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ORIGINAL ARTICLE

Mean Platelet Volume in Patients with Non-Alcoholic Fatty Liver Disease

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Abstract:

Background: Over the years, increasing obesity, hypertension and diabetes mellitus have led to higher incidence and prevalence of Non-alcoholic Fatty Liver Disease (NAFLD) in India, which was initially thought to be a disease of developed countries. NAFLD is the most common cause of chronic liver disease in the western countries and now it is in rapid rise in India. Liver biopsy is a gold standard in NAFLD diagnosis. As liver biopsy is an invasive procedure various non-invasive markers are being explored to assist in diagnosis of NAFLD. One such promising marker which is being studied is Mean Platelet Volume (MPV). Nevertheless, studies utilizing MPV for the diagnosis of NAFLD are rare. *Aim and Objectives:* To measure levels of MPV in NAFLD patients and compare with healthy controls. *Material and Methods:* A total of 86 subjects, 43 NAFLD and 43 healthy controls, were included. Baseline variables, laboratory parameters and MPV recorded were compared between both the groups. *Results:* Demographic variables [Body Mass Index (BMI), waist circumference], laboratory variables (total leukocyte count, plateletcrit, MPV), liver function tests (alanine transferase, alkaline phosphatase, gamma glutaryl transferase) and lipid parameters (high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein) were significantly higher in the NAFLD group. MPV correlated positively with aspartate aminotransferase (r: 0.2834, p=0.0082), alanine transferase level (r: 0.2834; p=0.0082) and the presence of NAFLD (0.6019; p<0.001). After adjusting all the covariates, only NAFLD was found to be the independent predictor of increased MPV [Odds Ratio (OR) =8.22 95% Confidence Interval (CI)(2.75 - 27.95) P < 0.001]. A cut-off MPV >10.6 fL yielded 72.09% sensitivity, 76.74% specificity, 75.61% positive predictive value and 73.33% negative predictive value. *Conclusion:* The study results show an increase in MPV in patients with NAFLD.

Keywords: Mean Platelet Volume, Metabolic Syndrome, Non-alcoholic Fatty Liver Disease, Non-alcoholic Steatohepatitis, Fatty Liver

Introduction:

Non-alcoholic Fatty Liver Disease (NAFLD) is described as a fatty liver in the initial stages and then as liver injury, in advanced stages. Histologic spectrum of NAFLD includes simple Non-alcoholic Fatty Liver (NAFL), Non-alcoholic Steatohepatitis (NASH) and cirrhosis [1]. NAFLD is linked strongly with metabolic syndrome and both histologic and clinical data are required to establish a definitive diagnosis. NAFLD patients are mostly evaluated due to chronic elevation of liver enzymes, with or without hepatomegaly [2]. A combination of the patient's history, results of blood tests, physical examination and radiological investigations are useful for liver disease diagnosis. The gold standard criteria to diagnose NAFLD and its components is liver biopsy [3]. However, various non-invasive markers are being explored to assist in the diagnosis of NAFLD as liver biopsy is an invasive procedure [4]. MPV (Mean Platelet

Volume) is a part of Complete Blood Count (CBC) which is an inexpensive and routine laboratory test. MPV has been studied in various diseases and its relationship has been established especially in case of thrombocytopenia, Myocardial Infarction (MI) and post MI prognosis. MPV has been studied in obesity and an increased MPV contributes to increased platelet activity, increased atherosclerosis and increased risk of vascular complications [5-6]. Recent studies have revealed an increase in MPV as an independent predictor of NAFLD [4]. Increase in obesity, hypertension and diabetes mellitus have led to a higher incidence and prevalence of NAFLD in India, initially thought to be a disease of developed countries [7]. Extensive literature search revealed that to date, only eight Indian studies have evaluated MPV as a marker of NAFLD. In a developing country like India, MPV can be utilized as a cheaper and non-invasive marker of NAFLD [8]. Hence this study aimed to measure MPV levels in NAFLD patients and compare the same with healthy controls.

