Original Article

Effect of Direct Acting Antivirals (DAA) on Thrombocytopenia in Chronic Hepatitis C Patients Without Cirrhosis

Shahzad Alam Khan[1], Talha Rasheeq[3], Muhammad Shahzad Nasir Khan[4], Ali Raza[5], Ahsanullah M Mirbahar[2] and Muhammad Tahir[3]

ABSTRACT

Objective: To determine frequency of thrombocytopenia and effect of direct acting antivirals (DAA) on thrombocytopenia in chronic hepatitis C patients without cirrhosis.

Study Design: Cross-sectional/Prospective observational study.

Place and Duration of Study: This study was conducted at the Department of Medicine, Nishtar Hospital, Multan, from 18th January 2022 to 17th January 2023.

Materials and Methods: A total of 105 patients with chronic hepatitis C without cirrhosis who were candidate for DAA having age range between 30 to 70 years were included while the patients with hepatocellular carcinoma and CRF were excluded. After this, 5 ml blood sample was sent to the institutional pathology laboratory for measuring the load of viremia, platelet levels, renal parameters and HCV RNA by PCR. Patients having positive HCV RNA by PCR in absence of cirrhosis were given DAA (Daclatasvir with Sofosbuvir) for three months. End treatment response (ETR) was labelled by a negative PCR for HCV RNA after completion of treatment. Platelet count was also checked at this stage also. Increase in platelet count by 10% from baseline in thrombocytopenic patients was considered as significant improvement in platelet count.

Results: Age ranged from 30 to 70 years in this study, with a mean age of 47.60 ± 11.32 years. The vast majority of patients i.e. 68 (64.76%) were between 30 to 50 years of age. 60 (57.14%) of the 105 patients were men, and 45 (42.86%) were women, with a male to female ratio of 1.3:1. In our study, frequency of thrombocytopenia in chronic hepatitis C patients without cirrhosis was found in 42 (40.0%) patients. Moreover 18 patients (42.8%) had improvement in thrombocytopenia with DAA after completion of treatment.

Conclusion: This study found that there were a sizable proportion of chronic hepatitis C patients with thrombocytopenia. Significant number of patients show improvement in thrombocytopenia with successful treatment and thus may not need other costly treatment options like thrombopoetin agonists or platelet transfusion.

Key Words: Hepatitis C, Thrombocytopenia, Prevalence.

Citation of article: Khan SA, Rasheeq T, Khan MSN, Raza A, Mirbahar AM, Tahir M. Effect of Direct Acting Antivirals (DAA) on Thrombocytopenia in Chronic Hepatitis C Patients Without Cirrhosis. **Med Forum 2023;34(5):28-32.**

INTRODUCTION

Thrombocytopenia is one of the most prevalent hematological abnormality in those with chronic hepatitis C virus (HCV) infection[1].

[1.] Department of Medicine / Health Research Institute[2] / Nishtar Medical University, Multan.
[3.] Department of Internal-Medicine, Bakhtawar Amin Medical & Dental College, Multan.
[4.] Department of Medicine, Multan Medical and Dental College, Multan.
[5.] Department of Medicine & Gastroenterology, Nishtar Medical University and Hospital, Multan.

Correspondence: Dr. Shahzad Alam Khan, Assistant Professor of Medicine, Nishtar Medical University and Hospital, Multan.
Contact No: 0300 7195857
Email: shahzadalam17735@gmail.com

