patients without cirrhosis compared with 6% without infection.¹² Aljaky et al. from Egypt found prevalence of gall stone in HCV positive subjects 15.68% vs.9.9% in healthy individuals.¹⁶ While studies from Pakistan showed increased prevalence with HCV infection 18.65% vs. 6.65% by Shah et al. and 22% vs. 8% by Haq et al. in healthy subjects.^{11,17} As observed in above mentioned studies, HCV infection has been found to be risk factor for gallstones development even without cirrhosis. We verified as 48% HCV positive patient did not have cirrhosis. The results of our study are in agreement with previous studies.

It has been observed that in HCV infected patients prevalence of gall stone increased with age. Lee et al. concluded that hepatitis B and C virus led to greater frequency of gallstones in elderly.¹⁸ In another study HCV infection increased the risk two to three fold in elderly when compared with HBV infection in the same age group. This difference was not observed in patients less than 60 years.¹⁹ Hu et al. declared that males older than 55 years who were HCV infected had higher frequency of gallstones

(7.8%) than HCV positive females (6.1%) of same age.²⁰ In our study we also observed greater prevalence of gallstones in patients more than 50 years of age in HCV infected patients. Our result was in contradiction to the observation made by Shah et al. from Pakistan. They found significantly higher prevalence of gallstones at or below 40 years of age in HCV positive subjects.¹¹

In general population, females have three times higher prevalence of gallstones than males. In some studies cirrhosis was considered a risk factor for gallstones formation for men but not for women.²¹ The reasoning for this gender specific dissimilarity is higher level of estrogen and progesterone in cirrhotic men which impair gall bladder emptying as in pregnant women. In Taiwan, study involving 1701 individuals HCV infection was related with gallstone formation specifically in male gender. Gallstone prevalence was not affected in females by HCV status.²² While a study from United States showed that HCV infection significantly enhanced development of gallstones among males but not in females.²³ Similarly Shah et al. HCV positive males had higher prevalence of gall stones as compared to HCV positive female. The reason why male gender is more prone to gallstone formation with HCV infection is not known. It may be due different gender specific risk factors. However we also found higher frequency of gallstones in HCV positive males. Cirrhosis augments the risk for gallstones. The risk of gallstones development is amplified two fold.¹⁹ Conte et al. observed 618 patients with cirrhosis for 4 years and 22.8% of them developed gallstones.²⁴ Major mechanisms involved in gall stones development are chronic haemolysis due to hypersplenism, abnormal biliary lipids, low synthesis of bile salts and unconjugated bilirubin.²⁵ Moreover gall bladder hypo motility and structural changes in its wall accounts for impaired emptying.²⁵ HCV infection exaggerate gallstones risk in elderly patients with cirrhosis.¹⁹

Literature review showed that prevalence of gallstones increased with severity of cirrhosis (increased child pugh score). This was characteristically seen in HCV positive cirrhosis. Our study showed that there was increased prevalence of gallstones in child class C. While other studies disputed significant difference in gallstones

prevalence with child pugh score.¹⁹

The high frequency of gallstones in HCV infected patients suggests that HCV is significant causative link. As there is high prevalence of HCV in Pakistan there is need to work on prevention of transmission, early diagnosis and treatment of HCV infected subjects. Most people are unaware of infection, delayed diagnosis results in increased morbidity and mortality.

Limitation of our study was small a sample size and that the study results may not apply to general population. There is need for large scale epidemiological studies to confirm the conclusion.

Conclusion

The HCV infection is associated with increased risk of gallstone disease.

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of paper.