Material and Methods:

This hospital-based case-control study was carried out at the General Medicine Outpatient Department of a tertiary hospital in Bengaluru from 1st October 2015 to 31st May 2017. Patients aged > 18 years with ultrasonography of abdomen showing features of hepatosteatosis with no comorbidities were a part of the study. Totally, 43 cases of NAFLD and 43 controls were included in the study. Patients with alcohol intake (>20g/day in men; >10 g/day in women), who were positive for serological markers for viral hepatitis Hepatitis B surface Antigen (HBsAg), anti-Hepatitis C Virus antibody (anti HCV), smokers, pregnant females, anaemic (haemoglobin <13g/dl in males, <11g/dl in females), patients with illnesses like diabetes mellitus, bronchial asthma, chronic obstructive pulmonary disease, malignancy, chronic renal failure, cardiovascular diseases, cerebrovascular accident and peripheral vascular disease or patients on medications that affect platelet indices (e.g.: aspirin, clopidogrel, heparin, warfarin etc), were not considered to be a part of the study. The ethical clearance (STD-1/EC/029/2015) for this study was obtained from the Institutional Ethics Committee prior to study initiation. After written informed consent was obtained from the patients, a detailed demographic history (age, gender) was recorded, and a general physical examination was done. Anthropometric measurements (weight, height) were taken for all patients and investigations like complete blood count, liver function tests, fasting lipid profile, fasting blood sugar, post-prandial blood sugar, ultrasonography of abdomen, HBsAg, anti HCV, renal function tests and electrocardiogram were done.

NAFLD diagnosis was made considering three criteria, including ultrasonography showing increased echogenicity of the liver compared to renal cortex and spleen, alcohol intake <20 g/day in males or <10 g/day in females, and testing negative for HBsAg and anti HCV. MPV was measured (reference range 7 to 13 fL) as a part of the automated CBC using SYSMEX XE 2100 and XT 2000i. Grading of steatosis was performed using ultrasonography based on liver echogenicity: Grade 0: normal; Grade 1: mild steatosis, Grade 2: moderate steatosis, and Grade 3: severe steatosis [9].

Statistical Analysis:

Assuming a high effect size of 0.75 for MPV values between NAFLD cases and controls, at 5% level of significance, and 90% power, a sample size of 39 subjects per each group was required for the study. Here, a sample size of 86 was included in the study with 43 subjects in each group. Data were analysed using statistical software R v4.0.3. Categorical variables were given in the form of frequency tables. Continuous variables were given in Mean ± SD/Median (IQR) form. Chi-square test was used to check the association between categorical variables. Two sample t-test and Mann Whitney U test were used to compare the difference between two independent variables. Spearman's rank correlation test was done to find the correlation between MPV and Alanine Transferase (AST), Alkaline Phosphatase (ALT), and presence of NAFLD. Logistic regression analysis was performed to determine whether NAFLD was really an independent determinant for increased MPV values. Positive Predictive Values (PPV), Negative Predictive Values (NPV), sensitivity, specificity as well as the best cut-off value for MPV were calculated using ROC curves. $P \leqslant 0.05$ indicates statistical significance.

Results:

The number of males among controls and cases was 22 and 23 (51.2% and 53.5%), respectively. The number of females among controls and cases were 21 and 20 (48.8% and 46.5%), respectively. Mean age among cases and controls was 45 ± 11.53 years and 46.95 ± 12.05 years respectively (P=0.668). In both the groups, the male: female ratio was almost equal, (23:20 in cases and 22:21 in controls) (P=0.829).

