Research Article

Prediction of Fibrosis in Chronic Hepatitis C by Mean Platelet Volume and Platelet to Lymphocyte Ratio

Mehmet Ali Kosekli*

Department of Gastroenterology, Abant Izzet Baysal University Hospital, Bolu, Turkey.

Abstract: Introduction: Hepatitis C is a chronic inflammatory condition that associated with fibrosis. Novel inflammatory markers have been suggested to be related inflammatory condition. Therefore, we aimed to investigate hemogram derived indices, such as, Mean Platelet Volume (MPV) and Platelet to Lymphocyte ratio (PLR) in hepatitis C subjects and to compare those in healthy controls.

Materials and Methods: In present retrospective study, 17 HCV patients having mild fibrosis, 23 patients having advanced fibrosis and 68 control subjects were included whom visited outpatient clinics of our institution between 1.10. 2017 and 30.11.2019. Hemogram indices and laboratory characteristics were compared.

Results: Median MPV values of the advanced fibrosis patients [8.3 (6.5-14) fL] was significantly higher than that of the mild fibrosis patients [7.9 (6.5-11.1) fL] (p=0.002) and control subjects [7.2 (4.6-10.7) fL] p<0.001) whereas MPV values of mild and advanced fibrosis patients were similar (p=0.750). Median PLR values of the mild fibrosis, advanced fibrosis and control groups were 103 (58-223) %, 86 (45-358) %, and 77 (64-96) %, respectively (p=0.010). A ROC analysis revealed that a MPV value greater than 7.3 fL determines advanced fibrosis with 76% sensitivity and 59% specificity. A PLR greater than 92% determines advanced fibrosis with 73% sensitivity and 64% specificity.

Conclusion: We suggest that elevated PLR and MPV could predict of advanced fibrosis in chronic hepatitis C.

Keywords: Hepatitis C, Fibrosis, Platelet to lymphocyte ratio, Mean platelet volume, Hemogram indices, Liver cirrhosis.

INTRODUCTION

Estimated 2 million people in the world died due to liver diseases according to the data of year 2018. Half of these are from liver cirrhosis complications, half from chronic hepatitis and hepatocellular cancer [1]. Approximately 2.5% of the global population is infected by Hepatitis C virus (HCV) and liver cirrhosis and hepatocellular carcinoma (HCC) are among its main consequences [2]. Liver degeneration and fibrosis level caused by hepatitis C infection is correlated with the complications. The level of fibrosis caused by hepatitis c is important in determining treatment strategies and in estimation of the prognosis and progression of the disease. Liver biopsy is a standard method in revealing the fibrosis caused by HCV [3]. However, due to the potential complications of this invasive method cause hesitation in patients and physicians [4]. The search for non-invasive markers to reveal liver fibrosis continues. It has been shown in many studies that hemogram parameters can be used to show chronic inflammatory conditions such as familial Mediterranean fever, rheumatoid arthritis and ulcerative colitis [5-7].

In present study, we investigated whether hemogram parameters could be used to estimate the level of hepatic fibrosis revealed in liver biopsy performed pre-treatment in chronic hepatic C patients. We aimed to seek correlation between groups, hemogram indices and established parameters such as APRI Fib-4 scores and hemogram parameters.

*Address correspondence to this author at the Department of Gastroenterology, Abant Izzet Baysal University Hospital, Bolu, Turkey. Email: kosekli@gmail.com

MATERIALS AND METHODS

Naive chronic hepatitis C patients whom presented to outpatient clinics of our institution (Bolu Abant Izzet Baysal University Hospital, Department of Gastroenterology) between 1.10. 2017 and 30.11.2019 were included in present retrospective study. Ethical approval was obtained from local ethics committee (approval number: 2021/47). Healthy volunteers who visited internal medicine outpatient clinics were included in control group. Patients with cancer, acute infection, active inflammatory condition, pregnancy and hematological disorders were excluded. We also excluded the subjects on anticoagulant therapy.

General characteristics of the participants; age, gender, comorbidity status, laboratory parameters including HCV RNA levels, HAI (histological activity index), gamma glutamyl transferase (GGT), alanine amino transferase (ALT), aspartate amino transferase (AST), neutrophil count (NEU), white blood cell count (WBC), hemoglobin (Hb), lymphocyte count (LYM), hematocrit (Htc), red cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV) and platelet count (PLT) of the study population were obtained from patients' files and hospital database. NLR and PLR were calculated with NEU/LYM and PLT/LYM formulas, respectively. AST-to-platelet ratio index (APRI) APRI = [(AST / ULN) / Platelet (109 / L)] × 100 and fibrosis-4 (FIB-4) scores were also considered in the study as

classical non-invasive methods in determination of liver fibrosis [8]. Fibrosis grade in liver biopsy of patients were evaluated according to the Ishak system. Patients grouped as mild fibrosis (fib score 0-2) or advanced fibrosis (fib score 3-6).