Received: February, 2023
Accepted: March, 2023
Printed: May, 2023

The consensus definition of thrombocytopenia (TCP) is platelet counts below 150×10^9/L. According to estimates, in the USA, there are between 2.7 and 3.9 million persons who have chronic hepatitis C and at least 71 million people worldwide have chronic hepatitis C[2]. Pathogenic mechanisms include the development of anti-platelet antibodies and/or immune complexes that attach to platelets and promote their early clearance, bone marrow suppression brought on by HCV itself or interferon treatment, and hypersplenism owing to portal hypertension[3]. When contemplating antiviral medication for these patients, the presence of thrombocytopenia was considered to be a limiting factor and linked to lower rates of sustained virological response in pre-DAA (direct antiviral agents) era[4,5]. Due to the danger of bleeding, thrombocytopenia might affect diagnostic procedures like liver biopsies. Most studies estimate a prevalence of >20 percent, however among those with chronic hepatitis C (CHC) the reported prevalence of thrombocytopenia ranges from 0.16 percent to 45.4 percent[7]. In two different local studies[6,7],

thrombocytopenia was found to be very common in people with chronic hepatitis C i.e. 53.0% and 22.6%. After HCV eradication, treatment with Sofosbuvir with Daclatasvir or ledipasvir has been demonstrated to increase platelet counts.[8,9]

Extensive search of data didn't provide evidence regarding thrombocytopenia prevalence and effect of DAA on thrombocytopenia in chronic hepatitis C in our local population. However, international data establishes a strong association of thrombocytopenia with chronic hepatitis C and improvement of thrombocytopenia with DAA. Our study will provide a baseline data for further research regarding identification of risk factors associated with thrombocytopenia and also determining impact of DAA on thrombocytopenia.

MATERIALS AND METHODS

This cross sectional study was carried out in Department of Medicine, Nishtar Hospital Multan from18th January 2022 to 17th January 2023 after taking permission from Institutional Ethical Committee. All patients provided their written informed consent. Non-probability consecutive sampling was the approach utilized for sampling and the WHO sample size calculator was used to determine the sample size, considering frequency of thrombocytopenia as 22.6% in patients with chronic hepatitis C[9], confidence interval of 95 % and margin of error 8%. One hundred and five (105) patients with age range of 30-70 years, either gender, and positive PCR for HCV RNA were included in study. Participants having pregnancy, cirrhosis on USG or Fibro scan, chronic renal failure (assessed on medical record (s/creatinine >1.5 mg/dl), patients with hepatitis B (evaluated by screening and PCR confirmation), patients with hepatocellular carcinoma (based on medical record and USG), were excluded from study.

Data was collected for sociodemographic characteristics including gender, age and duration of disease and previous history of treatment for chronic hepatitis C by using a standard questionnaire. Blood samples were collected for HCV RNA by PCR, viral load, HCV genotype, platelet count and renal function. Ultrasound and Fibro scan were done to exclude cirrhosis and hepatocellular cancer. All the information was collected in a pre-designed proforma. All those patients who had HCV RNA positive on PCR technique were given 400mg Sofosbuvir and 60mg Daclatasvir once daily for 3months. A negative PCR for HCV RNA after 3 months treatment was considered as successful end treatment response (ETR).

Data was analyzed by using Statistical Package for Social Science (SPSS) version 24. Quantitative data like age, platelet count, HCV RNA positivity was described using mean and standard deviation. Qualitative data like gender, previous history of treatment, residential status was described as frequency and percentages. Stratification of thrombocytopenia in chronic hepatitis C with respect to age groups, gender, duration of disease, viral load was done by using chi-square test. A p-value of ≤ 0.05 was taken as statistically significant. Platelet counts and HCV RNA by PCR were measured at the end of treatment i.e. 3rd month. Improvement in platelet count by 10% from baseline was considered as significant.

RESULTS

Table No. 1: Demographic Properties of study population (n=105)

Variables	Subdivision	Frequency	Percentage
Gender	Male	60	57.14%
	Females	45	42.86%
Residence	Rural	69	65.7%
	Urban	36	34.3%
Thrombocytopenia	Yes	42	40%
	No	63	60%
Age Groups	≤50 years	68	64.76%
	>50 years	37	35.24%
Socioeconomic Status	Poor	7 6	72.3%
	Average	29	27.6%
Viral load (copies/ml)	$\leq 10^3$	56	53.33%
	$\geq 10^3$	49	46.67%
Duration of disease	≤5 years	64	60.95%
	≥5 years	41	39.05%