Weight, BMI, and waist circumference were higher in cases and the difference was statistically significant (P<0.001). Total Leukocyte Count (TLC) was elevated in cases (8090.19 ± 1936.40 cells/mm^3) when compared with control (6525.12 ± 1126.39 cells/mm^3; P<0.001). MPV in cases with NAFLD (11.9 vs. 9.9, P<0.001) and PCT were also significantly higher in cases when compared to controls (0.31% vs. 0.28%; P = 0.012). Mean AST, ALT and Gamma Glutaryl Transferase (GGT) were higher among cases than controls and the difference was statistically significant ($P< 0.05$). Mean total bilirubin, direct bilirubin and ALP was also higher for cases than in controls, although the difference was not statistically significant (Table 2). A higher mean triglycerides levels and VLDL levels and lower HDL levels were observed in cases when compared to controls (Table 2). Among 43 NAFLD cases, the majority i.e., 34 (79.1%) had Grade 1 fatty liver, 5 (11.63%) had Grade 3 fatty liver and 4 (9.3%) had Grade 2 fatty liver (Table 3). MPV correlated positively with AST, ALT and the presence of NAFLD (Table 4). Logistic regression analysis was performed to understand whether NAFLD was really an independent determinant for increased MPV. Gender, BMI, waist circumference, HDL, and triglycerides were the covariables. Only NAFLD was found as an independent predictor of MPV (P<0.001). Odds of having NAFLD increased by 3.27 (1.95 – 6.15) with unit increase in MPV (Table 5).Table 6 presents cut-off values and accuracy indices of MPV in predicting NAFLD. A cut-off MPV >10.6 fL yielded 72.09% sensitivity, 76.74% specificity, 75.61% PPV and 73.33% NPV.

Table 1: Demographics and Haematological Parameters of the Individuals

Variables		**Controls (N=43)**	**Cases (N=43)**	***p***
Age (Years)	21-30	5 (11.63%)	4 (9.3%)	0.5577^{MC}
	31-40	7 (16.28%)	8 (18.6%)	
	41-50	13 (30.23%)	18 (41.86%)	
	51-60	12 (27.91%)	6 (13.95%)	
	61-70	6 (13.95%)	7 (16.28%)	
Gender	Female	21 (48.84%)	20 (46.51%)	0.8291^{C}
	Male	22 (51.16%)	23 (53.49%)	
Weight (kg)		68.14±10.43	73.35±13.00	**0.0435^{t}***
Height (cm)		170 (162.5, 176)	169 (160, 174)	0.4348^{MW}
BMI (kg/m^2)		23.77 ± 2.36	26.17 ± 3.36	**< 0.001^{t}***
Waist circumference (cm)		83.49 ± 4.82	91.60 ± 7.36	**< 0.001^{WT}***
Blood count	HB(g/dl)	14.10 ± 1.37	14.35 ± 1.56	0.4303^{t}
	TLC (cells/mm^3)	6525.12 ± 1126.39	8090.19 ± 1936.40	**< 0.001^{WT}***
	RDW (%)	12.9 (12.4, 13.6)	13 (12.45, 13.55)	0.4783^{MW}
	Platelet count (cells/mm^3)	268813.95 ± 59185.45	299837.2 ± 122738.38	0.1406^{WT}
	MPV (fL)	9.9 (9.65, 10.75)	11.9 (10.7, 12.9)	**< 0.001^{MW}***
	Plateletcrit (%)	0.28 (0.245, 0.32)	0.31 (0.265, 0.38)	**0.0123^{MW}***

*Hb – Haemoglobin, BMI - Body mass index, TLC - Total leukocyte count, RDW - Red cell distribution width, MPV - Mean platelet volume, C – Chi-square test, MC – Chi-square test with Monte Carlo simulation, t – Two-sample t test, WT – Two sample Welch t-test, MW – Mann-Whitney U test, * indicates statistical significance.*

Table 2: Liver Function Tests and Lipid Profile Tests of the Individuals

Variables		Control (N=43)	Cases (N=43)	*p*
Liver function tests	**Total Bilirubin (mg/dl)**	0.64 (0.485, 0.83)	0.68 (0.505, 0.985)	0.4394[MW]
	Direct Bilirubin (mg/dl)	0.14 (0.11, 0.175)	0.17 (0.13, 0.215)	0.0204[MW]
	Total protein(g/dl)	7.6 (7.3, 7.7)	7.5 (7.25, 7.9)	0.8522[MW]
	Albumin(g/dl)	3.8 (3.6, 4)	3.9 (3.7, 4.15)	0.2496[MW]
	AST(u/l)	21 (15.5, 23)	27 (21, 34.85)	**< 0.001[MW]***
	ALT(u/l)	26 (20.5, 37.5)	43 (25.5, 49)	**0.002[MW]***
	ALP(u/l)	81 (64, 97.5)	89.6 (68,101.5)	0.5745[MW]
	GGT(u/l)	24 (20, 31)	37 (25.5, 55.5)	**< 0.001[MW]***
Lipid parameters	**Total cholesterol (mg/dl)**	188.19 ± 37.92	186.21 ± 43.29	0.8224[t]
	Triglycerides (mg/dl)	114.93 ± 52.28	174.58 ± 96.07	**< 0.001[MW]***
	HDL (mg/dl)	45 (40, 51)	40 (35.5, 45)	**0.0136[MW]***
	LDL (mg/dl)	115 (101.1, 135.5)	111.4 (93.3, 134.7)	0.5115[MW]
	VLDL (mg/dl)	20 (15.8, 29.4)	27 (20.7, 31.8)	**0.0041[MW]***