STATISTICAL ANALYSIS

Statistical analysis were carried out with SPSS program (SPSS 15.0 for Windows, IBM, Chicago, IL, USA). Shapiro-Wilk test was used to assess whether variables were distributed normally or not. Normally distributed variables were expressed as mean ± standard deviation and compared by one way ANOVA test. Kruskal-Wallis test was used for comparison of non-normally distributed variables and they were expressed as median (min.-max.). Chi-square test was used for comparison of categorical variables. Pearson's correlation was used for correlation analysis. ROC analysis was used in determination of predictive ability of the test in detecting advanced fibrosis. Best cut off value was determined by Youden index. The p value was considered statistically significant when it is lower than 5%.

RESULTS

Study population was consisted of 108 subjects (mild fibrosis: 17, advanced fibrosis: 23 and control: 68). Age (p=0.390) and gender (p=0.660) were not statistically different between groups. The Hb (p=0.070), Htc (p=0.370), NEU (p=0.270), LYM (p=0.510), RDW (p=0.350), PDW (p=0.070) and NLR (p=0.160) of the study and control groups were not different. The WBC (p=0.020) and PLT (p<0.001) values of the groups were significantly different (Table **1**).

Table 1. Characteristics of the Mild and Advanced Fibrosis and Control Groups.

Variables	Mild Fibrosis n=17	Advanced Fibrosis n=23	Control n=68	p values
Male, n	12	13	43	
Female, n	5	10	25	0.660
Age (years)	51±15	52 ± 19	48 ± 9	0.390
Hb (g/dL)	14 ± 1.6	13.8 ± 1.6	14.6 ± 1.5	0.070
Htc (%)	42.7 ± 4.4	41.8 ± 4.1	43.2 ± 4.3	0.370
WBC (k/mm^3)	6.3 (5-9)	6 (4-10)	7 (4-11)	0.002
NEU (k/mm^3)	4.0 ± 1.1	3.48±1.1	3.5±1.2	0.270
LYM(k/mm^3)	1.8±0.5	2.0±0.6	2.0±0.6	0.510
PLT (k/mm^3)	181 (89-373)	178 (100-330)	234 (151-374)	<0.001
RDW (%)	15 (14-17)	16 (14-18)	15.7 (14-22)	0.350
PDW (%)	18 (16-22.1)	17.7 (14.3-21.4)	18 (16-22)	0.07
MPV$^{\&}$ (fL)	7.9 (6.4-11.1)	8.3 (6.5-14)	7.2 (4.6-10.7)	<0.001
NLR* (%)	2 (0.9-6.3)	1.4 (0.6-6.7)	1.5 (0.8-3.7)	0.160
PLR^x (%)	103 (58.1-223.2)	86 (44.8-358.7)	118 (64-196)	0.005

MPV$^{\&}$: Mean platelet volume, NLR*: Neutrophil to Lymphocyte Ratio. PLR^x: Platelet to Lymphocyte Ratio. n: population of the group.

In post Hoc Tukey test median MPV values of the advanced fibrosis patients [8.3 (6.5-14) fL)] was significantly higher than that of the mild fibrosis patients [7.9 (6.5-11.1) fL] (p=0.002) and control subjects [7.2 (4.6-10.7) fL] (p<0.001) whereas MPV values of mild and advanced fibrosis patients were similar (p=0.750).

Median PLR values of the mild fibrosis, advanced fibrosis and control groups were 103 (58-223) %, 86 (45-358) %, and 118 (64-196) %, respectively (p=0.010). Post Hoc Tukey test revealed that this difference was related with the difference between advanced fibrosis and control group (p=0.040), whereas PLR values of the mild and advanced fibrosis (p=0.730) groups and that of mild fibrosis and control subjects (p=0.610) were not statistically different.

PLR was not significantly correlated with fibrosis score (r=-0.27, p=0.090), APRI score (r=-0.23, p=0.150), and FIB4 score (r=-0.27, p=0.100). Similarly, MPV was not correlated with fibrosis score (r=0.27, p=0.080), APRI score (r=0.19, p=0.25), and FIB4 score (r=0.28, p=0.080).

A ROC analysis revealed that a MPV value greater than 7.3 fL determines advanced fibrosis with 76% sensitivity and 59% specificity. A PLR greater than 92% determines advanced fibrosis with 73% sensitivity and 64% specificity. Fig. (**1**) shows the ROC curves of MPV and PLR in determination of advanced fibrosis.