Table No.2: Stratification of various factors with thrombocytopenia in patient with chronic hepatitis c

VARIABLES		Thrombocytopenia		p-value
	GROUPS	Yes	No	
Gender	Male (N=221)	27	33	**0.227**
	Female (N=111)	15	30	
Age Group	≤50 years (N=68)	28	40	**0.739**
	>50 years (N=37)	14	23	
Residence	Rural (N=69)	27	42	**0.801**
	Urban (N=36)	15	21	
Duration of disease	>5 years (N=64)	29	35	**0.165**
	>5 years (N=41)	13	28	
Viral Load (copies /ml)	$\leq 10^3$ (N=56)	20	36	**0.338**
	$>10^3$ (N=49)	22	27	

Age ranged from 30 to 70 years in this study, with a mean age of 47.60 ± 11.32 years. 64.76% of the patients (68) were aged lesser than 50 years. 60 (57.14%) of the 105 patients were men, and 45 (42.86%) were women, with a male to female ratio of 1.3:1. Mean duration of disease in our study was 5.76 ± 2.32 years. Mean load of viremia was 10.57 ± 3.41 x 10^3 copies/ml.

In our study, thrombocytopenia in chronic hepatitis C patients without cirrhosis was found in 42 (40.0%) patients. HCV genotype prevalence was 3a in 83.8% (88 case), 3b in 4.7% (5 cases), genotype 1 in 2.8% (3 cases), genotype 2 in 2.8% (3 cases) and untypeable in 6 cases. End treatment response was noticed in 102 cases (97.1%). Significant improvement in platelet count with successful end treatment response was seen in 18 cases (42.8%).

Stratification of thrombocytopenia with respect to age groups, gender, and duration of hepatitis C and load of viremia was done and no significant association of thrombocytopenia was noticed with these parameters.

Table No. 3: Significant increase in platelet count with successful DAA therapy of CHC

Significant increase in platelet count	No of patients	Percentage
Present	26	61.9%
Absent	16	38.1%
Total	42	100%

DISCUSSION

Chronic HCV patients experience multifactorial thrombocytopenia; HCV promotes hepatic necroinflammation and fibrosis, which impairs liver function and reduces thrombopoetin synthesis and activity[10,11]. There are other pathways as well, such as autoantibodies causing persistent immunological thrombocytopenia and HCV-mediated bone marrow suppression.[12] According to research by Karasu et al., platelet count is adversely linked the hepatic fibrosis staging in those with chronic HBV and HCV.[13] Therefore, variations in platelet count may serve as a noninvasive technique to track the worsening of liver disease and portal pressure.[14] Since severe thrombocytopenia increases the risk of significant bleeding, intrusive procedures like staging biopsies may not be possible.[15] Additionally, thrombocytopenia might exacerbate bleeding symptoms like variceal hemorrhage. It might make it more difficult to start and maintain antiviral therapy, thus decreasing the possibility that HCV treatment would be effective.[14]

Chronic HCV treatment is rapidly evolving. Sofosbuvir, the first NS5B RNA-polymerase inhibitor, was authorized for the treatment of HCV in 2014. Since 2015, the primary therapy in the National Program of many countries has been Sofosbuvir/Daclatasvir with or without ribavirin.[16] DAA regimens are currently an important step in the strategy to eradicate HCV, with greater rates of SVR reaching 100 percent with specific DAA combinations.[17] Comparing DAA therapy to IFN-based therapy, it also demonstrated a better safety profile.[18]