*AST - Aspartate aminotransferase, ALT - Alanine transferase, ALP - Alkaline phosphatase, GGT - Gamma glutaryl transferase, HDL – High-density lipoprotein, LDL – Low-density lipoprotein, VLDL - Very low-density lipoprotein, t – Two-sample t-test, MW – Mann Whitney U test, *indicates statistical significance.*

Table 3: Ultrasound Abdomen Findings of Study Participants

		Controls		Cases	
		N (43)	%	N (43)	%
Ultrasound abdomen (Fatty Liver)	Normal	43	100	0	0
	Grade 1	0	0	34	79.1
	Grade 2	0	0	4	9.3
	Grade 3	0	0	5	11.6

Table 4: Correlation of MPV with Other Parameters

Variables	Correlation coefficient	*p*
AST (U/L)	0.2834	**0.0082***
ALT (U/L)	0.2834	**0.0082***
ALP (U/L)	0.01993	0.8555
NAFLD	0.6019	**< 0.001***
Platelet count (cells/mm^3)	-0.1934	0.0743
Creatinine (mg/dl)	0.1121	0.3041

*AST-Aspartate aminotransferase, ALT-Alanine transferase, ALP - Alkaline phosphatase, NAFLD: Non-alcoholic fatty liver disease; * indicates statistical significance*

Table 5: Multivariate Logistic Regression to Assess the Factors for Increased MPV

Variables	Logit coefficient	*p*	Odds Ratio (95% CI)
MPV	1.18	< 0.001*	3.27 (1.95 – 6.15)
Gender	0.45	0.55	1.56 (0.37 – 7.13)
BMI > 23.0	-0.04	0.95	0.96 (0.23 – 4.10)
Waist circumference	1.53	0.06	4.62 (0.98 – 25.06)
Triglycerides	1.22	0.05	3.38 (1.02 – 12.23)
HDL	0.47	0.47	1.60 (0.45 – 5.72)

*MPV- Mean Platelet Volume; NAFLD-Non-alcoholic fatty liver disease; BMI-Body Mass Index; HDL- High-density lipoprotein; *indicates statistical significance*

Table 6: Optimal Cut-off and Accuracy Indices of MPV for Predicting NAFLD

Variable	MPV
Cut off	(>) 10.6
Sensitivity (95 % CI)	72.09% (56.33% - 84.67%)
Specificity (95 % CI)	76.74% (61.37% - 88.24%)
PPV (95 % CI)	75.61% (59.88% - 86.89%)
NPV (95 % CI)	73.33% (57.86% - 86.22%)
AUC	0.847 (0.768 - 0.926)

*PPV- Positive predictive values, NPV- Negative predictive values, AUC - Area under the curve, * indicates statistical significance*

Note: *An optimal cut-off value was calculated based on the maximum values of sensitivity and specificity of the score identified from the ROC curve.*

Discussion:

In our study, MPV was higher in NAFLD patients as compared to controls and NAFLD significantly influences the increase in MPV. Furthermore, sensitivity, specificity, good PPV, and NPV of MPV indicates its diagnostic efficiency in evaluating NAFLD patients. Overall, we have highlighted the clinical significance of an elevated MPV and its relationship with NAFLD in this patient cohort.

