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ORIGINAL ARTICLE

# Association of Thrombocytopenia with Chronic Liver Disease Due to Hepatitis-C

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## ABSTRACT

**Introduction:** Patients with Chronic Liver Disease (CLD) including advanced fibrosis and cirrhosis commonly experience thrombocytopenia. Thrombocytopenia associated with chronic liver disease has been reported in 15–70% of patients with advanced fibrosis and portal hypertension, depending on the stage of disease. Thrombocytopenia may be caused by Hepatitis C virus (HCV) directly, or it may result from interferon based anti-viral therapy that affects platelet number or function, either directly or by suppression of thrombopoiesis in the bone marrow.

**Objectives:** To determine the frequency of thrombocytopenia in CLD patients due to Hepatitis C virus.

**Material and Methods:** This cross sectional study was conducted at Department of Medicine, Civil Hospital, Bahawalpur from 01-03-2013 to 28-12-2013. Non probability purposive sampling was done. The calculated sample size was 325 cases, with 5 % margin of error, 95 % confidence level. All the collected data was entered into computer software SPSS version 17 and analyzed.

**Results:** Study results show that majority of the patients were between 41-50 years i.e. 43.69% (n=142), mean age was 38.54±5.12 years. 59.38% (n=193) were male and 40.62% (n=132) females. Frequency of thrombocytopenia in CLD patients due to Hepatitis C virus was 21.23% (n=69) while 78.77% (n=256) had no findings of thrombocytopenia.

**Conclusion:** The frequency of thrombocytopenia is high among patients with Chronic Liver Disease (CLD). Therefore it is recommended that every patient who presents with Chronic Liver Disease should have work-up for thrombocytopenia.

**Key words:** Chronic Liver Disease, Thrombocytopenia, Hepatitis C Virus, Frequency

## INTRODUCTION

Chronic Liver Disease (CLD) is the tenth leading cause of death in adults with HBV and HCV being the most important underlying causes.<sup>1</sup> The World Health Organization (WHO) estimates that there are 170 million people living with chronic HCV infection worldwide.<sup>2,3</sup> Hepatitis C alone is estimated to result in 366 000 deaths annually.<sup>4</sup> Pakistan carries one of the world's highest burdens of chronic hepatitis and mortality due to liver failure and hepatocellular carcinomas.<sup>5</sup>

Thrombocytopenia (TCP) is one of the most frequent hematological disorders in patients with chronic liver disease.<sup>6</sup> Thrombocytopenia is defined as any decrease in platelet count below the lower normal limit (i.e.  $<150 \times 10^9/L$ ). However, it is often operatively considered as the level below which performing invasive maneuvers (e.g. liver biopsy) or administering interferon therapy could be dangerous (i.e.  $<50-75 \times 10^9/L$ ), or, lastly, as a

threshold below which platelet transfusion is indicated (i.e.  $<10 \times 10^9/L$ ).<sup>7,8,9,10</sup>

Thrombocytopenia in HCV infection has been known since 1993.<sup>11,12</sup> This condition may be an isolated symptom or may coexist with other extra hepatic manifestations (EM).<sup>13</sup> Additionally, in patients with untreated hepatitis C, both prevalence and severity of thrombocytopenia enhance in relation to the extent of disease.<sup>14</sup> Thrombocytopenia is exclusively attributable to increased pooling of platelets in the enlarged spleen because of portal hypertension.<sup>15</sup>

According to Pakistan Research Council on Water Resources (PRCWR), 10 million Pakistanis are suffering from Hepatitis C. Most cases are reported in poor areas like Interior Sindh, Southern Punjab and Southern Khyber-PK.<sup>16,17</sup> Punjab reports suggested a higher prevalence of HCV (4.3% weighted average, range 0.4–31.9%) compared to Sindh, Balochistan, and Khyber-PK. Wide variations in different areas within Punjab

## Association of Thrombocytopenia with Chronic Liver Disease Due to Hepatitis-C

were noted (range 0.4-31.9%). Southern Punjab is among the high affected areas with more than 7% prevalence range.<sup>5</sup>