Age ranged from 30 to 70 years in our study, with a mean age of 47.60 ± 11.32 years. A large proportion of the patients 68 (64.76%) were under 50 years. In our settings, 60 (57.14%) of the 105 patients were men, and 45 (42.86%) were women, with a male to female ratio of 1.3:1. In our study, thrombocytopenia occurrence in patients of chronic hepatitis C without cirrhosis was noted in 42(40.0%) patients. In two local studies, thrombocytopenia occurrence in chronic hepatitis C was found to be 53.0%[6] and 22.6%.[7] In a study conducted by Bano S et al[19], the patients had 42.2±11.4 years average age, and 43.3 percent of those who had hepatitis C had thrombocytopenia. These results are very much similar to our results. A study conducted by Rehman S et al[20] showed that mean age was 39 ± 10.24, male to female ratio was 1.4:1, and frequency of thrombocytopenia was 22%. In an Egyptian study[21], thrombocytopenia is seen in 12% cases.

HCV genotype prevalence was 3a in 83.8% (88 case), 3b in 4.7% (5 cases), genotype 1 in 2.8% (3 cases), genotype 2 in 2.8% (3 cases) and untypeable in 6 cases. End treatment response was noticed in 102 cases (97.1%). Petruzziello A et al[22] reported that genotype 1 is 61.0% followed by genotype 3 which is 20.0% and genotype 4 was10.0% in various European countries. These results don't match our findings. However, multiple previous studies have also shown dominance of genotype 1 in European and US population in contrast to Asian population where genotype is more common. In another Pakistani study[23], genotype 3a frequency is noted up to 87%. These finding are very much similar to our results.

In our settings, baseline platelet count in thrombocytopenic population was 106.67±26.45 and at the end of treatment it was 133±38.27 and significant improvement in platelet count was seen in 61.9%. Saif-Al-Islam M et al[24] noticed that baseline mean platelet count was 112.55±30.19 and at the end of treatment mean platelet count was 146.91±46.02 and significant improvement in platelet count was 73%. These results were almost similar to our findings. El-Kholy AM et al[26] discovered in their study that mean platelet count was 93.56 ± 33.09 at baseline, 116.20 ± 40.17 at 12 weeks, and the mean ± SD platelet count at 24 weeks of starting the antiviral treatment was 125.98 ± 44.21 and significant improvement in platelet count was seen in 69% patients.

CONCLUSION

This study concluded that thrombocytopenia is quite prevalent and is a major constraint for many procedures in patients with chronic hepatitis C even in the absence of cirrhosis. However, successful curative DAA treatment leads to considerable increase in platelet count. In all those patients who have chronic hepatitis C and thrombocytopenia should be treated with DAA prior to any elective procedure in order to avoid untoward effects caused by thrombocytopenia.

Author's Contribution:

Concept & Design of Study:	Shahzad Alam Khan
Drafting:	Talha Rasheeq, Muhammad Shahzad Nasir Khan
Data Analysis:	Ali Raza, Ahsanullah M Mirbahar, Muhammad Tahir
Revisiting Critically:	Shahzad Alam Khan, Talha Rasheeq
Final Approval of version:	Shahzad Alam Khan