We further compared mild and advanced fibrosis groups in terms of HCV RNA, ALT, AST, GGT, APRI, HAI and FIB4

scores. HCV RNA (p=0.840), ALT (p=0.060), GGT (p=0.380), and FIB4 (p=0.190) scores were not statistically different. However, AST (p=0.008), HAI (p=0.002) and APRI (p=0.020) scores were significantly higher in advanced fibrosis group. There were also no significant difference between mild and advanced fibrosis groups according to the comorbidities (p=0.400).

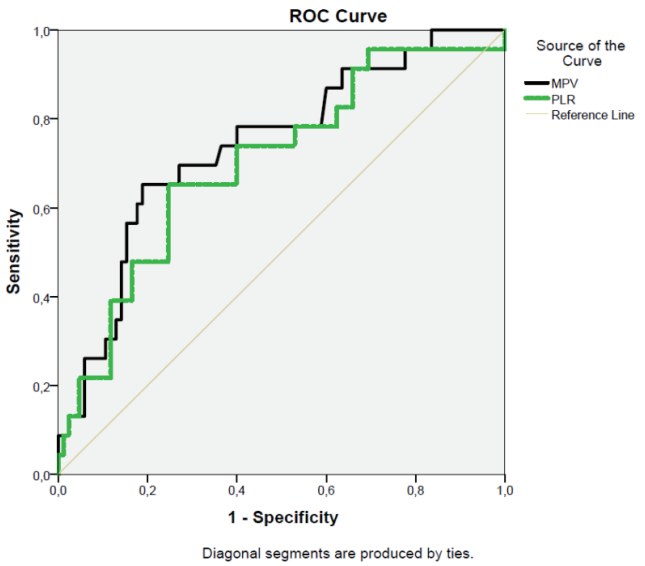

Fig. (1). ROC Curve of the MPV and PLR in Detecting Advanced Fibrosis.

DISCUSSION

Results of the present study indicate that (i) PLR and MPV may be surrogate markers of chronic hepatitis C, (ii) PLR has significant positive correlation with fibrosis score, (iii) both MPV and PLR has considerable sensitivity and specificity in prediction of advanced fibrosis in chronic hepatitis C patients, and (iv) APRI, HAI and AST levels of the HCV patients with advanced fibrosis were higher than those of the subjects with mild fibrosis.

The roles of MPV and PLR in inflammatory conditions have been well established. MPV has been suggested to be associated with thyroid gland malignancies [9], hypovitaminosis D [10], coronary artery disease [11], obesity [12], nasal polyposis [13], irritable bowel disease [14], and lumbar disc pathologies [15]. On the other hand, ratio of MPV to lymphocyte count has been associated with diabetic nephropathy [16], with increased HbA1c [17], and with frailty [18], in type 2 diabetic subjects. Therefore, association of MPV and inflammatory conditions is an indisputable fact. Similarly, elevated PLR values have been reported in irritable bowel syndrome [19] in type 2 diabetes mellitus [20], in cancer [21], and in rheumatologic conditions [22]. Elevated PLR and MPV values in chronic hepatitis C reported in present study are compatible with current literature data.

Inflammation has crucial role in chronic hepatitis C infection [23-25]. Moreover, inflammation is considered a risk factor for increased fibrosis in hepatitis C patients [25]. Authors reported that inflammatory burden has been related degree of fibrosis in chronic hepatitis C [25, 26]. These data confirm that chronic hepatitis C causes significant amount of inflammatory burden in affected subjects. Since MPV and PLR are increased in inflammatory conditions, they tend to be elevated in chronic hepatitis C, as reported in present study.

We may speculate about elevation of MPV in chronic hepatitis C. Inflammation causes activation of the platelets and activated platelets became larger in diameter [27]. As a result, chronic inflammation in chronic hepatitis C may interact with the platelet production in bone marrow and may cause release of larger platelets from megakaryocytes, thus, leading to an increase in MPV value in hemogram.

The causes of elevated PLR in subjects with chronic hepatitis C compared to controls need to be elucidated. Inflammatory stimuli may enhance platelet production and increase the number of platelets produced in bone marrow. Indeed, Akinsegun et al. reported that production of the thrombocytes is increased in subjects with diabetes mellitus, which is also considered as an inflammatory disease [28]. Chronic hepatitis C is also a cause of chronic, low grade, continuous inflammation alike with type 2 diabetes mellitus, thus, platelet production may be stimulated in these patients before splenomegaly developed. On the other hand, inflammatory cytokines, such as, interleukin may cause a decrease in circulating lymphocyte count [29]. Increased platelet production and decreased lymphocyte count may cause together elevation of PLR in chronic hepatitis C.