REFERENCES

- Scherber PR, Zúniga SE, Glanemann M, Lammert F. Gallstone disease - interdisciplinary treatment. *Dtsch Med Wochenschr.* 2020; 145(5):287-95.
- Figueiredo JC, Haiman C, Porcel J, Buxbaum J, Stram D, Tambe N, et al. Sex and ethnic/racial-specific risk factors for gallbladder disease. *BMC gastroenterology.* 2017; 17(1):153.
- Zhang JW, Xiong JP, Xu WY, Sang XT, Huang HC, Bian J, et al. Fruits and vegetables consumption and the risk of gallstone disease: A systematic review and meta-analysis. *Medicine.* 2019; 98(28): e16404.
- Moosavy SH, Davoodian P, Nazarnezhad MA, Nejatizadeh A, Eftekhari E, Mahboobi H et al. Epidemiology, transmission, diagnosis, and outcome of hepatitis C virus infection. *Electron Physician.* 2017; 9(10):5646–56.
- Manns MP, Buti M, Gane E, Pawlotsky JM, Razavi H, Terrault N, et. Hepatitis C virus infection. *Nat Rev Dis Primers.* 2017 2; 3(1):1-9.
- Wijarnpreecha K, Thongprayoon C, Panjawatanan P, Lekuthai N, Ungprasert P. Hepatitis C virus infection and risk of gallstones: A meta-analysis. *J Evid Based Med.* 2017; 10(4):263-70.
- Cacoub P, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun D. Extrahepatic manifestations of chronic hepatitis C virus infection. *Therapeut Adv Infect Dis.* 2016; 3(1):3-14.
- Buzas, C., Chira, O., Mocan, T. & Acalovschi, M. Comparative study of gallbladder motility in patients with chronic HCV hepatitis and with HCV cirrhosis. 2011; 49 (1):37–44.
- Loriot 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.
- 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.
- Shah SI, Shah S, Hannan A. Hepatitis C—a risk factor for gallstone disease. *J Ayub Med Coll Abbottabad.* 2014; 26(1):84-7.12. Chang TS, Lo SK, Shyr HY, Fang JT, Lee WC, Tai DI, et al. Hepatitis C virus infection facilitates gallstone formation. *J Gastroenterol Hepatol.* 2005; 20 (9):1416-21.
- World Health Organization. Global hepatitis report 2017. World Health Organization; 2017.
- Heller MT, Tublin ME. The role of ultrasonography in the evaluation of diffuse liver disease. *Radiol Clin North Am.* 2014; 52(6):1163-1175
- Cooperberg PL, Burhenne HJ. Real-time ultrasonography: diagnostic technique of choice in calculous gallbladder disease. *N Engl J Med.* 1980; 302(23):1277-9.16. Eljaky MA, Hashem MS, El-Bahr O, El-Idat HA, El-Shennawy H, El-Kher SA. Prevalence of Gall Stones in Egyptian Patients with Chronic Liver Disease,“. *J Amer Sc.* 2012; 8(1):734-7.
- Haq AR, Shamim AR, Ali MA. Prevalence of Gallstone Disease in Patients of Hepatitis C Virus Infection. *Pak J of Med & Heal Sc.* 2017; 11(3):1065-7.
- Lee YC, Wu JS, Yang YC, Chang CS, Lu FH, Chang CJ. Hepatitis B and hepatitis C associated with risk of gallstone disease in elderly adults. *J Am Geriatr Soc.* 2014; 62(8):1600-2.
- Li Xu, Gao P. Hepatitis C virus infection increases risk of gallstone disease in elderly Chinese patients with chronic liver disease. *Scientific reports.* 2018 15; 8(1):1-6.
- Hu JH, Chen MY, Yeh CT, Chiu WN, Chiang MS, Chang ML. Effects of gender and age on prevalence of cholelithiasis in patients with chronic HCV infection: A community-based cross-sectional study in an HCV-hyperendemic area. *Medicine.* 2018; 97(22):e10846.
- Fornari F, Civardi G, Buscarini E, Cavanna L, Imberti D, Rossi S, et al. Cirrhosis of the liver. A risk factor for development of cholelithiasis in males. *Dig Dis Sci.* 1990; 35(11):1403-8.
- Dai CY, Lin CI, Yeh ML, Hsieh MH, Huang CF, Hou NJ, et al. Association between gallbladder stones and chronic hepatitis C: ultrasonographic survey in a hepatitis C and B hyperendemic township in Taiwan. *Kaohsiung J Med Sci* 2013; 29:430–5.
- 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.
- 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; 159:49–52.
- Acalovschi M. Gallstones in patients with liver cirrhosis: incidence, etiology, clinical and therapeutical aspects. *World J Gastroenterol.* 2014; 20(23):72-77.