In the observed urban population of Multan (n=1166), prevalence of HCV was (6.68%). The prevalence of HCV when studied in different age groups of both sexes, it was found that prevalence of HCV was maximum (8.92%) in mature males as compared to young males (6.66%) and old males (7.69%). The prevalence of Hepatitis C was higher (5.68%) in old females as compared to mature females (5.03%) and young females (5.17%).<sup>18</sup> A study conducted in Pediatric Department of Bahawal Victoria Hospital, Bahawalpur to know the hepatitis c virus infection in children. The results were alarming as 7.6% children were positive for HCV.<sup>19</sup>

As per above researches & news data the prevalence of Hepatitis C is more in Southern Punjab than other areas and till now no study is carried out in this region, hence it is important to determine the association of thrombocytopenia in CLD patients due to Hepatitis C in Southern Punjab as different climatic and hygienic conditions may affect this association differently. A previous study carried out in Pakistan suggest that out of 155 patients with HCV infection fifty patients (32.3%) had thrombocytopenia.<sup>20</sup> The local studies related to frequency of thrombocytopenia carried out in different regions of Pakistan show a variation of almost 7.5% in their end results so an additional study may help in result substantiation. The preliminary data on the topic in that area may help in further research plans and protocol preparations, the study can also provide a guideline to make some early treatment plan in the disease to prevent serious complications.

### Objective

The objective of this study was to determine frequency of thrombocytopenia in CLD patients due to Hepatitis C virus.

## MATERIALS AND METHODS

### Study Design:

- A cross sectional study

### Setting:

- Department of Medicine, 410 bedded Civil Hospital, Bahawalpur which is affiliated with Quaid-i-Azam Medical College Bahawalpur.

### Duration of Study:

- 01-03-2013 to 28-12-2013.

### Sample Size:

- The calculated sample size was 325 cases, with 5 % margin of error, 95 % confidence level.

### Sample Technique:

- Non probability purposive sampling

### Inclusion criteria

- Gender: Patients of either sex
- Age: All patients above 18 and up to 60 years.
- All the patients (already diagnosed and new one) admitted in Medicine Department with Chronic Liver Disease due to HCV (anti HCV antibodies by ELISA).

### Exclusion criteria

- Patients with history of alcoholism or any other drug abuse.
- Patient receiving interferon therapy (current or preceding 06 months)
- Patients having liver mass on abdominal ultrasonography.
- Patients having co-infection with hepatitis B & C.
- Patients having history of drug usage (cytotoxic, antimetabolites, thiazides) and sign and symptoms of any infiltrative disorders like (leukemia, myeloma, myelofibrosis, carcinoma) disseminated intravascular coagulation, idiopathic thrombocytopenic purpura, septicemia, thrombotic thrombocytopenic purpura.

### Data Collection

For the study an approval was taken from the Ethical Committee of Civil Hospital Bahawalpur. Three hundred and twenty five cases fulfilling inclusion criteria were recruited in the study in the Department of Medicine, Civil Hospital, Bahawalpur. Demographic history including age (in years) and sex (male or female) was recorded. A written informed consent was taken from patients. Blood specimen was sent to the laboratory for ELISA test of HCV and thrombocyte count in diagnosed cases of CLD. Data was collected on proforma and results were documented.

### Data Analysis

All the collected data was entered into computer software SPSS version 17 and analyzed. The percentages/ frequencies were given for qualitative variables (e.g. sex; male or female and thrombocytopenia) and means and standard deviations were given for Quantitative variables (e.g. age in years) of all the selected cases.

Frequencies were calculated, univariate and bivariate tables were constructed. Frequency of thrombocytopenia was determined.

## RESULTS

A total of 325 patients fulfilling the inclusion/exclusion criteria were enrolled to determine frequency of thrombocytopenia in CLD patients due to Hepatitis C virus.

Age distribution of the patients was done, which shows majority of the patients between 41-50 years i.e. 43.69% (n=142), 9.54% (n=31) between 18-30 years, 25.54% (n=83) between 31-40 years, 21.23% (n=69) between 51-60 years. Mean and SD was calculated as 38.54+5.12 years. (Table No. 1)

Gender distribution shows 59.38% (n=193) male and 40.62% (n=132) females. (Table No. 2). Frequency of thrombocytopenia in CLD patients due to hepatitis C virus revealed in 21.23% (n=69) while 78.77% (n=256) had no findings of thrombocytopenia. (Table No. 3)