Recent research in literature suggest fibrosis score (FIB-4 index) as a valuable marker for hepatic fibrosis assessment in chronic hepatitis C subjects [30]. Moreover, it has significant role in excluding prominent liver fibrosis in chronic hepatitis B [31]. Therefore, we assessed the possible correlation between PLR and fibrosis score and revealed significant positive correlation between two parameters. However, MPV was not significantly correlated with the fibrosis score in present study.

APRI scores reflect fibrosis in chronic liver diseases [32]. In accordance with literature, AST, HAI and APRI scores of the patients with advanced fibrosis were higher than those of the subjects with mild fibrosis among HCV population.

There are two important limitation of present work; retrospective design and relatively low number of study population. Nevertheless, present study's results of which confirmed

association of hepatitis C with MPV and PLR, and significant correlation between PLR and fibrosis degree are important findings for current literature.

CONCLUSION

In conclusion, we suggest that elevated PLR and MPV could predict advanced fibrosis in chronic hepatitis C subjects.

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2019; 70(1): 172-93. DOI: 10.1016/j.-jhep.2018.06.024

[2] Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013; 57(4): 1333-42. DOI: 10.1002/hep.26141

[3] Sebastiani G, Alberti A. Non invasive fibrosis biomarkers reduce but not substitute the need for liver biopsy. World J Gastroenterol 2006; 12(23): 3682-94. DOI: 10.3748/w-jg.v12.i23.3682

[4] Cadranel J-F, Rufat P, Degos F. Practices of liver biopsy in France: Results of a prospective nationwide survey. Hepatology 2000; 32(3): 477-81. DOI: 10.1053/jhep.2000.16602

[5] Makay B, Türkyilmaz Z, Ünsal E. Mean platelet volume in children with familial Mediterranean fever. Clin Rheumatol 2009; 28(8): 975-8. DOI: 10.1007/s10067-009-1148-5

[6] Lee YH. Association between the neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio and rheumatoid arthritis and their correlations with the disease activity: A meta-analysis. J Rheum Dis 2018; 25(3): 169-78. DOI: 10.4078/-jrd.2018.25.3.169

[7] Kapsoritakis AN, Koukourakis MI, Sfiridaki A, *et al*. Mean platelet volume: A useful marker of inflammatory bowel disease activity. Am J Gastroenterol 2001; 96(3): 776-81. DOI: 10.1111/j.1572-0241.2001.03621.x

[8] Sterling RK, Lissen E, Clumeck N, *et al*. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology (Baltimore, Md) 2006; 43(6): 1317-25. DOI: 10.1002/hep.21178

[9] Sit M, Aktas G, Ozer B, *et al*. Mean platelet volume: An overlooked herald OF malignant thyroid nodules. Acta Clin Croatica 2019; 58(3): 417-20. DOI: 10.20471/acc.2019.58.03.03

[10] Erkus E, Aktas G, Atak BM, Kocak MZ, Duman TT, Savli H. Haemogram parameters in vitamin D deficiency. J Coll Physicians Surg Pak 2018; 28(10): 779-82.

[11] Sincer I, Gunes Y, Mansiroglu AK, Cosgun M, Aktas G. Association of mean platelet volume and red blood cell distribution width with coronary collateral development in stable coronary artery disease. Postepy Kardiol Interwencyjnej 2018; 14(3): 263-9. DOI: 10.5114/aic.2018.78329

[12] Aktas G, Kocak MZ, Duman TT, *et al*. Mean Platelet Volume (MPV) as an inflammatory marker in type 2 diabetes mellitus and obesity. Bali Med J 2018; 7(3): 650-3. DOI: 10.15562/b-mj.v7i3.806

[13] Aktaş G, Sit M, Tekce H, *et al*. Mean platelet volume in nasal polyps. West Indian Med J 2013; 62(6): 515-8. DOI: 10.7727/wimj.2013.011

[14] Aktas G, Alcelik A, Tekce BK, Tekelioglu V, Sit M, Savli H. Red cell distribution width and mean platelet volume in patients with irritable bowel syndrome. Prz Gastroenterol 2014; 9(3): 160-3. DOI: 10.5114/pg.2014.43578

[15] Dagistan Y, Dagistan E, Gezici AR, *et al*. Could red cell distribution width and mean platelet volume be a predictor for lumbar disc hernias? Ideggyogy Sz 2016; 69(11-12): 411-4. DOI: 10.18071/isz.69.0411