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

REFERENCES

1. Chen, Yen-Chun, Tseng, Chih-Wei, Tseng, Kuo-Chih. Rapid platelet count improvement in chronic hepatitis C patients with thrombocytopenia receiving direct-acting antiviral agents. Medicine 2020;99(19):e20156.
2. Blach S, Zeuzem S, Manns M, Altraif I, Duberg AS, Muljono DH, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterolo Hepatol 2017; 2:161–176.
3. Rawi S, Wu GY. Pathogenesis of Thrombocytopenia in Chronic HCV Infection: A Review. J Clin Transl Hepatol 2020;8(2):184-191.
4. Dahal S, Upadhyay S, Banjade R, Dhakal P, Khanal N, Bhatt VR. Thrombocytopenia in Patients with Chronic Hepatitis C Virus Infection. Mediterr J Hematol Infect Dis 2017;9(1): e2017019.
5. Louie KS, Micallef JM, Pimenta JM, Forssen UM. Prevalence of thrombocytopenia among patients with chronic hepatitis C: a systematic review. J Viral Hepatitis 2011;18(1):1-7.
6. Nawaz Z, Aurangzeb M, Imran K, Rasheed T, Alam MT, Jaffery MF, et al. Frequency of thrombocytopenia; patients with chronic hepatitis C infection. Profess Med J 2014;21(4):684-90.
7. Aziz M, Khan S. Frequency of thrombocytopenia in chronic active hepatitis c patients – a hindrance in treatment. Biomedica 2014;30(3):1–4.
8. Welzel TM, Petersen J, Herzer K, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut 2016;65:1861–70.
9. Sayyar MW, Saidi M, Zapatka SA, et al. Tu1542-platelet count increases after viral suppression in chronic HCV, independent of fibrosis stage. Gastroenterol 2018;154:S-1245–6.
10. Fouad MY. Chronic hepatitis C-associated thrombocytopenia: aetiology and management. Tropical Gastroenterol 2013;34(2):58–67.
11. Afdhal N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. J Hepatol 2008;48(6):1000–1007..
12. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatol 2003;38(2):518–526.
13. Karasu Z, Tekin F, Ersoz G, et al. Liver fibrosis is associated with decreased peripheral platelet count in patients with chronic hepatitis B and C. Digestive Diseases and Sci 2007;52(6):1535–1539.
14. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterol 2013;144(1):102–11.e1.
15. Seeff LB, Everson GT, Morgan TR, Curto TM, Lee WM, Ghany MG, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol 2010;8(10): 877–883.
16. Kanda T, Matsuoka S, Moriyama M, Hepatitis C virus genotype 4-infection and interferon-free treatment in Egypt. Hepatol Int 2018;12(4): 291–293.
17. Omran D, Alboraie M, Zayed RA, et al. Towards hepatitis C virus elimination: Egyptian experience, achievements, and limitations. World J Gastroenterol 2018;24(38):4330–4340.
18. Atsukawa M, Tsubota A, Toyoda H, et al. Efficacy and safety of ombitasvir/ paritaprevir/ ritonavir and ribavirin for chronic hepatitis patients infected with genotype 2a in Japan. Hepatol Res 2019;49(4): 369–376.
19. Bano S, Qureshi J, Raza A, Zafar Hashmi K. Thrombocytopenia as a Clinical Manifestation of Hepatitis C Among Patients With a Positive Anti-HCV Test. Int J Infect 2016;3(3):e35094.
20. Rehman S, Rahman S, Khan S, Ahmad N, Rahman N. Frequency of thrombocytopenia in hepatitis c patients. J Med Sci 2019;27(3):190-3.
21. Ibrahim AA, Taha HA, Mohammed RA, Khalil SH, Abd-Allah N. Study of Prevalence of

Autoimmune Manifestations of Chronic Hepatitis C Infection in Beni-Suef Governorate. Egyp J Hosp Med 2022;87(1):1736-42.

22. Petruzziello A, Loquercio G, Sabatino R, Balaban DV, Ullah Khan N, Piccirillo M, et al. Prevalence of Hepatitis C virus genotypes in nine selected European countries: A systematic review. J Clin Lab Analysis 2019;33(5):e22876.
23. Haqqi A, Munir R, Khalid M, Khurram M, Zaid M, Ali M, et al. Prevalence of hepatitis C virus genotypes in Pakistan: current scenario and review of literature. Viral Immunol 2019;32(9):402-13.
24. Saif-Al-Islam M, Abdelaal UM, Younis MA, Alghany Algahlan HA, Khalaf S. Effect of direct-acting antiviral therapy on thrombocytopenic patients with hepatitis C virus-related chronic liver disease. Gastroenterol Res Pract 2021;2021:1-10.
25. El-Kholy AM, Shoeib SA, Zagla HA, Abdelhafez MA, Abdelhamid AE, Kasemy ZA,et al. Effect of direct-acting antiviral agents on hepatitis C virus-associated thrombocytopenia. Menoufia Med J 2020;33(1):76.

.