**Table 1:** Age Distribution of The Patients (n=325)

Age(in years)	No. of patients	%
18-30	31	9.54
31-40	83	25.54
41-50	142	43.69
51-60	69	21.23
Total	325	100
Mean and S.D	38.54+5.12	

**Table 2:** Gender Distribution of The Subjects (n=325)

Gender	No. of patients	%
Male	193	59.38
Female	132	40.62
Total	325	100

**Table 3:** Frequency of Thrombocytopenia In CLD Patients Due to Hepatitis C Virus (n=325)

Thrombocytopenia	No. of patients	%
Yes	69	21.23
No	256	78.77
Total	325	100

Stratification of thrombocytopenia for age of the patients was done, where 25.81% (n=8) out of

31 cases were between 18-30 years, 25.30% (n=21) out of 83 were between 31-40 years, 22.54% (n=32) out of 142 cases were between 41-50 years, while 11.59% (n=8) out of 69 were between 51-60 years of age. (Table No. 4)

**Table 4:** Stratification of Thrombocytopenia for Age of The Patients (n=325)

Age(in years)	No. of patients	Thrombocytopenia (n=69)	
		No. of patients	%
18-30	31	8	25.81
31-40	83	21	25.30
41-50	142	32	22.54
51-60	69	8	11.59
Total	325	69	

## DISCUSSION

We planned this study to determine the association of thrombocytopenia in CLD patients due to Hepatitis C. The local studies related to frequency of thrombocytopenia carried out in different regions of Pakistan show a variation of almost 7.5% in their end results so an additional study may help in result substantiation.<sup>20</sup> The preliminary data on the topic in Southern Punjab area may help in further research plans and protocol preparations, the study can also provide a guideline to make some early treatment plan in the disease to prevent serious complications.

Majority of the patients were between 41-50 years i.e. 43.69% (n=142), mean age was 38.54+5.12 years, 59.38% (n=193) were male and 40.62% (n=132) females, frequency of thrombocytopenia in CLD patients due to hepatitis C virus was 21.23% (n=69) while 78.77% (n=256) had no findings of thrombocytopenia.

Louie KS and colleagues<sup>21</sup> demonstrate that the prevalence of TCP ranged from 0.16% to 45.4% and more than half of the studies reported a TCP prevalence of 24% or more. Because of the different TCP definitions, heterogeneity in study design and insufficient data on study characteristics such as age, gender, HCV treatment rates and disease severity an overall summary estimate of TCP prevalence among patients with HCV was not feasible. However, the relatively large prevalence in the majority of the studies suggests that there may be a substantial number of HCV patients at risk of bleeding

## Association of Thrombocytopenia with Chronic Liver Disease Due to Hepatitis-C

complications and reduced likelihood of successful HCV antiviral treatment.

In the study by Wang<sup>22</sup> et al (in Taiwan, community wide survey), HCV infection was strongly associated with thrombocytopenia, which is correlated with hepatocellular damage and hepatic fibrosis. The prevalence of thrombocytopenia was 10.2% among anti-HCV-positive subjects and 5.2% among co-infected subjects (anti-HCV and HBsAg-positive). Their results are comparable to our study.

The most recent examination of thrombocytopenia at the national level in United States was conducted using the National Health and Nutrition Examination Survey (NHANES) III.<sup>23</sup> In that study, 13% of individuals with positive HCV antibody had platelet counts below  $175 \times 10^9/L$ .

In the study by Kauf, <sup>24</sup> among 467 HCV-infected individuals in the survey (weighted population = 3,597,039), mean weighted age was 46.7 years (standard deviation = 15.5) and 61.7% were male. Overall, 7.6% met the study definition of TCP at the  $150 \times 10^9/L$  threshold.

Finally, the frequency of thrombocytopenia in CLD patients due to Hepatitis C virus is remarkably higher and needs attention to timely management.

### CONCLUSION

The frequency of thrombocytopenia is high among patients with Chronic Liver Disease (CLD). Therefore it is recommended that every patient who presents with Chronic Liver Disease should have a work-up for thrombocytopenia.