[16] Kocak MZ, Aktas G, Erkus E, Duman TT, Atak BM, Savli H. Mean platelet volume to lymphocyte ratio as a novel marker for diabetic nephropathy. J Coll Physicians Surg Pak 2018; 28(11): 844-7. DOI: 10.29271/jcpsp.2018.11.844

[17] Bilgin S, Aktas G, Zahid Kocak M, *et al*. Association between novel inflammatory markers derived from hemogram indices and metabolic parameters in type 2 diabetic men. Aging Male 2020; 23(5): 923-7. DOI: 10.1080/13685538.2019.1632283

[18] Bilgin S, Aktas G, Kahveci G, Atak B, Kurtkulagi O, Duman TT. Does mean platelet volume/lymphocyte count ratio associate with frailty in type 2 diabetes mellitus? Bratisl Lek Listy 2021; 122(2): 116-9. DOI: 10.4149/BLL_2021_017

[19] Aktas G, Duman T, Atak B, *et al*. Irritable bowel syndrome is associated with novel inflammatory markers derived from hemogram parameters. Fam Med Prim Care Rev 2020; 22(2): 107-10. DOI: 10.5114/fmpcr.2020.95311

[20] Atak B, Aktas G, Duman TT, Erkus E, Kocak MZ, Savli H. Diabetes control could through platelet-to-lymphocyte ratio in hemograms. Rev Assoc Med Bras 2019; 65(1): 38-42. DOI: 10.1590/1806-9282.65.1.38

[21] Li B, Zhou P, Liu Y, *et al*. Platelet-to-lymphocyte ratio in advanced cancer: Review and meta-analysis. Clin Chim Acta 2018; 483: 48-56. DOI: 10.1016/j.cca.2018.04.023

[22] Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M,

Kitas GD. The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases. Ann Lab Med 2019; 39(4): 345. DOI: 10.3343/alm.2019.39.4.345

[23] Naggie S. Hepatitis C virus, inflammation, and cellular aging: Turning back time. Top Antivir Med 2017; 25(1): 3-6.

[24] Barnaba V. Hepatitis C virus infection: A "liaison a trois" amongst the virus, the host, and chronic low-level inflammation for human survival. J Hepatol 2010; 53(4): 752-61. DOI: 10.1016/j.jhep.2010.06.003

[25] Nieminen U, Arkkila PE, Kärkkäinen P, Färkkilä MA. Effect of steatosis and inflammation on liver fibrosis in chronic hepatitis C. Liver Int 2009; 29(2): 153-8. DOI: 10.1111/j.1478-3231.2008.01779.x

[26] Leandro G, Mangia A, Hui J, *et al*. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: A meta-analysis of individual patient data. Gastroenterology 2006; 130(6): 1636-42.

[27] Cakir L, Aktas G, Enginyurt O, Cakir SA. Mean platelet volume increases in type 2 diabetes mellitus independent of HbA1c level. Acta Medica Mediterranea 2014; 30(2): 425-8. DOI: 10.1053/j.gastro.2006.03.014

[28] Akinsegun A, Olusola DA, Sarah J-O, *et al*. Mean platelet volume and platelet counts in type 2 diabetes: Mellitus on treatment and non-diabetic mellitus controls in Lagos, Nigeria. Pan Afr Med J 2014; 18: 42. DOI: 10.11604/pamj.2014.18.42.3651

[29] Chung K-P, Chang H-T, Lo S-C, *et al*. Severe lymphopenia is associated with elevated plasma interleukin-15 levels and increased mortality during severe sepsis. Shock 2015; 43(6): 569-75. DOI: 10.1097/SHK.0000000000000347

[30] Vallet-Pichard A, Mallet V, Nalpas B, *et al*. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology 2007; 46(1): 32-6. DOI: 10.1002/hep.21669

[31] Mallet V, Dhalluin-Venier V, Roussin C, *et al*. The accuracy of the FIB-4 index for the diagnosis of mild fibrosis in chronic hepatitis B. Aliment Pharmacol Ther 2009; 29(4): 409-15. DOI: 10.1111/j.1365-2036.2008.03895.x

[32] Wang CC, Liu CH, Lin CL, *et al*. Fibrosis index based on four factors better predicts advanced fibrosis or cirrhosis than aspartate aminotransferase/platelet ratio index in chronic hepatitis C patients. J Formos Med Assoc 2015; 114(10): 923-8. DOI: 10.1016/j.jfma.2015.07.004

Received: September 15, 2021 Revised: October 27, 2021 Accepted: November 03, 2021