Non-invasive techniques like fibroscan and ultrasonography eliminate sampling errors that are common with liver biopsy. Nevertheless, the high cost of the machine and its availability at all the private centres are the major obstacles for their use in developing countries like India [10]. Hence, ongoing interest is focusing on the cheaper and easily accessible markers for the detection of liver fibrosis and steatosis and its severity grades. Current literature suggested that platelets, along with their renowned role in haemostasis, participates in the progression of liver fibrosis [11]. Platelet indices-MPV, PDW, and PCT-are the indicators of platelet function and activation [11]. Platelet activation is a characteristic feature in the pathophysiology of various diseases, such as inflammatory and vascular disorders [12-13].

Larger platelets are enzymatically and metabolically more active and they have more aggregability as well as they are more thrombogenicin nature thereby increasing platelet activation. Per se, platelet size and function can be used as a useful biomarker in such disorders [14]. The cause of increased MPV in NAFLD patients is a low-grade inflammatory state induced by hepatic steatosis leading to platelet activation [15]. Moreover, this is a simple cost-effective test that

can be done during a routine complete blood picture. Hence, the MPV parameter was used in our study to diagnose NAFLD.

Waist circumference and BMI were significantly higher in cases in comparison to controls. Similar findings were noted in other studies [16-18]. This emphasizes the key role of metabolic syndrome in NAFLD [16]. Consistent with our findings, Celikbilek *et al*. [14] and Kocabay *et al*. [19] noted that the liver enzymes-AST, ALT, and GGT-were significantly higher among cases with NAFLD as compared to controls [16-17]. However, they did not notice a significant increase in mean total bilirubin, direct bilirubin, and ALT in cases with NAFLD compared to controls [16-17].

Consistent with our study results, Ozhan *et al*. found MPV among cases with NAFLD was 10.43 ± 1.14 fL and 9.09 ± 1.25 fL (P<0.001) among healthy controls [17]. This was more significant when compared to detection of NAFLD by liver transient elastography using Fibroscan (p=0.068) [19]. Similarly, Aktas *et al*. [20] demonstrated higher mean platelet count in NAFLD cases than those in healthy controls (267000 ± 107000 cells/mm^3 vs. 248000 ± 53000 cells/mm^3) [20]. In our study, MPV positively correlated with NAFLD, AST, and ALT levels. Increased ALT indicates disease progression and worsening in NAFLD patients [21]. In another study ALT elevation positively correlated with carotid atherosclerosis after adjusting covariates (age, sex, and metabolic syndrome) [22]. Hence, ALT levels correlation with MPV indicates predictability of NAFLD. Similar to our study Ozhan *et al*. [17], where NAFLD was found to be the independent predictor of increased MPV among covariates including age, gender, NAFLD, BMI, HDL, triglycerides, fasting and postprandial plasma glucose [OR:21.98, 95% CI: 2.404–201.048; P=0.006] [16]. Overall, the results indicated that MPV increased in NAFLD patients.

The major strength of the study is that very few studies have assessed the diagnostic efficacy of MPV in prognosticating NAFLD. This study found that MPV alone had Area Under the Curve (AUC) of 0.84 and a cut-off of a >10.6 with PPV (59.88-86.89%) and NPV (57.86-86.22%). Similar other studies reported AUROC of 0.83, cut-off of 10.05 with good positive (20-24%) and negative predictive values (94-97%) [14]. This indicates that this single parameter can be used as an initial screening tool for early diagnosis for NAFLD at primary and secondary health centres.

The study has a few potential limitations that need to be acknowledged. First, as the baseline analyses may not reflect the patient's condition over a prolonged period, liver biopsy is warranted for NAFLD diagnosis. Second, low AUC suggests the need for a larger cohort study. Third, NAFLD correlates well with an increase in cardiovascular morbidity; however, patients with diabetes, cardiovascular diseases were excluded from the current study. Hence, the findings may lack generalizability.

Conclusion:

The study results showed an increase in MPV in patients with NAFLD. Rise in MPV in NAFLD can suggest the need for early evaluation and appropriate treatment by clinicians. It can also be considered as an economical marker in the diagnosis of NAFLD, especially in developing countries like India.

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