### REFERENCES

1. Pontisso P, Ruveletto GR, Fattovich G. Clinical and virological profiles in patients with multiple hepatitis virus infections. *Gastroenterol.* 1993;105:1529-33.
2. Previsani N, Lavanchy D. Hepatitis B. WHO/CDS/CSR/LYO/2002. 2: Hepatitis B, Geneva: World Health Organization; 2002.
3. World Health Organization fact sheets, Hepatitis C, Geneva: World Health Organization; 2000.
4. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol.* 2006;45:529-38.
5. Ali SA, Donahue MJ, Qureshi H, Vermund SH. Hepatitis B and hepatitis C in Pakistan: prevalence and risk factors. *Infectious Diseases J.* 2009;13:9-19.
6. Giannini EG. Review article: thrombocytopenia in chronic liver disease and pharmacologic treatment options. *Aliment Pharmacol Ther.* 2006;23:1055-65.
7. Handin RJ. Disorders of the platelet and vessel wall. In: Kasper DL, Braunwald E, Hauser SL, Fauci AS, Jameson JL, Longo DL, editors. *Harrison's principles of internal medicine*, New York: McGraw-Hill Medical Pub. 2004;673-80.
8. Grant A, Neuberger J. Guidelines on the use of liver biopsy in clinical practice. *Gut.* 1999;45:1-11.
9. Strader DB, Wright T, Thomas DL, Seeff LB. American association for the study of liver diseases. diagnosis, management, and treatment of hepatitis C. *Hepatology.* 2004;39:1147-71.
10. Slichter SJ. Relationship between platelet count and bleeding risk in thrombocytopenic patients. *Transfus Med Rev.* 2004;18:53-67.
11. Pawlotsky JM, Bouvier M, Fromont P, Deforges L, Duval J, Dhumeaux D, et al. Hepatitis C virus infection and autoimmune thrombocytopenic purpura. *J Hepatol.* 1995;23:635-9.
12. Durand JM, Lefevre P, Telle H, Kaplanski G, Quiles N, Soubeyrand J. Thrombocytopenic purpura and hepatitis C virus infection. *Haematologica.* 1993;78:135.
13. Zarebska-Michaluk DA, Lebensztejn DM, Kryczka WM, Skiba E. Extrahepatic manifestations associated with chronic hepatitis C infections in Poland. *Adv Med Sci.* 2010;55(1):67-73.
14. Weksler BB. Review article: the pathophysiology of thrombocytopenia in hepatitis C virus infection and chronic liver disease. *Aliment Pharmacol Ther.* 2007;26:13-9.
15. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. *J Clin Invest.* 1966;45:645-57.
16. Amitrano L, Guardascione MA, Brancaccio V, Balzano A. Coagulation disorders in liver disease. *SemLiv Dis.* 2002;22:83-96.
17. Achakzi J. "1,500 more Hepatitis C patients to get free treatment." *Daily Times - Leading News Resource of Pakistan.* 9 Jul, 2008.
18. Ali M, Kanwal L, Tassaduqe K, Iqbal R. Prevalence of Hepatitis C Virus (HCV) in

- Relation to Its Promotive Factors Among Human Urban Population of Multan, Pakistan. *Eur J Gen Med.* 2009; 6(2):94-98.
19. Naeem M, Ahmad A, Ahmad F, Qaisar I. Status of hepatitis c virus (HCV) infection; children admitted in paediatric ward of bahawal victoria hospital bahawalpur. *Professional Med J.* 2011;18(3):445-49.
  20. Dodhy MA, Zafar H, Mujtaba A, Frequency of risk factor for hepatitis B (HBV) and Hepatitis C (HCV): Thrombocytopenia a presenting feature of hepatitis C. *Ann Pak Inst Med Sci.* 2010;6(3):148-51.
  21. Louie KS, Micallel JM, Pimenta JM. Prevalence of thrombocytopenia among patients with chronic hepatitis C: a systematic review. *J Viral Hep* 2011;18:1-7.
  22. Wang CS, Yao WJ, Wang ST, Chang TT, Chou P. Strong association of hepatitis C virus (HCV) infection and thrombocytopenia: implications from a survey of a community with hyperendemic HCV infection. *Clin Infect Dis* 2004; 39: 790–6.
  23. Streiff MB, Mehta S, Thomas DL. Peripheral blood count abnormalities among patients with hepatitis C in the United States. *Hepatology.* 2002;35:947–952.
  24. Kauf TL, Nelson DR, Schelfhout J, Delaney JA, Wang PF. Trends in the prevalence of thrombocytopenia among individuals infected with hepatitis C virus in the United States, 1999-2008. *BMC Res Notes.* 2012;5:142.